Original research

Subtyping emphysematous COPD by respiratory volume change distributions on CT

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ABSTRACT

Background There is considerable heterogeneity among patients with emphysematous chronic obstructive pulmonary disease (COPD). We hypothesised that in addition to emphysema severity, ventilation distribution in emphysematous regions would be associated with clinical-physiological impairments in these patients.

Objective To evaluate whether the discordance between respiratory volume change distributions (from expiration to inspiration) in emphysematous and non-emphysematous regions affects COPD outcomes using two cohorts.

Methods Emphysema was quantified using a low attenuation volume percentage on inspiratory CT (iLAV%). Local respiratory volume changes were calculated using non-rigidly registered expiratory/inspiratory CT. The Ventilation Discordance Index (VDI) represented the log-transformed Wasserstein distance quantifying discordance between respiratory volume change distributions in emphysematous and non-emphysematous regions.

Results Patients with COPD in the first cohort (n=221) were classified into minimal emphysema (iLAV% <10%; n=113) and established emphysema with high VDI and low VDI groups (n=46 and 62, respectively). Forced expiratory volume in 1 s (FEV_1) was lower in the low VDI group than in the other groups, with no difference between the high VDI and minimal emphysema groups. Higher iLAV%, more severe airway disease and hyperventilated emphysematous regions in the upper-middle lobes were independently associated with lower VDI. The second cohort analyses (n=93) confirmed these findings and showed greater annual FEV_1 decline and higher mortality in the low VDI group than in the high VDI group independent of iLAV% and airway disease on CT.

Conclusion Lower VDI is associated with severe airflow limitation and higher mortality independent of emphysema severity and airway morphological changes in patients with emphysematous COPD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Inspiratory/expiratory CT can be used to evaluate the extent of emphysema and regional respiratory volume changes in patients with emphysematous chronic obstructive pulmonary disease (COPD). However, whether ventilation distributions in emphysematous regions affect clinical outcomes independent of the extent of emphysema remains unclear.

WHAT THIS STUDY ADDS

⇒ Lower discordant distributions of respiratory volume changes in emphysematous and non-emphysematous regions are associated with severe airflow limitation and higher long-term mortality independent of the overall emphysema severity and airway disease on CT in patients with emphysematous COPD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Discordant distributions of respiratory volume changes in emphysematous and non-emphysematous regions on CT can help explain the clinical and physiological heterogeneity in emphysematous COPD and allow for more clinically relevant subtyping of patients with emphysematous COPD towards better personalised management.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is simply diagnosed by the presence of respiratory symptoms and airflow limitation on spirometry[1]; however, the underlying structural changes in the parenchyma and airways are complex. Emphysema is a primary pathology in COPD that can be quantified on CT and is generally associated with impaired pulmonary function,[2–4] accelerated disease progression[5–7] and mortality.[8] However, a subgroup of emphysematous COPD exhibits only mild airflow limitation and less severe prognosis.[9 10] There is considerable heterogeneity among patients with emphysematous COPD, and better quantification of the structural and physiological changes associated with emphysema and airway disease is central to defining these patients.

Inspiratory CT is widely used to quantify emphysema and airway disease,[2–4] but it cannot be used to evaluate ventilation distribution. In contrast, on functional MRI, increased ventilation heterogeneity is associated with airflow limitation and predicts exacerbations,[11] and emphysematous regions that appear identical on inspiratory CT are classified into ventilated and non-ventilated

emphysematous regions.[12] Additionally, non-rigid registration of inspiratory and expiratory CT enables estimating ventilation distribution by calculating local respiratory volume changes.[13] This technique has shown that abnormal respiratory local expansion near emphysematous regions contributes to future progression of airflow limitation,[14] and normally and abnormally ventilated emphysematous regions are heterogeneously distributed within each lung.[15] These findings suggest that ventilation distribution in emphysematous regions may vary among patients and may be a determinant of airflow limitation in emphysematous COPD.

Ventilation distribution is also affected by diseases of peripheral small airways and proximal medium-to-large airways, such as luminal narrowing, wall remodelling and mucus plugs.[16–18] Because of a complex mixture of emphysema and airway disease in COPD,[1 19–21] a large variation in ventilation distributions should exist in emphysematous and non-emphysematous regions. Moreover, a study using human lung tissue specimens showed that on pressure-volume curves, a whole emphysematous lung is more compliant than normal lungs, but local centrilobular emphysematous spaces in the same emphysematous lung are less compliant than normal lungs.[22] Therefore, local elastic properties in the lung parenchyma might vary among emphysematous regions and affect ventilation distribution.

It was hypothesised that in addition to the overall emphysema severity, the discordance between ventilation distributions in emphysematous and non-emphysematous regions could be associated with the clinical-physiological impairments in patients with emphysematous COPD. This study evaluated the discordance of ventilation distributions between the two regions by quantifying respiratory volume change distributions from end-tidal expiration to full inspiration using inspiratory/expiratory CT. The study established a novel imaging marker, the Ventilation Discordance Index (VDI) and investigated whether VDI was associated with airflow limitation and long-term mortality independent of the CT indices of emphysema and airway disease using two independent COPD cohorts.

MATERIALS AND METHODS

Study protocol

The details are provided in online supplemental methods 1–1. Briefly, among smokers aged ≥40 years with ≥10 smoking pack-years enrolled in the Kyoto-Himeji cohort between 2018 and 2020,[21] patients with COPD were included (discovery cohort). The Kyoto-Himeji cohort study was approved by the Ethics Committee of Kyoto University (approval no. C1311) and was registered with the University Hospital Medical Information Network (UMIN000028387). The validation of the findings in the discovery cohort and longitudinal and prognostic evaluation were performed using data from the Hokkaido COPD cohort study[5 23] that was approved by the Health Authority Research Ethics Committee of Hokkaido University School of Medicine (no. med02-001) and enrolled patients between 2003 and 2005.

CT acquisitions

Inspiratory/expiratory CT was performed at full inspiration (total lung capacity (TLC) level) and end-tidal expiration (functional residual capacity (FRC) level) in both the Kyoto-Himeji cohort and Hokkaido COPD cohort (online supplemental methods 1–2 for details).

Conventional CT analyses

Figure 1 shows the primary CT evaluations in this study (online supplemental methods 1–3 for details). Emphysema severity was assessed as the percentage of low attenuation volume (LAV) <-950 Hounsfield units (HU) on inspiratory CT (iLAV%)[4 8 21 24] and air trapping was assessed as the percentage of LAV <-856 HU on expiratory CT (eLAV%)[25 26] using a SYNAPSE VINCENT volume analyser (FUJIFILM, Tokyo, Japan). Following lobe segmentation (figure 1B), the ratio of iLAV% in the upper lung (right upper-middle and left upper lobes) to that in the lower lung (right and left lower lobes) ($iLAV\%_{upper}/iLAV\%_{lower}$) was calculated.[27] The presence of centrilobular emphysema and paraseptal emphysema was visually evaluated.[2]

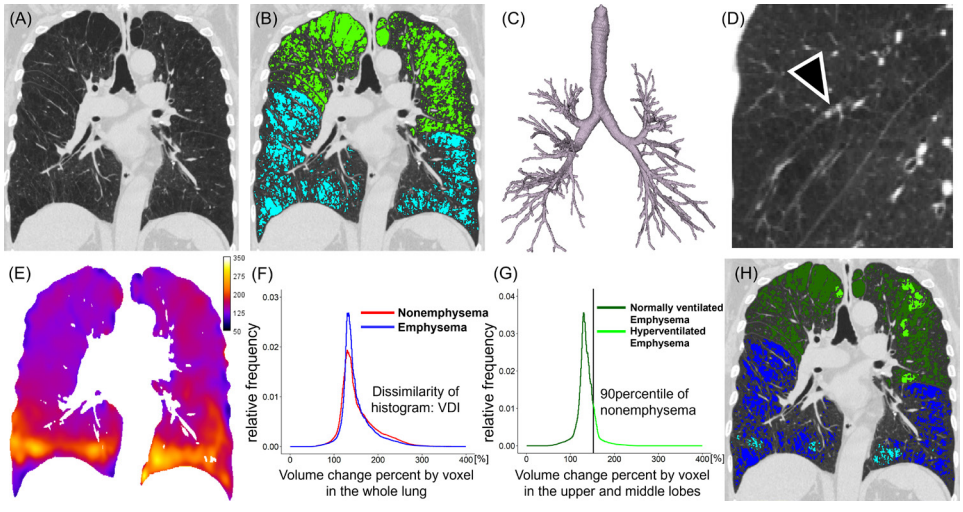

Figure 1 Overall CT evaluations. (A) Original inspiratory CT. (B) Emphysema (low attenuation voxels) in the upper-middle lobes and lower lobes (green and blue colours). (C) Extracted airway tree to calculate the total airway count. (D) Mucus plugs in the airway. (E) Distributions of the respiratory volume change percentages were visualised as a heatmap. (F) Histograms of the frequency distribution of volume change percentages in the emphysematous and non-emphysematous regions, the discordance of which was quantified using the Wasserstein distance. The Ventilation Discordance Index (VDI) was defined as the log-transformed Wasserstein distance. (G) Histogram of the emphysematous region in the upper-middle lobes. The dark and light green lines indicate normally ventilated emphysema and hyperventilated emphysema, respectively. (H) Hyperventilated (light green and blue) and normally ventilated (dark green and blue) emphysematous regions were visualised in the upper middle and lower lobes.

To quantify airway disease, the wall area percentage (WA%) at the right apical and basal posterior subsegmental airways[21] and total airway count (TAC) were measured[4] (figure 1C). The total mucus score was obtained by visual inspection of all the airway segments[28] (figure 1D), and the presence of a mucus plug was defined as a total mucus score ≥1.

Novel method to calculate VDI

The details are provided in online supplemental methods 1–4. Following extraction of the lung fields, the images on expiratory CT were non-rigidly registered onto those on inspiratory CT.[29] A displacement matrix was generated during lung deformation to calculate the respiratory volume change percentage for each voxel according to a previous report on the calculation of Jacobians[30] (figure 1E). To estimate the discordance between distributions of the local respiratory volume change percentages in emphysematous and non-emphysematous regions, relative frequency histograms of respiratory volume change percentages in the two regions were separately generated (figure 1F and online supplemental figure E1).The discordance between the two histograms was calculated as the Wasserstein distance,[31] which represents the cost of the difference using the Python package 'pyemd'.[32] Because of the non-normal distribution of the Wasserstein distances in all the patients, log-transformation was performed (online supplemental figure E2). The VDI was defined as the log-transformed Wasserstein distance.

Additionally, hyperventilated emphysematous regions were defined as emphysematous voxels whose respiratory volume change percentage was higher than the 90% tile of respiratory volume change percentages in non-emphysematous regions (figure 1G). Then, the percentage of the hyperventilated emphysematous region to the total emphysematous region (hyperventilated emphysema ratio) was calculated in the upper and lower lungs separately (figure 1H). Furthermore, small airway disease (SAD) voxels were identified as voxels ≥−950 HU on inspiratory CT and <−856 HU on expiratory CT. The percentage of SAD voxels to the whole lung voxels was calculated as SAD%.[29]

Clinical and physiological examinations

Postbronchodilator spirometry and measurements of the lung subvolumes and diffusing capacity were performed.[33] In the Hokkaido COPD cohort, the annual change in forced expiratory volume in 1 s (FEV_1) was estimated using a mixed-effect linear model and 5-year longitudinal data, time to first exacerbation was recorded over 5 years, and mortality was evaluated over 10 years after enrolment.[5 8 23] For details, see online supplemental methods 1–5.

Statistical analysis

R statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used. For details, see online supplemental methods 1–6. The patients were divided into three groups based on a cut-off value of 10% in iLAV% and the median value of VDI (2.06) in all patients of the Kyoto-Himeji cohort. The three VDI groups (minimal emphysema, established emphysema with high VDI (the high VDI group), and established emphysema with low VDI (the low VDI group)) were defined as iLAV%<10% with any VDI, iLAV% ≥10% with≥the median VDI, and iLAV% ≥10% with<the median VDI, respectively. Relationships between FEV_1, VDI, and the variables, including other CT indices, could

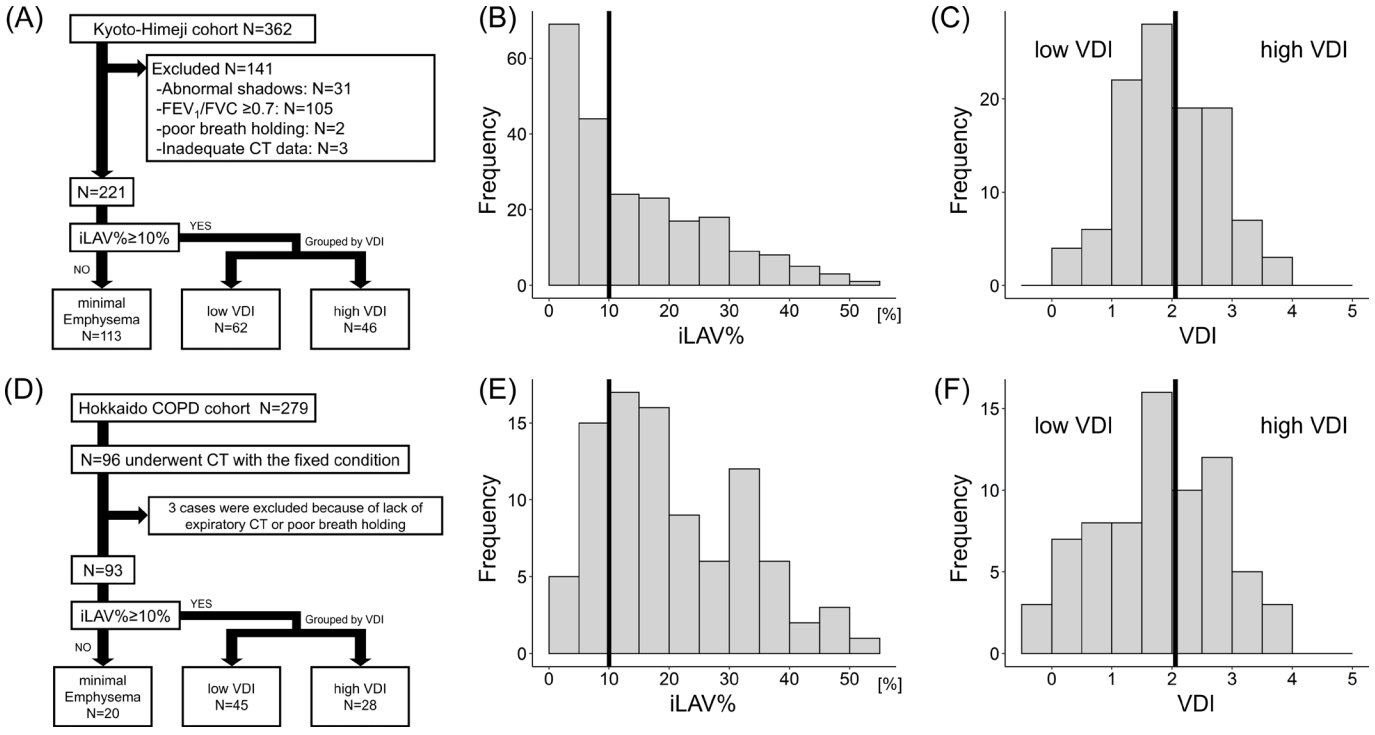

Figure 2 Patient flow chart and distributions of emphysema severity and the Ventilation Discordance Index (VDI) in the two cohorts. (A) Patient flowchart in the Kyoto-Himeji cohort. (B) Patients were classified into minimal and established emphysema groups using a cut-off value of 10% in the low attenuation volume % on the inspiratory scan (iLAV%). (C) Patients with established emphysema were further classified into low and high VDI groups using a cut of the median VDI of the Kyoto-Himeji cohort. (D) Patient flow chart, (E) distribution of iLAV% and (F) VDI in the Hokkaido COPD cohort defined using the same cut-off values used in the Kyoto-Himeji cohort. COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 1 Patient demographics in the Kyoto-Himeji cohort

	Minimal emphysema (N=113)	High VDI (N=46)	Low VDI (N=62)
Male, %	96	93	95
Age, years	72 (8)	74 (7)	72 (9)
Height, cm	165 (7)	164 (6)	165 (7)
BMI, kg/m^2	25 (3)	22 (3)*	22 (4)*
Current smoker, %	31	28	16
Pack-years	55 (30)	67 (33)	62 (30)
LAMA use, %	45	72	82*
LABA use, %	51	65	84
ICS use, %	43	39	50
mMRC (0/1/2/3/4), %	46/40/8/4/2	33/44/16/7/0	26/36/26/9/3*
CAT	10 (7)	11 (7)	14 (8)*
GOLD stage (1/2/3/4), %	42/49/10/0	37/41/15/7	11/37/29/23*†
PaO_2, mm Hg	82 (9)	78 (6)	73 (8)*†
Pulmonary function			
FVC, % predicted	93 (19)	104 (25)*	83 (23)†
FEV_1, % predicted	75 (18)	71 (25)	50 (21)*†
FEV_1/FVC, %	62 (7)	51 (11)*	44 (12)*†
D_{LCO}, % predicted	77 (15)	53 (13)*	45 (17)*
TLC, % predicted	95 (11)	102 (10)*	98 (13)
RV, % predicted	87 (18)	88 (22)	108 (29)*†
FRC, % predicted	96 (17)	107 (17)*	113 (22)*
RV/TLC, %	38 (6)	36 (8)	45 (9)*†
CT index			
iLAV%, %	4.4 (2.7)	23.1 (9.4)*	24.2 (10.7)*
eLAV%, %	30.2 (14.5)	50.2 (12.1)*	61.0 (10.6)*†
SAD%, %	22.8 (12.8)	26.8 (8.9)	36.1 (8.8)*†
MLD, HU	−861 (25)	−890 (20)*	−889 (20)*
LA, mm^2	13.4 (4.4)	15.6 (4.6)*	12.6 (3.1)†
WA%, %	65 (4)	62 (4)*	65 (3)†
TAC	332 (76)	375 (83)*	301 (56)*†
Mucus (presence), %	52	39	66†
Mucus score	2.8 (4.1)	1.4 (2.5)	3.6 (4.2)†
CLE, %	19	89*	84*
PSE, %	40	76*	65*

The data are expressed as the mean (SD) and %. Analysis of variance followed by Tukey's post hoc test was performed.
*and † indicate p <0.05 compared with the minimal emphysema group and the established emphysema with high VDI group, respectively. D_{LCO} was acquired from 127 patients, TLC, RV and FRC were from 135 patients, mMRC and CAT were from 201 patients, and PaO_2 was from 111 patients.
BMI, body mass index; CAT, COPD assessment test; CLE, centrilobular emphysema; COPD, chronic obstructive pulmonary disease; DLCO, diffusing lung capacity for carbon monoxide; eLAV%, LAV percentage on the expiratory scan; FEV_1, forced expiratory volume in 1s; FRC, functional residual capacity; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; iLAV%, low attenuation volume percentage on the inspiratory scan; LA, luminal area; LABA, long-acting beta 2-agonist; LAMA, long-acting muscarine antagonist; MLD, mean lung density; mMRC, modified Medical Research Council dyspnoea scale; PaO2, arterial oxygen tension; PSE, paraseptal emphysema; RV, residual volume; SAD%, small airway disease percentage; TAC, total airway count; TLC, total lung capacity; VDI, ventilation discordance index; WA%, wall area percentage.

be considered linear based on scatter plots. Multivariable linear regression models were constructed to test whether the VDI group was associated with FEV_1 cross-sectionally and with a longitudinal change in FEV_1. The models included CT indices (the VDI group, iLAV%, WA%, mucus and TAC) and demographic factors (age, height, smoking status, pack-years and institution) as independent variables. Baseline FEV_1 was also included in the model for the longitudinal FEV_1 change. The association of CT indices with VDI values was also tested using multivariable linear regression models. The association of the VDI group with mortality was tested using the Cox proportional hazards model in the Hokkaido COPD cohort, with covariates including baseline FEV_1 and D_{LCO}, iLAV%, WA%, the presence of mucus, TAC, the VDI group and demographic factors (age, smoking status, pack-years). To explore a minimal adjustment set of variables for the multivariable models, the causal directed acyclic graph (DAG) was constructed using the web platform 'DAGitty'.[34]

RESULTS

Characteristics of the two cohorts

The basic information of the two cohorts is summarised in online supplemental table E1. Figure 2 shows that 221 smokers with COPD in the Kyoto-Himeji cohort were divided into the minimal emphysema (iLAV%<10%, n=113), high VDI (iLAV%≥10% and VDI≥2.06, n=42) and low VDI (iLAV%≥10% and VDI<2.06, n=62) groups. In the Hokkaido COPD cohort, 93 patients with COPD were divided into minimal emphysema and high and low VDI groups (n=20, 28 and 45, respectively) using the same cut-off values (iLAV%=10% and VDI=2.06) used for the Kyoto-Himeji cohort. The good reproducibility of the VDI measurements was confirmed in multiple inspiratory/expiratory CT scans from 24 patients in the Kyoto-Himeji cohort (online supplemental results 2–1 and figure E3).

Cross-sectional analysis in the two cohorts

Table 1 and online supplemental table E2 compare clinical features among the three groups in the Kyoto-Himeji and Hokkaido COPD cohorts (online supplemental results 2–2). The CT measures of the upper and lower lung regions are summarised in online supplemental table E3.

Table 2 shows associations of iLAV%, WA%, the presence of mucus, TAC, $iLAV\%_{upper}$/$iLAV\%_{lower}$, and the hyperventilated emphysema ratio in the upper lung with VDI. In multivariable analyses, iLAV%, the airway disease index (WA% or TAC), and the hyperventilated emphysema ratio in the upper lung were independently associated with VDI in both cohorts.

Figure 3 shows that as the GOLD spirometric grade increased, the prevalence of the low VDI group, but not that of the high VDI group, increased. Associations among airflow limitation, VDI, and other confounding factors are summarised in the DAG (figure 3B) and shown in online supplemental table E4. In the multivariable model, FEV_1 was significantly lower in the low VDI group than in the other two groups after adjusting for iLAV%, WA%, TAC and the presence of mucus, while no difference was found between the high VDI and minimal emphysema groups in the two cohorts (figure 3C,D and online supplemental table E5).

Figure 4 visualises respiratory volume change distributions in two representative patients with COPD. Although iLAV% was comparable between patients (21.2% and 23.3%), VDI was lower in the patient with severe airflow limitation than in the patient with non-severe airflow limitation (%predicted FEV_1=38% vs 75% and VDI=0.65 vs 3.34, respectively).

Longitudinal analysis in the Hokkaido COPD cohort

Table 3 shows that in the multivariable models, the annual decline in FEV_1 was significantly greater in the low VDI group than in the high VDI group independent of iLAV%, WA%, the presence of mucus and TAC.

Analyses of mortality and time to first exacerbation in the Hokkaido COPD cohort

Figure 5 shows that all-cause mortality and respiratory mortality significantly differed among the three groups (log-rank

Table 2 Univariable and multivariable regression analyses to explore whether the CT indices are associated with the ventilation discordance index in both cohorts

Kyoto-Himeji cohort	Univariable	Multivariable		
		Model 1	Model 2	Model 3
iLAV%	−0.21* (-0.34 to −0.08)	−0.24* (-0.37 to −0.12)	−0.21* (-0.33 to −0.08)	−0.15* (-0.28 to −0.03)
WA%	−0.24* (-0.37 to −0.11)	−0.26* (-0.39 to −0.13)	−0.09 (−0.24 to 0.06)	−0.10 (−0.24 to 0.05)
Mucus	−0.21* (-0.34 to −0.08)		−0.07 (−0.2 to 0.06)	−0.05 (−0.18 to 0.08)
TAC	0.36* (0.23 to 0.48)		0.27* (0.12 to 0.42)	0.27* (0.12 to 0.41)
$iLAV\%_{upper}/iLAV\%_{lower}$	0.21* (0.08 to 0.34)			0.13* (0.01 to 0.26)
Hyperventilated emphysema ratio in the upper lung	−0.23* (-0.36 to −0.10)			−0.22* (-0.35 to −0.09)
Hyperventilated emphysema ratio in the lower lung	−0.03 (−0.17 to 0.10)			0.10 (−0.03 to 0.23)
Hokkaido COPD cohort		**Multivariable**		
	Univariable	**Model 1**	**Model 2**	**Model 3**
iLAV%	−0.53* (−0.70 to −0.36)	−0.50* (−0.67 to −0.33)	−0.45* (−0.62 to −0.29)	−0.37* (−0.54 to −0.2)
WA%	−0.30* (−0.49 to −0.10)	−0.22* (−0.4 to −0.05)	0.02 (−0.22 to 0.26)	0.07 (−0.17 to 0.3)
Mucus	−0.25* (−0.45 to −0.05)		−0.15 (−0.32 to 0.02)	−0.15 (−0.32 to 0.01)
TAC	0.41* (0.23 to 0.60)		0.30* (0.05 to 0.54)	0.34* (0.1 to 0.59)
$iLAV\%_{upper}/iLAV\%_{lower}$	0.23* (0.03 to 0.43)			0.02 (−0.15 to 0.19)
Hyperventilated emphysema ratio in the upper lung	−0.36* (−0.55 to −0.17)			−0.24* (−0.44 to −0.05)
Hyperventilated emphysema ratio in the lower lung	−0.11 (−0.31 to 0.09)			0.01 (−0.17 to 0.19)

The data are expressed as standardised estimates (95% CI). Institution was adjusted for the model of the Kyoto-Himeji cohort.
*Indicates a p<0.05.
COPD, chronic obstructive pulmonary disease; eLAV%, LAV percentage on the expiratory scan; iLAV%, low attenuation volume percentage on the inspiratory scan; TAC, total airway count; WA%, wall area percentage.

p=0.001 and 0.001, respectively). Higher mortality was found in the low VDI group than in the high VDI group in the univariable Cox proportional hazards model (online supplemental results 2–3). By including potential confounding factors visualised on the DAG (figure 5C), the multivariable Cox proportional hazards model revealed that the low VDI group exhibited significantly higher all-cause mortality than the high VDI group (HR (95% CI)=4.11 (1.34 to 12.60)) independent of FEV_1, iLAV%, WA%, the presence of mucus and TAC (figure 5D and online supplemental table E6). The time to first exacerbation did not differ among the three groups (log-rank p=0.12, online supplemental figure E4).

Analysis using different cut-off values for defining established emphysema, mucus severity and classification into high and low VDI groups

To confirm the validity of the findings based on the iLAV% cut-off value of 10% to define the established emphysema, multivariable analyses were performed using 5% and 15% as iLAV% cut-off values. In the models using the 5% iLAV% cut-off, the low VDI group was associated with lower FEV_1, greater annual decline in FEV_1, and higher mortality (online supplemental tables E7-9 and figure E5). Similar trends were confirmed in models using 15% as the iLAV% cut-off.

In the multivariable models using the high (≥5) and low (<5) mucus score groups (online supplemental figure E6) instead of the absence (score=0) and presence (score ≥1) of mucus, the low VDI group was associated with lower FEV_1, annual decline in FEV_1, and mortality (online supplemental tables E10, E11).

When classification into the high and low VDI groups was performed based on the median VDI of patients with established emphysema (VDI=1.87) instead of the median of all patients (VDI=2.06), the low VDI group was associated with lower FEV_1, greater annual decline in FEV_1 and higher mortality (online supplemental tables E12, E13).

DISCUSSION

This study established VDI as a novel imaging biomarker and showed in two independent cohorts that FEV_1 was lower in the low VDI group than in the high VDI group even after adjustment for emphysema severity and airway disease on CT. In contrast, no difference was found in FEV_1 between the high VDI and minimal emphysema groups. Additionally, higher iLAV%, lower TAC and a higher hyperventilated emphysema ratio in the upper

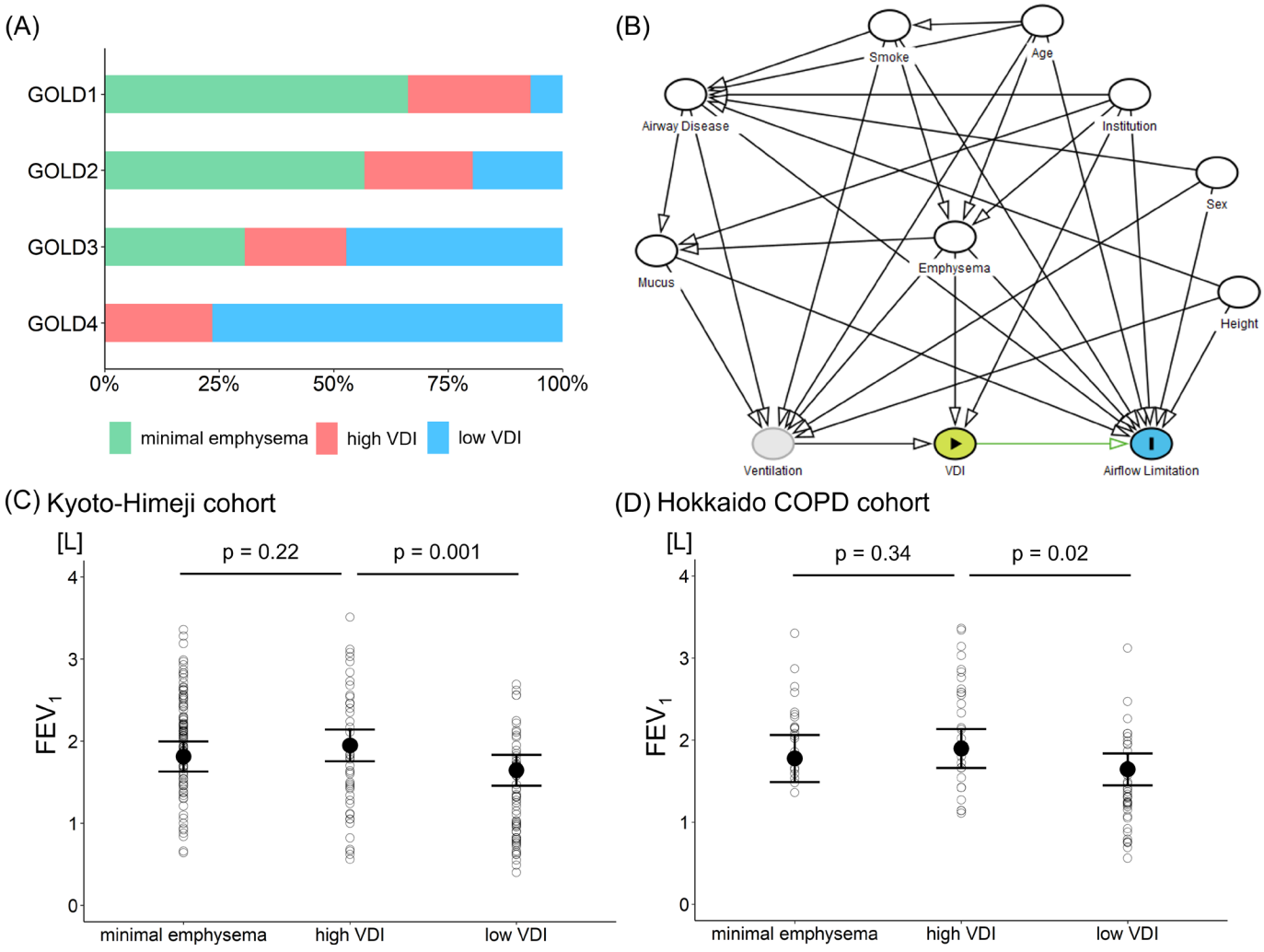

Figure 3 Association between the Ventilation Discordance Index (VDI) and airflow limitation in patients with COPD. (A) The prevalence of the low VDI group increased and that of the minimal emphysema group decreased as the GOLD spirometry grade increased in the Kyoto-Himeji cohort. (B) The causal directed acyclic graph visualised factors associated with airflow limitation (outcome). Emphysema (low attenuation volume percentage on the inspiratory scan (iLAV%)), airway disease (wall area percentage (WA%) and total airway count (TAC)), mucus plugs, age, sex, height, smoking status, pack-years and institution were considered potential confounders. The green, blue, white, red and grey circles indicate exposure, outcome, adjusted variables, ancestor of exposure and unobserved variables in the subsequent analysis, respectively. (C) The forced expiratory volume in 1 s (FEV_1) was lower in the low VDI group than in the high VDI and minimal emphysema groups in the Kyoto-Himeji cohort in the multivariable linear regression model adjusted for age, height, sex, institution, iLAV%, WA%, mucus, and TAC. The closed circle and bars indicate the least square mean with 95% CI of FEV_1. The open circles indicate raw data. The p values were calculated from the multivariable regression models for FEV_1, where the high VDI group was used as a reference. (D) A similar association between FEV_1 and the three groups was found in the Hokkaido COPD cohort using the multivariable model including the same variables. COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

lung were independently associated with lower VDI. Furthermore, the low VDI group was associated with greater longitudinal decline in FEV_1 and higher all-cause mortality than the high VDI group independent of baseline FEV_1, iLAV%, WA% and TAC. These findings suggest that lower VDI is associated with more severe airflow limitation and worse long-term COPD outcomes independent of overall emphysema severity and airway morphological changes and indicate the potential of VDI as a CT biomarker to manage patients with emphysematous COPD.

VDI was calculated as the log-transformed Wasserstein distance, which allows for the mathematical quantification of the discordance between the two frequency distributions.[31] Because respiratory volume change from inspiration to expiration in global and local lungs varies among patients, creating a universal definition of respiratory volume change distribution in normal regions for all patients was considered challenging. Alternatively, we used the respiratory volume change distribution in the non-emphysematous region as the reference and compared it with that in the emphysematous region for each patient. This idea increases the novelty of VDI because, to our knowledge, it has not been applied to CT indices derived from non-rigid registration of inspiratory/expiratory scans, such as parametric response mapping (PRM), which localises emphysema and functional small airway disease (SAD% in this study; for further comparisons between VDI and PRM, see online supplemental discussion 3–1).

SAD% was higher in the low VDI group than in the high VDI group. To compare SAD% with VDI from clinical perspectives, additional analyses were performed by classifying patients with emphysematous patients into high and low SAD% groups instead of the high/low VDI groups. As shown in online supplemental tables E14, E15, the high SAD% group was associated

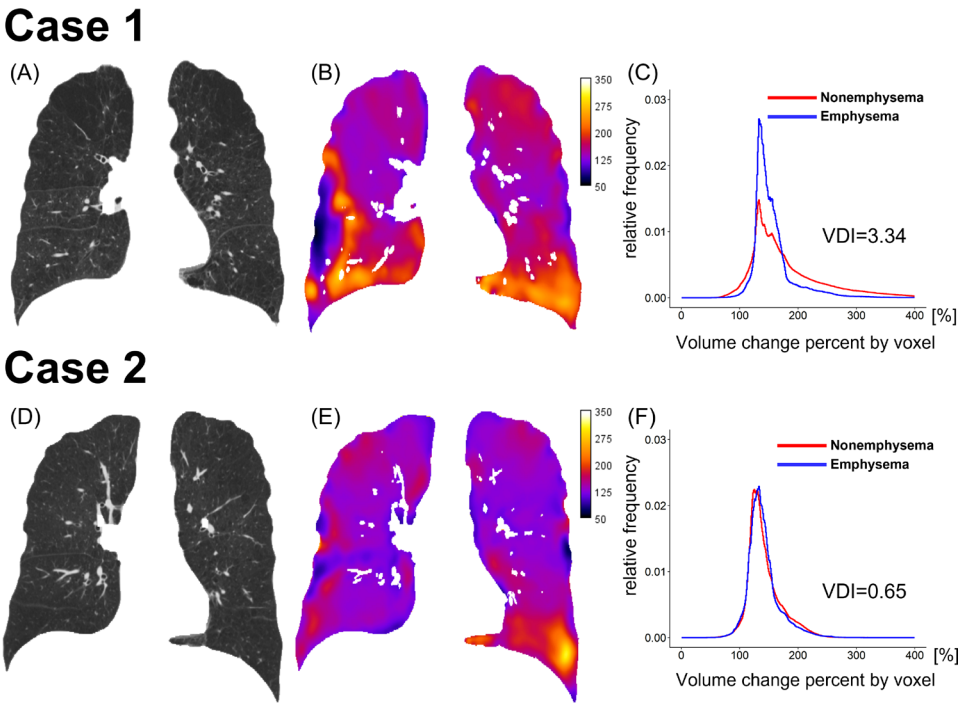

Figure 4 Representative patients with established emphysema with high and low Ventilation Discordance Index (VDI) values. The VDI was compared between two representative patients with COPD with non-severe and severe airflow limitations but comparable emphysematous changes (case 1: forced expiratory volume in 1 s (FEV_1)=1.91 L, % predicted FEV_1=75% and low attenuation volume % on the inspiratory scan (iLAV%)=23.3%; case 2: FEV_1=1.03 L, % predicted FEV_1=38% and iLAV%=21.2%). (A–E) Show emphysema, distribution of local respiratory volume changes on the heatmap, and discordance between frequency distributions of the respiratory volume changes in emphysematous and non-emphysematous regions in case 1 and case 2, respectively. Notably, despite the comparable iLAV%, VDI differed between case 1 and case 2 (3.34 and 0.65, respectively), suggesting that airflow limitation was associated with a lower VDI. COPD, chronic obstructive pulmonary disease.

with lower FEV_1 and higher mortality but not with greater longitudinal FEV_1 decline. Combined with a previous study showing that the association between SAD% and longitudinal FEV_1 decline is stronger in patients with mild COPD than in those with severe COPD,[35] we speculate that SAD% may sensitively detect future FEV_1 decline in patients with minimal emphysema, whereas VDI may be more useful than SAD% to evaluate patients with established emphysema.

Table 3 Multivariable regression analysis to explore whether the CT indices are associated with annual decline in FEV_1

	Model 1	Model 2
VDI group		
Minimal emphysema	1.91 (−11.31 to 15.12)	1.46 (−12.47 to 15.40)
High VDI	Ref	Ref
Low VDI	−15.82* (-27.02 to −4.61)	−16.60* (-28.35 to −4.85)
iLAV%	−0.08 (−0.56 to 0.41)	−0.07 (−0.56 to 0.42)
WA%	1.20* (0.11 to 2.30)	0.99 (−0.40 to 2.38)
Mucus (presence)		1.04 (−8.29 to 10.36)
TAC		−0.02 (−0.11 to 0.07)

The data are expressed as estimates (95% CI). Baseline FEV_1, age, height, sex, smoking status and pack-years were also adjusted for the models.
*Indicates a p<0.05.
FEV_1, forced expiratory volume in 1s; iLAV%, low attenuation volume percentage on the inspiratory scan; TAC, total airway count; VDI, ventilation discordance index; WA%, wall area percentage.

Higher iLAV% and either higher WA% or lower TAC were independently associated with lower VDI. WA% reflects wall remodelling of proximal airways, and TAC mainly reflects luminal narrowing of the proximal airway tree visible on CT.[4] Therefore, the present data suggest that more severe emphysema and proximal airway disease independently alter respiratory volume change distributions.

Independent of iLAV%, WA%, and TAC, a higher hyperventilated emphysema ratio in the upper lung was associated with lower VDI, and lower VDI was associated with lower FEV_1 in the two cohorts. Because the loss of elastic recoil in emphysema impairs forced expiratory airflow, this finding suggests that although emphysema in the upper lung can expand in static full inspiration, the hyperexpanded emphysematous regions cannot efficiently shrink during forced expiration. This phenomenon could be identified as lower FEV_1 in the low VDI group.

In contrast, the hyperventilated emphysema ratio was lower in the high VDI group. We speculate that a smaller amount of air breaths in emphysematous regions and that the influence of emphysema on forced expiratory airflow is smaller in the high VDI group than in the low VDI group. Together with the data showing that the high VDI group exhibited comparable pulmonary function to the minimal emphysema group, this finding explains why a subgroup of patients with COPD shows less airflow limitation despite the presence of emphysema and confirms that clinical outcomes are not always worse in emphysematous COPD than in non-emphysematous COPD.[10]

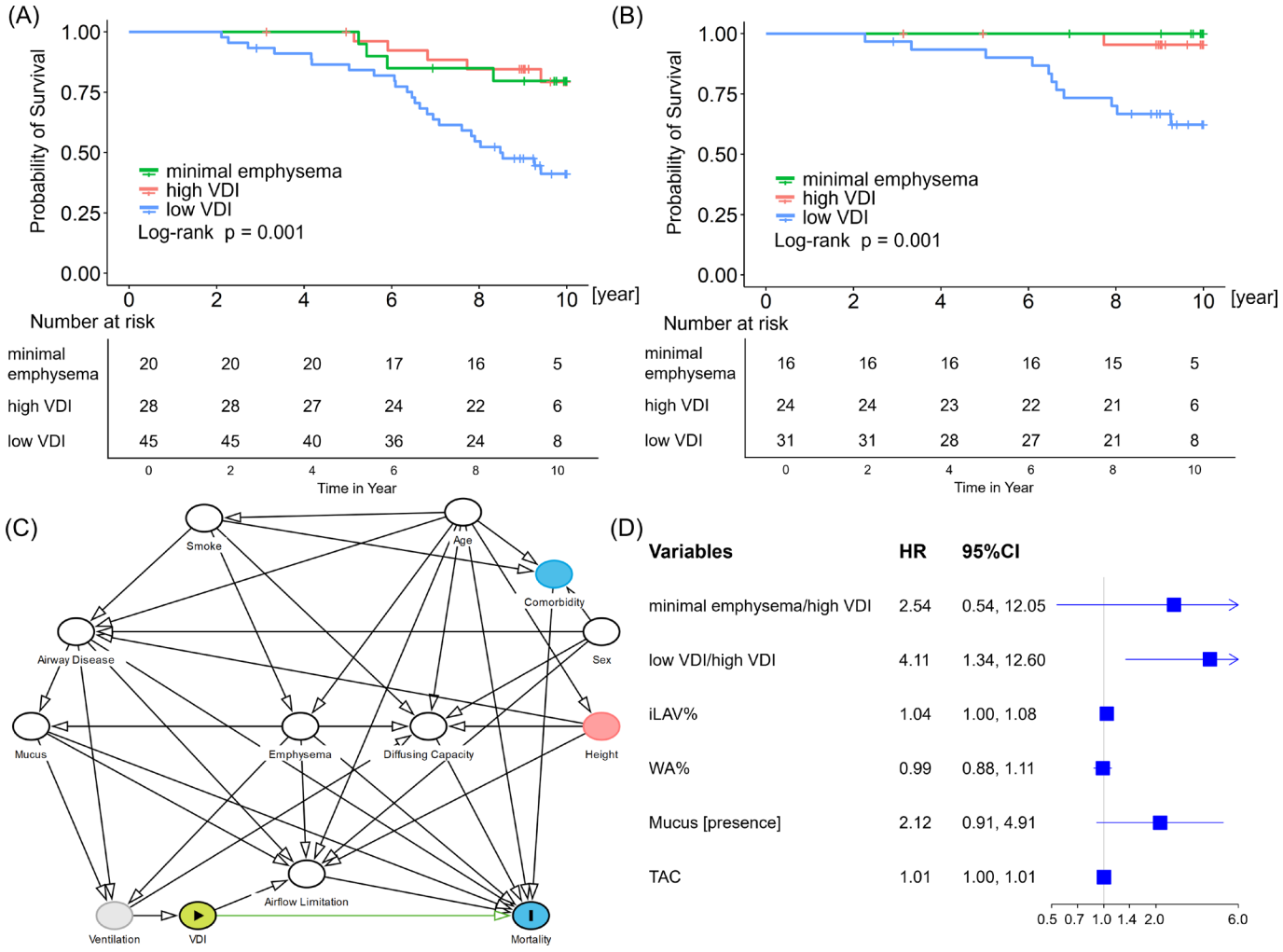

Figure 5 Association of the Ventilation Discordance Index (VDI) with mortality in the Hokkaido COPD cohort. (A) All-cause mortality significantly differed among the three groups (log-rank p=0.001). All-cause mortality was higher in the low VDI group than in the high VDI and minimal emphysema groups. (B) Respiratory mortality significantly differed among the three groups (log-rank p=0.001). Respiratory mortality was also higher in the low VDI group. (C) in the causal directed acyclic graph (DAG), emphysema (low attenuation volume percentage on the inspiratory scan (iLAV%)), airway disease (wall area percentage (WA%), total airway count (TAC) and mucus plugs), airflow limitation (forced expiratory volume in 1 s (FEV_1)), diffusing lung capacity for carbon monoxide (D_{LCO}), age, sex, smoking status and pack-years were considered potential confounders when exploring the association between VDI and mortality. The green, blue, white, red, blue and grey circles show exposure, outcome, adjusted variables, ancestor of exposure, ancestor of outcome and unobserved variables in the subsequent analysis, respectively. (D) Forest plot showing that a low VDI was associated with higher all-cause mortality in the multivariable Cox proportional hazards model adjusted for confounding factors in the DAG. COPD, chronic obstructive pulmonary disease.

Lower VDI was associated with greater annual decline in FEV_1 and higher mortality independent of baseline FEV_1 and CT indices of emphysema and airway disease. Because residual volume (RV), FRC, RV/TLC, and FEV_1/forced vital capacity (FVC) are also used in clinical practice, additional multivariable models were constructed using these variables instead of FEV_1. As shown in online supplemental table E16, lower VDI was associated with higher all-cause mortality independent of RV, FRC, RV/TLC and FEV_1/FVC. Collectively, these findings further confirm that VDI can be a marker associated with clinical outcomes independent of pulmonary function, emphysema severity, and airway disease.

There is a need to estimate the physiological effects of therapeutic interventions that affect regional lung mechanics, such as lung cancer resection, lung volume reduction surgery and bronchoscopic lung volume reduction (BLVR). Various factors, including regional differences in emphysema severity and lung perfusion, fissure integrity and pleural adhesions, affect outcomes for lung volume reduction interventions.[36 37] Moreover, ventilation distribution on functional MRI is not always consistent with the spatial emphysema distribution on inspiratory CT and complementarily predicts outcomes for BLVR.[38] Together with the observed association between lower VDI, a higher hyperventilated emphysema ratio in the upper lung, and lower FEV_1, we speculate that using VDI and visualising hyperventilated emphysematous regions might improve estimation of the response to BLVR. This possibility should be tested in future studies of patients eligible for lung volume reduction interventions.

Because eLAV% increases as airflow limitation increases[25 26] and the calculation of eLAV% is easier than that of VDI, the single use of eLAV% without VDI might be sufficient to subtype emphysematous COPD. To address this issue, we constructed additional multivariable models including both the VDI group and eLAV% (online supplemental discussion 3–2, tables E17,

E18). Consequently, the low VDI group was associated with greater decline in FEV_1 and higher mortality, whereas high eLAV% was associated with mortality but not with a greater decline in FEV_1. Additionally, eLAV%, the airway disease index (WA% or TAC), and the hyperventilated emphysema ratio in the upper lung were independently associated with VDI (online supplemental table E19). These results suggest that VDI and eLAV% are differently associated with the pathophysiological features and clinical outcomes of emphysematous COPD.

Additional analyses using 5% and 15% as the iLAV% cut-off to define established emphysema confirmed the findings from the main analyses using 10% as the cut-off. The selection of 10% was based on a study by Vestbo *et al*, who defined clinically significant emphysema as >10% low attenuation area on inspiratory CT to show the association between emphysema and a greater decline in FEV_1 in a large COPD cohort.[6] Meanwhile, Han *et al* showed that ≥5% emphysema on CT was associated with poor clinical outcomes in patients with COPD in two different large cohorts.[24] The appropriate iLAV% cut-off for VDI-based emphysema subtyping needs to be further explored.

Despite the same ethnicity and similar FEV_1 and D_{LCO} in the two cohorts, the percentage of patients with minimal emphysema differed (online supplemental discussion 3–3). The discordance of respiratory volume change distributions between non-emphysematous and emphysematous regions may be smaller when the CT density in non-emphysematous regions is closer to −950 HU (online supplemental discussion 3–4). The possible influences of the use of bronchodilators and inhaled corticosteroids are discussed in online supplemental discussion 3–5. Furthermore, the VDI values of many patients were near the VDI cut-off value. Thus, classification into the high and low VDI groups might be affected by a slight difference in VDI.

This study has limitations. First, the two cohorts comprised a relatively small number of patients. Second, spirometry gating was not performed during CT scans. Alternatively, all the patients were coached to inspire the TLC and expire to the FRC level before the CT scan. Third, the high predominance of males might have affected the extent of emphysema and airway disease because emphysema is less severe and airway disease is more severe in females than males with COPD.[39] Fourth, both cohorts recruited patients with the same ethnicity in the same country. Whether our findings, including the VDI cut-off value to define the high/low VDI groups, can be applied to different populations should be further investigated. Fifth, CT and spirometry were performed in the supine and sitting positions, respectively, although inspired gas distribution differs between the supine and sitting positions.[40]

CONCLUSION

This study established VDI using non-rigid registration of inspiratory/expiratory CT and showed that lower VDI was associated with more severe airflow limitation, greater FEV_1 decline and higher mortality in patients with emphysematous COPD independent of whole-lung emphysema severity and airway tree morphology. VDI should be integrated into quantitative CT evaluation to subtype emphysematous COPD and improve disease management.

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Contributors HS: Concept and design of the study, data acquisition, statistical analysis, data interpretation and drafting of the manuscript; NT: concept and design of the study, data acquisition, data interpretation, manuscript editing, the guarantor of the paper; AO: analyses of CT data and data interpretation; KS: data interpretation; SK: data interpretation; KT: data acquisition and interpretation; TO: data interpretation and creating software to analyse the airway structure; TK: data interpretation; MS: data interpretation; HM: data acquisition and interpretation; AS: data acquisition and interpretation; MN: data acquisition, data interpretation, and critical revision of the manuscript; SS: data acquisition and interpretation; SK: data interpretation and revision of the manuscript; TH: data interpretation and revision of the manuscript for important intellectual content.

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Subtyping emphysematous COPD by respiratory volume change distributions on computed tomography

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Online Supplementary Materials

Contents

6. References

1. Supplementary Methods

1-1. Study protocol

Kyoto-Himeji cohort (discovery cohort)

The Kyoto-Himeji cohort is an ongoing prospective observational cohort at the Kyoto University Hospital and Terada Clinic[1]. Smokers aged ≥40 years with a smoking history of ≥10 pack-years were enrolled between 2018 and 2020. All patients had undergone inspiratory/expiratory CT scans during an exacerbation-free period. COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[2]. The exclusion criteria were as follows: (1) a history of other respiratory diseases, such as interstitial lung disease and lung cancer; (2) a current primary diagnosis of asthma; (3) α1-antitrypsin deficiency; and (4) lung surgical resection. The Kyoto-Himeji cohort study was approved by the Ethics Committee of Kyoto University (approval no. C1311) and is registered with the University Hospital Medical Information Network (UMIN000028387).

Hokkaido COPD cohort (validation cohort)

In the Hokkaido COPD cohort[3–8], patients with COPD were enrolled between 2003 and 2005. The exclusion criteria comprised physician-diagnosed asthma and the presence of other respiratory disorders, such as interstitial lung disease or lung cancer. Patients were followed up for 5 years to determine the longitudinal decline in FEV_1 and detect exacerbations. Moreover, mortality was recorded for 10 years. The Hokkaido COPD cohort study was approved by the Health Authority Research Ethics Committee of Hokkaido University School of Medicine (no. med02–001). The data were used to validate the findings from cross-sectional analyses in the discovery cohort and to evaluate longitudinal decline in FEV_1, mortality, and time to first exacerbation.

1-2. CT acquisitions

In the Kyoto-Himeji cohort, inspiratory/expiratory CT was performed at full inspiration (total lung capacity [TLC] level) and end-tidal expiration (functional residual capacity [FRC] level) using an Aquilion Precision scanner at the Kyoto University Hospital and an Aquilion lightning scanner at Terada Clinic (Canon Medical, Otawara, Japan). The scanning conditions of both scanners were as follows: 120 kVp, 0.5-s exposure time, and autoexposure control. Images with 1-mm slice thickness were generated using soft (FC13) and sharp (FC51) reconstruction kernels[1].

In the Hokkaido COPD cohort, inspiratory and expiratory images were acquired at the TLC and FRC levels using a Somatom plus Volume Zoom scanner (Siemens AG, Berlin, Germany), and images with 1.25-mm slice thickness were reconstructed using standard (B30) and sharp (B60) kernels.

1-3. Conventional CT analyses

Figure 1 shows the main CT evaluations performed in this study. Emphysema severity was assessed as the percentage of low attenuation volume (LAV) <-950 Hounsfield units (HU) on inspiratory CT (iLAV%)[1,9,10] , and air trapping was defined as the

percentage of LAV <-856 HU on expiratory CT (eLAV%)[11,12]using a SYNAPSE® VINCENT volume analyser (FUJIFILM, Tokyo, Japan). Following lobe segmentation on inspiratory CT, iLAV% was calculated in the upper (right upper-middle and left upper lobes) and lower (right and left lower lobes) lungs separately[13] (Figure 1B). The mean lung density (MLD) and ratio of iLAV% in the upper lung to that in the lower lung ($iLAV\%_{upper}/iLAV\%_{lower}$) were calculated[14].

Additionally, the Fleischner Society classification system[15] was used to visually evaluate centrilobular emphysema (CLE) and paraseptal emphysema (PSE). Moderate, confluent, and advanced CLE and substantial PSE indicated the presence of CLE and PSE, respectively.

Regarding the analyses of airway disease, the luminal area (LA) and wall area (WA) were measured at the right apical and basal posterior subsegmental airways, and the wall area percentage (WA%), a ratio of LA to the sum of LA and WA, was calculated and averaged[1,13,16,17]. The total airway count (TAC) was measured by summing all airway segments from the segmented airway tree (Figure 1C)[9]. Mucus plugs were visually identified for all airway segments except those located within the 2-cm peripheral area (Figure 1D)[18]. When mucus plugs were present in a given segment, the score was 1. After evaluating all the segments, all the scores were summed to yield the total mucus score. Based on the total score, patients with a score =0 were classified as having “mucus absence”, and those with a score ≥1 were classified as having “mucus presence”. For additional analyses, patients were divided into those with a high (≥5) mucus score and those with a low (<5) mucus score based on a previous report[19].

Interobserver variability in the visual estimation of PSE and CLE and the presence of mucus plugs were assessed using the kappa score. The interrater variability of the two analysts (NT and HS) in identifying PSE and CLE was excellent (kappa = 0.85 and 0.81). The interrater variability of the two analysts in identifying the presence/absence and scores of mucus plugs were good (HS and YS, kappa = 0.71 and 0.91, respectively).

1-4. Novel method to calculate VDI

The lung fields were automatically extracted from the original inspiratory and expiratory CT. Using nonrigid image registration for voxel-by-voxel matching, the images on expiratory CT were registered onto those on inspiratory CT[20]. A displacement matrix was generated during lung deformation and subsequently used to calculate the respiratory volume change percentage for each voxel according to a previous report on the calculation of Jacobians[21]. These processes were performed using a SYNAPSE® VINCENT volume analyser, and subsequent analyses were performed using a custom-made Python script.

To estimate the discordance between distributions of the local respiratory volume change percentages in the emphysematous and nonemphysematous regions, relative frequency histograms of respiratory volume change percentages in the two regions were separately generated. In each histogram, the x-axis indicates the respiratory volume change percentage (bin width = 1), the y-axis indicates the relative frequency for each

bin, and the area of the histogram equals 1. The discordance between the two histograms was calculated as the Wasserstein distance, which represents the cost of the difference using the package "pyemd"[22] implemented in Python (version 3.7.7). Intuitively, the Wasserstein distance[23], also known as the earth mover's distance, is the minimum total cost to transform one histogram to the other if they were considered piles of dirt. The Wasserstein distance has several advantages over other dissimilarity measures for histograms; it satisfies the axioms of distances and is robust against noise. Because the distribution of the Wasserstein distances in all the patients was not normally distributed, log-transformation of the Wasserstein distances was performed (Supplementary Figure E2). The ventilation discordance index (VDI) was defined as the log-transformed Wasserstein distance.

1-5. Clinical and physiological examinations

Postbronchodilator spirometry and measurements of lung subvolumes and diffusing capacity were performed using Chestac-8900 (Chest M.I. Inc., Tokyo, Japan) in Kyoto University, Microspiro HI-302U (Nihon Kohden, Tokyo, Japan) in the Terada Clinic (the Kyoto-Himeji cohort) and rolling seal Chestac-33 spirometer (Chest M.I., Inc., Tokyo, Japan) in the Hokkaido COPD cohort. The results were normalized to the predicted values of the forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1)[24]. According to the GOLD spirometry grade, the patients were categorized based on FEV_1. GOLD 1, GOLD2, GOLD3, and GOLD 4 were defined as FEV_1 >80%, between 50 and 80%, between 30 and 50%, and <30% predicted, respectively. The diffusing lung capacity for carbon monoxide (D_{LCO}) was adjusted by haemoglobin[25] and normalized by the predicted values[26]. TLC, residual volume (RV), and FRC were normalized by predicted values[27]. Arterial blood gas measurements were obtained in the sitting position while breathing room air with a 15-minute rest at Kyoto University Hospital. A symptomatic assessment using the chronic obstructive pulmonary disease (COPD) Assessment Test (CAT)[28,29] was performed in the Kyoto-Himeji cohort, whereas the modified Medical Research Council (mMRC) Dyspnoea Scale was examined in both cohorts. An exacerbation of COPD was defined as a worsening of symptoms compared with baseline requiring oral corticosteroids and/or antibiotics or hospitalization. The time to first exacerbation was recorded over 5 years[7], and mortality was evaluated over 10 years after enrolment in the Hokkaido COPD cohort[4,6].

1-6. Statistical analysis

R statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. A p value less than 0.05 was considered significant.

The patients were divided into three groups based on a cut-off value of 10% in iLAV% and the median value of VDI (2.06) in all patients of the Kyoto-Himeji cohort. The same cut-off values were used to divide patients into the three groups in the Hokkaido COPD cohort. The three VDI groups (minimal emphysema, established emphysema with high VDI [the high VDI group], and established emphysema with low VDI [the low VDI group]) were defined as iLAV% <10% with any VDI, iLAV% ≥10% with < the median VDI, and iLAV% ≥10% with ≥ the median VDI, respectively.

Categorical variables and continuous variables were compared among the three groups using multiple chi-squared tests with Bonferroni correction and one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test, respectively.

Based on scatter plots for each pair of two variables, including VDI, other CT indices, and FEV_1, relationships between these variables could be considered linear. Thus, multivariable linear regression models were constructed.

To test whether the VDI group was associated with FEV_1, univariable and multivariable linear regression models were constructed. The multivariable models included CT indices (the VDI group, iLAV%, WA%, the presence/absence of mucus, and TAC) and demographic factors (age, height, smoking status, pack-years, and institution) as independent variables.

To test whether the VDI group was associated with a longitudinal change in FEV_1, multivariable linear regression models were constructed by including CT indices (the VDI group, iLAV%, WA%, the presence/absence of mucus, and TAC) and demographic factors (age, height, smoking status, and pack-years) and baseline FEV_1.

The association of CT indices with the VDI value was also tested using univariable and multivariable linear regression models. The multivariable models included iLAV%, WA%, $iLAV\%_{upper}/iLAV\%_{lower}$, the presence of mucus, TAC, and the hyperventilated emphysema ratio in the upper and lower lungs as independent variables and VDI as a dependent variable.

To test whether the VDI group was associated with the time to first exacerbation and mortality, univariable and multivariable Cox proportional hazards models were constructed in the Hokkaido COPD cohort. The multivariable models included age, sex, smoking status, pack years, baseline FEV_1, D_{LCO}, iLAV%, WA%, the presence of mucus, TAC, and the VDI group as independent variables. The baseline FEV_1, but not FEV_1/FVC, was used because while the presence of airflow limitation is assessed using FEV_1/FVC, the severity of airflow limitation is assessed using FEV_1[30]. Moreover, FEV_1 is more closely associated with mortality than FEV_1/FVC[31].

To test the validity of the findings from analyses using 10% as the iLAV% cut-off to define established emphysema, additional analyses using different iLAV% cut-off values (5% and 15%) were performed by constructing multivariable models for FEV_1, longitudinal changes in FEV_1 and mortality.

To test the validity of the findings from analyses using mucus presence (defined as a mucus score ≥1), additional analyses using different mucus score-based categories were performed. In these analyses, instead of the absence/presence of mucus plugs, the patients were categorized into those with scores <5 (low mucus score) and scores ≥5 (high mucus score).

For additional analyses that categorized patients based on SAD% instead of VDI, the patients were categorized into three groups (minimal emphysema, low SAD%, and high SAD% groups) based on the iLAV% cut-off value of 10% and median SAD% (= 27.5%).

For additional analyses using eLAV%, because of the close association between iLAV% and eLAV%, multivariable models were constructed using eLAV% instead of iLAV%. The models included CT indices (the VDI group, eLAV%, WA%, the presence/absence of mucus, and TAC) and demographic factors (age, height, smoking status, pack-years, and institution) as independent variables. The baseline FEV_1 was also included in the models for longitudinal change and mortality in FEV_1.

To explore a minimal adjustment set of variables for the multivariable models, the causal directed acyclic graph (DAG) was constructed using the web platform "DAGitty"[32]. DAGs represent simple qualitative causal path diagrams of the presence and absence of causal effects. In the DAGs, the green, blue, white, red, blue, and grey circles show exposure, outcome, adjusted variables, ancestor of exposure, ancestor of outcome, and unobserved variables. The green and black arrows show the causal and unbiased paths.

2. Supplementary Results

2-1. Reproducibility of the VDI measurement

In the Kyoto-Himeji cohort, 24 patients had undergone inspiratory and expiratory CT twice with a short interval (mean, 352 days). No patient showed exacerbations between the first and second CT scans. Established emphysema was found in 12 patients on the first scan. Of the 5 patients who were assigned to the established emphysema group with the high VDI on the first scan, 4 (80%) were assigned to the same group on the second scan. Additionally, of 7 patients who were assigned to the established emphysema group with the low VDI, 6 (86%) were assigned to the same group on the second scan. Furthermore, the Bland–Altman plot for VDI on the first and second scans showed no significant bias (Supplementary Figure E3). These results indicate the good reproducibility of categorization of patients in the high and low VDI groups.

2-2. Comparisons of clinical characteristics among the three VDI groups

Compared with the high VDI group, the low VDI group in the Kyoto-Himeji cohort had lower FEV_1, FVC, FEV_1/FVC, PaO_2, RV and RV/TLC (Table 1). The low VDI group also showed higher eLAV%, WA%, and frequencies and scores of mucus plugs and lower TAC and LA than the high VDI group, while age, sex, smoking status, the use of long-acting muscarine antagonist (LAMA), long-acting beta 2-agonist (LABA), inhaled corticosteroid (ICS), MLD, and the prevalence of CLE and PSE did not differ between the high and low VDI groups. Similar trends for FEV_1, FEV_1/FVC, RV, RV/TLC, eLAV%, LA, WA%, TAC, and frequency of mucus plugs were found in the Hokkaido COPD cohort (Supplementary Table E2). The use of LABA was significantly higher in the low VDI group than in the high VDI group. Table 1 and Supplementary Table E2 show that iLAV% did not differ between the high and low VDI groups in the Kyoto-Himeji cohort, whereas iLAV% was higher in the low VDI group than in the high VDI group in the Hokkaido COPD cohort.

2-3. Analyses of mortality in the Hokkaido COPD cohort

In univariable Cox proportional hazards models, the 10-year all-cause mortality was higher in the low VDI group than in the high VDI group (hazard ratio (HR) [95% confidence interval (CI)] = 3.95 [1.51, 10.34]), while the mortality in the high VDI group did not differ from that in the minimal emphysema group (HR [95% CI] = 1.09 [0.29, 4.05]). Respiratory mortality in the low VDI group showed a higher risk than that in the high VDI group (HR [95% CI] = 9.82 [1.27, 76.12]).

3. Supplementary Discussion

3-1. Comparisons between VDI and SAD% based on nonrigid registration of inspiratory and expiratory CT scans

The nonrigid registration of inspiratory and expiratory scans has been applied to lung structural analysis in COPD. Galbán *et al*.[20] established parametric response mapping (PRM) and defined regions ≥-950 HU on inspiratory CT but also <-856 HU on expiratory CT as functional small airway disease (SAD% in this study) and regions <-950 HU on inspiratory CT and <-856 HU on expiratory CT as emphysema. Therefore, the PRM for emphysema reflects emphysematous regions on inspiratory CT that are identified as air trapping on expiratory CT. Notably, the PRM for emphysema does not include low attenuation regions on inspiratory CT but normal attenuation regions on expiratory CT (normally deflated region). In contrast, VDI is an index to quantify the respiratory volume changes in emphysematous regions, which we simply defined as low attenuation regions <-950 HU on inspiratory CT irrespective of CT values on expiratory CT. Thus, in the VDI calculation, the emphysematous regions included both normally and poorly deflated regions on expiration.

Additionally, VDI quantified respiratory volume change distributions in emphysematous regions by comparing them with those in nonemphysematous regions within the same lungs. This idea is not applied in the PRM method.

From a clinical perspective, when patients were classified into the high and low SAD% groups instead of the high/low VDI group, multivariable analyses in Supplementary Tables E14 and E15 and Supplementary Figure E7 show that the high SAD% group was associated with lower FEV_1 and higher mortality than the low SAD% group. However, the high SAD% group was not associated with a greater annual change in FEV_1. Combined with a previous study showing that the association between SAD% and longitudinal FEV_1 decline is stronger in mild COPD than in severe COPD[33], we speculate that SAD% may sensitively detect future FEV_1 decline in patients with minimal emphysema so that the physiological impacts of SAD% are different from those of VDI. Therefore, VDI may be more useful to evaluate patients with COPD and established emphysema than SAD%.

3-2. Comparisons between VDI and eLAV%

Because a low attenuation volume percentage on expiratory CT (eLAV%, reflecting air-trapping regions) increases as airflow limitation increases and the calculation of eLAV% is easier than that of VDI, a single use of eLAV% without using VDI may be sufficient to subtype emphysematous COPD. To address this issue, we performed additional multivariable analyses, including eLAV%. First, the association of the low VDI and eLAV% with annual decline in FEV_1 was evaluated using multivariable linear models adjusted for demographic factors (age, height, sex, smoking status, and pack-years) as independent variables (Supplementary Table E17). Second, the association of the low VDI and eLAV% with mortality was assessed using multivariable Cox proportional hazards models adjusted for the baseline FEV_1, D_{LCO}, and demographic factors (age, sex, smoking status, and pack-years) (Supplementary Table E18). Because of the high

collinearity between iLAV% and eLAV%, iLAV% was excluded when the models included eLAV%. Consequently, in the models that included either the eLAV% or the VDI group, higher eLAV% and the low VDI group were associated with greater annual decline in FEV_1 and higher mortality. However, in the models that included both eLAV% and the VDI groups, the low VDI group was consistently associated with a greater decline in FEV_1 and higher mortality, whereas a higher eLAV% was associated with mortality but not with greater decline in FEV_1. Furthermore, multivariable linear regression models were constructed to test whether CT indices other than eLAV% were associated with VDI independent of eLAV% (Supplementary Table E19). The models showed that eLAV% and the airway disease index, such as WA% or TAC, were independently associated with VDI, suggesting that the low VDI reflects not only the extent of eLAV% (air trapping on peripheral lungs due to emphysema and small airway disease) but also the morphological changes in relatively proximal airways visible on CT. Based on these findings, we postulate that VDI reflects distinct pathophysiological aspects different from eLAV% and is more closely associated with the clinical outcomes of emphysematous COPD.

3-3. Comparisons of the percentage of patients with minimal emphysema between the Kyoto-Himeji cohort and Hokkaido COPD cohort

The percentage of patients with minimal emphysema (iLAV% <10%) differed between the Kyoto-Himeji cohort and Hokkaido COPD cohort, although the two cohorts were based on Japanese patients and exhibited similar FEV_1 and D_{LCO}. The reason may be that the CT protocol differed between the two cohorts. However, the clinical relevance of VDI was confirmed in the two independent cohorts, further increasing the validity of VDI as a CT index.

3-4. Association of the mean lung density and ventilation discordance index

In the analysis of CT density, no significant difference was found in the MLD in the entire lungs between the high and low VDI groups (mean [standard deviation, SD] MLD in the entire lungs, -880[13] HU vs. -881[15] HU). No significant difference was found in the MLD in nonemphysematous regions between the high and low VDI groups (mean [SD] MLD = -851[13] HU vs. -851[16] HU. Additionally, only weak correlations were observed between VDI and MLD in the entire lungs (Pearson's correlation = 0.18) and between VDI and MLD in nonemphysematous regions (Pearson's correlation = 0.07). These results suggest that the association between VDI and CT density is weak and that VDI may enable quantitation of the pathophysiological changes in emphysema that are challenging to detect using a single cut-off of -950 HU.

3-5. Potential influences of the use of bronchodilators and inhaled corticosteroids

In the Kyoto-Himeji cohort (Table 1), the use of LAMA, LABA, and ICS in the low VDI group was 82%, 84%, and 50%, respectively. This finding suggests that patients in the low VDI group were appropriately treated according to the current GOLD ABCD system[2], in which LAMA and LABA are recommended in many patients with COPD. Moreover, there was no significant difference in the percentages of patients treated with LAMA, LABA, and ICS between the high and low VDI groups. Therefore, we postulate that the influence of LAMA, LABA, and ICS on the associations between the lower VDI and lower FEV_1 is small.

In the Hokkaido COPD cohort (Supplementary Table E2), only 1 patient was treated with LAMA at enrolment because the cohort enrolled patients between 2003 and 2005, and LAMA was commercially available from 2004 in Japan. Table E2 also shows that the use of LABA was more frequent in the low VDI group than in the high VDI group, whereas there was no significant difference in the use of ICS between the groups. Thus, it should be noted that despite the more intense treatment in the low VDI group than in the high VDI group, the low VDI group was associated with a greater decline in FEV1 and higher mortality than the high VDI group. This finding further supports the potential of the VDI as a prognostic marker.

4. Supplementary Tables

Table E1. Basic information of the Kyoto-Himeji cohort and Hokkaido COPD cohort

	Kyoto-Himeji cohort	Hokkaido COPD cohort
N	221	93
Male, %	95	92
Age, years	73 (8)	70 (8)
Height, cm	165 (7)	163 (7)
BMI, kg/m^2	23 (4)	23 (3)
Current smoker, %	26	28
Pack-years	60 (31)	61 (28)
Pulmonary function		
FVC, % predicted	93 (22)	99 (14)
FEV_1, % predicted	67 (23)	68 (20)
FEV_1/FVC, %	55 (12)	52 (13)
D_{LCO}, % predicted	62 (21)	63 (17)
TLC, % predicted	98 (12)	102 (14)
RV, % predicted	93 (24)	115 (33)
FRC, % predicted	104 (20)	118 (24)
RV/TLC, %	39 (8)	46 (10)

The data are expressed as the means (standard deviation, SD) and %. BMI = body mass index; FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 second; D_{LCO} = diffusing lung capacity for carbon monoxide; TLC = total lung capacity; RV = residual volume; FRC = functional residual capacity. In the Kyoto-Himeji cohort, D_{LCO} was acquired from 127 patients, and TLC, RV, and FRC were acquired from 137 patients.

Table E2. Patient demographics in the Hokkaido COPD cohort

	Minimal Emphysema (N=20)	High VDI (N=28)	Low VDI (N=45)
Male, %	90	93	93
Age, years	67 (8)	68 (9)	72 (7)*
Height, cm	163 (6)	165 (7)	161 (8)†
BMI, kg/m^2	25 (4)	23 (3)	22 (3)*
Current smoker, %	45	18	27
Pack-years	60 (24)	61 (35)	61 (25)
LAMA use, %	0	0	2
LABA use, %	20	21	53†
ICS use, %	5	7	22
mMRC (0/1/2/3/4), %	25/45/30/0/0	36/36/29/0/0	11/31/56/0/2
GOLD stage (1/2/3/4), %	70/30/0/0	68/32/0/0	27/58/16/0*†
Pulmonary function			
FVC, % predicted	94 (11)	105 (14)*	98 (15)
FEV_1, % predicted	78 (14)	79 (20)	57 (17)*†
FEV_1/FVC, %	64 (7)	57 (10)*	44 (10)*†
D_{LCO}, % predicted	75 (14)	67 (12)	54 (16)*†
TLC, % predicted	92 (10)	100 (12)*	108 (14)*†
RV, % predicted	95 (21)	103 (21)	131 (35)*†
FRC, % predicted	100 (20)	112 (18)	129 (24)*†
RV/TLC, %	41 (5)	41 (7)	51 (9)*†
annual decline in FEV_1, L	-17.3 (21.4)	-20.3 (21.9)	-36.2 (19.2)*†
CT index			
iLAV%, %	6.0 (3.1)	20.0 (7.4)*	28.4 (11.5)*†
eLAV%, %	27.4 (10.6)	42.9 (11.3)*	64.4 (12.2)*†
SAD%, %	19.7 (9.3)	23.5 (6.9)	37.4 (9.2)*†
MLD, HU	-830 (29)	-872 (17)*	-882 (17)*
LA, mm^2	15.7 (4.8)	15.1 (5.2)	12.6 (4.9)
WA%, %	63 (5)	62 (4)	65 (4)†
TAC	292 (83)	299 (69)	239 (69)*†
Mucus [presence], %	65	21*	62†
Mucus score	2.0 (2.4)	0.9 (3.1)	2.8 (3.7)†
CLE, %	20	36	76*†
PSE, %	35	61	58

The data are expressed as the means (SD) and %. VDI = ventilation discordance index; BMI = body mass index; LAMA = long-acting muscarine antagonist; LABA = long-acting beta 2-agonist; ICS = inhaled corticosteroid; mMRC = modified Medical Research Council dyspnoea scale; GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; D_{LCO} = diffusing lung capacity for carbon monoxide; TLC = total lung capacity; RV = residual volume; FRC = functional residual capacity; iLAV% = low attenuation volume percentage on the inspiratory scan; eLAV% = low attenuation volume percentage on the expiratory scan; SAD% = small airway disease percentage; MLD = mean lung density; LA = luminal area; WA% = wall area percentage; TAC =

total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment); CLE = centrilobular emphysema; PSE = paraseptal emphysema. Analysis of variance followed by Tukey's post-hoc test was performed. * and † indicate p values <0.05 compared with the minimal emphysema group and established emphysema with high VDI group, respectively.

Table E3. Summary of the CT indices of the whole, upper and lower lungs in the ventilation discordance index group

	Minimal Emphysema	High VDI	Low VDI
iLAV%, %			
Whole lung	4.4 (2.7)	23.1 (9.4)*	24.2 (10.7)*
Upper lung	5.2 (3.6)	25.3 (11.3)*	25.4 (11.9)*
Lower lung	3.4 (2.8)	19.2 (11.9)*	22.0 (11.9)*
SAD%, %			
Whole lung	22.8 (12.8)	26.8 (8.9)	36.1 (8.8)*†
Upper lung	16.3 (8.5)	18.4 (5.0)	22.4 (6.4)*
Lower lung	13.8 (12.5)	19.2 (11.9)	29.6 (10.2)*†
WA%, %			
Mean (RB^1, RB^{10})	64.5 (4.1)	62.4 (3.5)*	65.4 (3.0)†
RB^1	64.8 (4.8)	62.5 (4.5)	65.4 (4.1)†
RB^{10}	64.1 (5.1)	62.4 (4.3)	65.7 (4.2)†
Mucus score			
Whole lung	2.8 (4.1)	1.4 (2.5)	3.6 (4.2)†
Upper lung	1.3 (2.1)	0.6 (1.0)	1.4 (1.9)
Lower lung	1.5 (2.3)	0.8 (1.7)	2.2 (2.7)†

The data are expressed as the means (SD). iLAV% = low attenuation volume percentage on the inspiratory scan; SAD% = small airway disease percentage; WA% = wall area percentage; RB^1 = right apical subsegmental airway; RB^{10} = right basal posterior subsegmental airway. * and † indicate p values <0.05 compared with the minimal emphysema group and established emphysema with high VDI group, respectively.

Table E4. Univariable regression models to explore the association of CT indices with FEV_1

Cohort	Kyoto-Himeji	Hokkaido COPD
VDI group		
Minimal Emphysema	3.76 [-3.16, 10.67]	-0.99 [-10.78, 8.80]
High VDI	Ref	Ref
Low VDI	-21.00* [-28.7, -13.31]	-21.92* [-29.97, -13.87]
iLAV%	-0.81* [-1.03, -0.58]	-0.80* [-1.09, -0.52]
eLAV%	-0.68* [-0.81, -0.55]	-0.68* [-0.84, -0.51]
WA%	-1.93* [-2.68, -1.18]	-2.34* [-3.14, -1.54]
Mucus [presence]	-19.36* [-24.82, -13.9]	-14.97* [-22.56, -7.37]
TAC	0.15* [0.12, 0.18]	0.15* [0.11, 0.19]

The data are expressed as estimates [95% CI]. FEV_1 = forced expiratory volume in 1 second; VDI = ventilation discordance index; iLAV% = low attenuation volume percentage on the inspiratory scan; eLAV% = low attenuation volume percentage on the expiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment). * indicates a p value <0.05.

Table E5. Multivariable regression models to explore the association of CT indices with FEV_1

Cohort	Kyoto-Himeji		Hokkaido COPD	
	Model 1	Model 2	Model 1	Model 2
VDI group				
Minimal Emphysema	-0.32* [-0.55, -0.09]	-0.14 [-0.35, 0.08]	-0.21 [-0.45, 0.03]	-0.12 [-0.37, 0.13]
High VDI	Ref	Ref	Ref	Ref
Low VDI	-0.46* [-0.65, -0.27]	-0.30* [-0.48, -0.13]	-0.35* [-0.54, -0.15]	-0.25* [-0.46, -0.05]
iLAV%	-0.03* [-0.04, -0.02]	-0.02* [-0.03, -0.01]	-0.01* [-0.02, 0.00]	-0.01* [-0.02, 0.00]
WA%	-0.04* [-0.06, -0.03]	-0.01 [-0.03, 0.00]	-0.04* [-0.06, -0.02]	-0.02 [-0.05, 0.00]
Mucus [presence]		-0.24* [-0.37, -0.12]		-0.17* [-0.34, -0.01]
TAC		0.002* [0.001, 0.003]		0.001 [0.000, 0.003]

The data are expressed as estimates [95% CI]. Age, height, sex, smoking status, pack-years, and institution were also adjusted for the models. FEV_1 = forced expiratory volume in 1 second; VDI = ventilation discordance index; iLAV% = low attenuation volume percentage on the inspiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment). * indicates a p value <0.05.

Table E6. Cox proportional hazards model for all-cause mortality in the Hokkaido COPD cohort

	Model 1	Model 2
VDI group		
Minimal Emphysema	2.94 [0.65, 13.28]	2.54 [0.54, 12.05]
High VDI	Ref	Ref
Low VDI	3.49* [1.16, 10.53]	4.11* [1.34, 12.60]
iLAV%	1.05* [1.01, 1.09]	1.04* [1.00, 1.08]
WA%	0.98 [0.89, 1.07]	0.99 [0.88, 1.11]
Mucus [presence]		2.12 [0.91, 4.91]
TAC		1.01 [1.00, 1.01]

The data are expressed as hazard ratios [95% CI]. FEV_1, D_{LCO}, age, sex, smoking status, and pack-years were also adjusted for the models. VDI = ventilation discordance index; iLAV% = low attenuation volume percentage on the inspiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment); FEV_1 = forced expiratory volume in 1 second; D_{LCO} = diffusing lung capacity for carbon monoxide. * indicates a p value <0.05.

Table E7. Multivariable regression models for FEV_1 using 5%, 10%, and 15% cut-off values to define established emphysema

	iLAV% cut-off = 5%		iLAV% cut-off = 10%		iLAV% cut-off = 15%	
Cohort	**Kyoto-Himeji**	**Hokkaido COPD**	**Kyoto-Himeji**	**Hokkaido COPD**	**Kyoto-Himeji**	**Hokkaido COPD**
VDI group						
Minimal Emphysema	-0.11 [-0.28, 0.07]	-0.01 [-0.38, 0.35]	-0.14 [-0.35, 0.08]	-0.12 [-0.37, 0.13]	-0.22 [-0.47, 0.02]	-0.11 [-0.36, 0.15]
High VDI	Ref	Ref	Ref	Ref	Ref	Ref
Low VDI	-0.23* [-0.38, -0.08]	-0.29* [-0.48, -0.11]	-0.30* [-0.48, -0.13]	-0.25* [-0.46, -0.05]	-0.32* [-0.51, -0.12]	-0.27* [-0.50, -0.04]
iLAV%	-0.02* [-0.03, -0.01]	-0.01* [-0.02, 0.00]	-0.02* [-0.03, -0.01]	-0.01* [-0.02, 0.00]	-0.02* [-0.03, -0.01]	-0.01 [-0.02, 0.00]
WA%	-0.02 [-0.03, 0.00]	-0.02 [-0.04, 0.00]	-0.01 [-0.03, 0.00]	-0.02 [-0.05, 0.00]	-0.02 [-0.03, 0.00]	-0.02 [-0.05, 0.00]
Mucus [presence]	-0.25* [-0.38, -0.13]	-0.18* [-0.33, -0.02]	-0.24* [-0.37, -0.12]	-0.17* [-0.34, -0.01]	-0.24* [-0.36, -0.11]	-0.18* [-0.34, -0.02]
TAC	0.002* [0.001, 0.003]	0.001 [-0.001, 0.003]	0.002* [0.001, 0.003]	0.001 [0.000, 0.003]	0.002* [0.002, 0.003]	0.001 [0.000, 0.003]

The data are expressed as estimates [95% CI]. Age, height, sex, smoking status, pack-years, and institution were also adjusted for the models. FEV_1 = forced expiratory volume in 1 second; iLAV% = low attenuation volume percentage on the inspiratory scan; VDI = ventilation discordance index; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment). * indicates a p value <0.05.

Table E8. Multivariable regression models for the annual decline in FEV_1 using 5%, 10%, and 15% cut-off values to define established emphysema

	iLAV% cut-off = 5%	**iLAV% cut-off = 10%**	**iLAV% cut-off = 15%**
VDI group			
Minimal Emphysema	0.20 [-20.88, 21.29]	1.46 [-12.47, 15.40]	-1.70 [-16.40, 13.01]
High VDI	Ref	Ref	Ref
Low VDI	-13.74* [-24.96, -2.53]	-16.60* [-28.35, -4.85]	-11.72 [-25.39, 1.95]
iLAV%	-0.23 [-0.66, 0.20]	-0.07 [-0.56, 0.42]	-0.19 [-0.76, 0.39]
WA%	1.11 [-0.29, 2.52]	0.99 [-0.40, 2.38]	1.15 [-0.37, 2.67]
Mucus [presence]	1.33 [-7.91, 10.57]	1.04 [-8.29, 10.36]	1.58 [-7.83, 10.98]
TAC	-0.01 [-0.10, 0.08]	-0.02 [-0.11, 0.07]	0.00 [-0.09, 0.09]

The data are expressed as estimates [95% CI]. Baseline FEV_1, age, height, sex, smoking status, pack-years, and institution were also adjusted for the models. FEV_1 = forced expiratory volume in 1 second; iLAV% = low attenuation volume percentage on the inspiratory scan; VDI = ventilation discordance index; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment). * indicates a p value <0.05.

Table E9. Cox proportional hazards models for all-cause mortality using 5%, 10%, and 15% cut-off values to define established emphysema in the Hokkaido COPD cohort

	iLAV% cut-off = 5%	**iLAV% cut-off = 10%**	**iLAV% cut-off = 15%**
VDI group			
Minimal Emphysema	(No death event)	2.54 [0.54, 12.05]	6.08* [1.12, 33.00]
High VDI	Ref	Ref	Ref
Low VDI	2.63* [1.01, 6.87]	4.11* [1.34, 12.60]	9.00* [1.78, 45.53]
iLAV%	1.04 [1.00, 1.07]	1.04* [1.00, 1.08]	1.05* [1.00, 1.09]
WA%	0.97 [0.86, 1.09]	0.99 [0.88, 1.11]	1.00 [0.88, 1.14]
Mucus [presence]	2.48* [1.06, 5.78]	2.12 [0.91, 4.92]	2.39* [1.01, 5.65]
TAC	1.00 [1.00, 1.01]	1.00 [1.00, 1.01]	1.00 [1.00, 1.01]

The data are expressed as hazard ratios [95% CI]. FEV_1, D_{LCO}, age, sex, smoking status, and pack-years were also adjusted for the models. VDI = ventilation discordance index; iLAV% = low attenuation volume percentage on the inspiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment); FEV_1 = forced expiratory volume in 1 second; D_{LCO} = diffusing lung capacity for carbon monoxide. * indicates a p value <0.05.

Table E10. Multivariable regression models for FEV_1 and the annual decline in FEV_1 using mucus scores

Cohort	FEV_1 Kyoto-Himeji	FEV_1 Hokkaido COPD	Annual decline in FEV_1 Hokkaido COPD
VDI group			
Minimal Emphysema	-0.17 [-0.39, 0.04]	-0.17 [-0.41, 0.07]	0.75 [-12.57, 14.07]
High VDI	Ref	Ref	Ref
Low VDI	-0.33* [-0.51, -0.15]	-0.29* [-0.49, -0.09]	-16.56* [-28.03, -5.09]
iLAV%	-0.02* [-0.03, -0.01]	-0.01 [-0.02, 0.00]	-0.13 [-0.63, 0.36]
WA%	-0.02 [-0.04, 0.00]	-0.02 [-0.05, 0.00]	0.93 [-0.45, 2.31]
Mucus score			
Low (score <5)	Ref	Ref	Ref
High (score ≥5)	-0.22* [-0.37, -0.07]	-0.21 [-0.43, 0.02]	8.50 [-3.92, 20.93]
TAC	0.002* [0.001, 0.003]	0.001 [0.000, 0.003]	-0.023 [-0.110, 0.064]

The data are expressed as estimates [95% CI]. Age, height, sex, smoking status, and pack-years were also adjusted for the FEV_1 models. Baseline FEV_1, age, height, sex, smoking status, and pack-years were also adjusted for the model of annual FEV_1 decline. FEV_1 = forced expiratory volume in 1 second; VDI = ventilation discordance index; iLAV% = low attenuation volume percentage on the inspiratory scan; WA% = wall area percentage; TAC = total airway count. * indicates a p value <0.05.

Table E11. Cox proportional hazards model for all-cause mortality using mucus scores in the Hokkaido COPD cohort

Variables	HR [95% CI]
VDI group	
Minimal Emphysema	3.24 [0.72, 14.63]
High VDI	Ref
Low VDI	4.78* [1.49, 15.37]
iLAV%	1.05* [1.01, 1.09]
WA%	1.00 [0.89, 1.13]
Mucus score	
Low (score <5)	Ref
High (score ≥5)	2.51 [0.99, 6.38]
TAC	1.01 [1.00, 1.01]

The data are expressed as hazard ratios [95% CI]. FEV_1, D_{LCO}, age, sex, smoking status, and pack-years were also adjusted for the models. VDI = ventilation discordance index; iLAV% = low attenuation volume percentage on the inspiratory scan; WA% = wall area percentage; TAC = total airway count; FEV_1 = forced expiratory volume in 1 second; D_{LCO} = diffusing lung capacity for carbon monoxide. * indicates a p value <0.05.

Table E12. Multivariable regression models for FEV_1 and the annual decline in FEV_1 using the median VDI value of the established emphysema patients as the cut-off to define the high and low VDI groups

Cohort	FEV_1 Kyoto-Himeji	FEV_1 Hokkaido COPD	Annual decline in FEV_1 Hokkaido COPD
VDI group			
Minimal Emphysema	-0.13 [-0.34, 0.08]	-0.08 [-0.32, 0.16]	3.94 [-9.33, 17.22]
High VDI	Ref	Ref	Ref
Low VDI	-0.31* [-0.48, -0.14]	-0.29* [-0.50, -0.08]	-19.50* [-31.42, -7.58]
iLAV%	-0.02* [-0.03, -0.01]	-0.01 [-0.02, 0.00]	0.03 [-0.47, 0.53]
WA%	-0.01 [-0.03, 0.00]	-0.02 [-0.05, 0.00]	1.04 [-0.33, 2.40]
Mucus [presence]	-0.23* [-0.35, -0.10]	-0.19* [-0.35, -0.03]	-0.20 [-9.28, 8.89]
TAC	0.002* [0.002, 0.003]	0.001 [-0.001, 0.002]	-0.03 [-0.12, 0.06]

The data are expressed as estimates [95% CI]. Age, height, sex, smoking status, and pack-years were also adjusted for the FEV_1 models. Baseline FEV_1, age, height, sex, smoking status, and pack-years were also adjusted for the model of annual FEV_1 decline. FEV_1 = forced expiratory volume in 1 second; VDI = ventilation discordance index; the VDI group was defined according to the median value of VDI from the established emphysema patients in the Kyoto-Himeji cohort. iLAV% = low attenuation volume percentage on the inspiratory scan; WA% = wall area percentage; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment); TAC = total airway count. * indicates a p value <0.05.

Table E13. Cox proportional hazards model for all-cause mortality in the Hokkaido COPD cohort using the median VDI value of the established emphysema patients as the cut-off to define the high and low VDI groups

	Model
VDI group	
Minimal Emphysema	1.54 [0.37, 6.32]
High VDI	Ref
Low VDI	3.86* [1.29, 11.56]
iLAV%	1.03 [0.99, 1.07]
WA%	0.97 [0.85, 1.10]
Mucus [presence]	2.53* [1.08, 5.93]
TAC	1.00 [1.00, 1.01]

The data are expressed as hazard ratios [95% CI]. FEV_1, D_{LCO}, age, sex, smoking status, and pack-years were also adjusted for the models. The VDI groups were defined according to the median value of the VDI from the established emphysema patients in the Kyoto-Himeji cohort. VDI = ventilation discordance index; iLAV% = low attenuation volume percentage on the inspiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment); FEV_1 = forced expiratory volume in 1 second; D_{LCO} = diffusing lung capacity for carbon monoxide. * indicates a p value <0.05.

Table E14. Multivariable regression models for FEV_1 and the annual decline in FEV_1 using the small airway disease group

Cohort	FEV_1 Kyoto-Himeji	FEV_1 Hokkaido COPD	Annual FEV_1 decline Hokkaido COPD
SAD group			
Minimal Emphysema	-0.25* [-0.48, -0.03]	-0.14 [-0.41, 0.12]	7.00 [-8.22, 22.23]
High SAD%	-0.40* [-0.58, -0.23]	-0.21* [-0.41, -0.01]	-0.54 [-12.27, 11.18]
Low SAD%	Ref	Ref	Ref
iLAV%	-0.02* [-0.03, -0.01]	-0.01* [-0.02, 0.00]	-0.25 [-0.75, 0.25]
WA%	-0.01 [-0.03, 0.00]	-0.03* [-0.05, 0.00]	1.21 [-0.28, 2.71]
Mucus [presence]	-0.23* [-0.35, -0.11]	-0.20* [-0.36, -0.04]	-1.11 [-10.75, 8.54]
TAC	0.002* [0.001, 0.003]	0.001 [-0.001, 0.003]	0.004 [-0.091, 0.099]

The data are expressed as estimates [95% CI]. Age, height, sex, smoking status, and pack-years were also adjusted for the FEV1 models. Baseline FEV_1, age, height, sex, smoking status, and pack-years were also adjusted for the model of annual FEV_1 decline. FEV_1 = forced expiratory volume in 1 second; SAD = small airway disease; iLAV% = low attenuation volume percentage on the inspiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment). * indicates a p value <0.05.

Table E15. Cox proportional hazards model for all-cause mortality using the small airway disease group in the Hokkaido COPD cohort

Variables	HR [95% CI]
SAD group	
Minimal Emphysema	2.42 [0.49, 11.82]
High SAD%	3.03* [1.10, 8.31]
Low SAD%	Ref
iLAV%	1.05* [1.01, 1.09]
WA%	1.00 [0.87, 1.14]
Mucus [presence]	2.51* [1.05, 5.99]
TAC	1.01 [1.00, 1.01]

The data are expressed as hazard ratios [95% CI]. FEV_1, D_{LCO}, age, sex, smoking status, and pack-years were also adjusted for the models. SAD = small airway disease; iLAV% = low attenuation volume percentage on the inspiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment); FEV_1 = forced expiratory volume in 1 second; D_{LCO} = diffusing lung capacity for carbon monoxide. * indicates a p value <0.0

Table E16. Cox proportional hazards models for all-cause mortality in the Hokkaido COPD cohort using pulmonary function other than FEV_1

	Model 1	Model 2	Model 3	Model 4
VDI group				
Minimal Emphysema	2.90 [0.61, 13.89]	2.55 [0.54, 12.00]	2.48 [0.51, 12.01]	1.86 [0.41, 8.47]
High VDI	Ref	Ref	Ref	Ref
Low VDI	4.61* [1.49, 14.26]	4.26* [1.40, 12.97]	4.07* [1.32, 12.57]	3.69* [1.24, 10.97]
RV	0.64 [0.32, 1.27]			
FRC		0.65 [0.32, 1.32]		
RV/TLC			1.01 [0.95, 1.06]	
FEV_1/FVC				1.04 [0.98, 1.10]
iLAV%	1.07* [1.01, 1.13]	1.07* [1.01, 1.14]	1.04 [0.99, 1.09]	1.05* [1.01, 1.10]
WA%	0.99 [0.88, 1.11]	0.98 [0.87, 1.11]	0.99 [0.88, 1.11]	0.98 [0.87, 1.11]
Mucus [presence]	1.92 [0.82, 4.49]	2.04 [0.88, 4.75]	2.15 [0.91, 5.07]	2.30 [0.95, 5.59]
TAC	1.01 [1.00, 1.01]	1.00 [1.00, 1.01]	1.00 [1.00, 1.01]	1.00 [1.00, 1.01]

The data are expressed as hazard ratios [95% CI]. D_{LCO}, age, sex, smoking status, and pack-years were also adjusted for the models. VDI = ventilation discordance index; FEV_1 = forced expiratory volume in 1 second; RV = residual volume; FRC = functional residual capacity; TLC = total lung capacity; FVC = forced vital capacity; iLAV% = low attenuation volume percentage on the inspiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment); D_{LCO} = diffusing lung capacity for carbon monoxide. * indicates a p value <0.05.

Table E17. Multivariable regression models for the annual decline in FEV_1 using the low attenuation volume percentage on the expiratory scan

	Model 1	Model 2	Model 3
VDI group			
Minimal Emphysema	2.40 [-9.79, 14.58]		2.87 [-10.79, 16.54]
High VDI	Ref		Ref
Low VDI	-17.03* [-28.31, -5.76]		-17.53* [-30.47, -4.58]
eLAV%		-0.33* [-0.63, -0.04]	0.03 [-0.38, 0.44]
WA%	1.00 [-0.38, 2.39]	1.14 [-0.29, 2.57]	1.01 [-0.38, 2.40]
Mucus [presence]	1.00 [-8.27, 10.27]	-0.27 [-9.52, 8.98]	1.04 [-8.30, 10.37]
TAC	-0.02 [-0.11, 0.07]	0.00 [-0.09, 0.09]	-0.02 [-0.11, 0.07]

The data are expressed as estimates [95% CI]. Baseline FEV_1, age, height, sex, smoking status, and pack-years were also adjusted for the models. FEV_1 = forced expiratory volume in 1 second; VDI = ventilation discordance index; eLAV% = low attenuation volume percentage on the expiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment). * indicates a p value <0.05.

Table E18. Cox proportional hazards models for all-cause mortality using the low attenuation volume percentage on the expiratory scan in the Hokkaido COPD cohort

	Model 1	Model 2	Model 3
VDI group			
Minimal Emphysema	1.41 [0.34, 5.85]		2.43 [0.51, 11.66]
High VDI	Ref		Ref
Low VDI	4.30* [1.45, 12.81]		3.61* [1.13, 11.58]
eLAV%		1.04* [1.01, 1.07]	1.03 [1.00, 1.07]
WA%	0.98 [0.88, 1.10]	0.96 [0.85, 1.09]	0.99 [0.87, 1.12]
Mucus [presence]	2.22 [0.96, 5.11]	2.60* [1.13, 5.98]	2.47* [1.06, 5.74]
TAC	1.01 [1.00, 1.01]	1.00 [1.00, 1.01]	1.01 [1.00, 1.01]

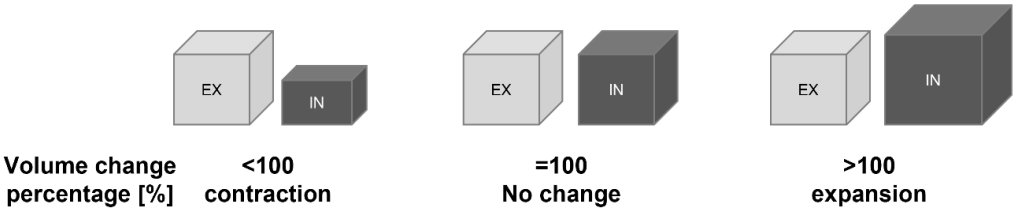
The data are expressed as hazard ratios [95% CI]. FEV_1, D_{LCO}, age, sex, smoking status, and pack-years were also adjusted for the models. VDI = ventilation discordance index; eLAV% = low attenuation volume percentage on the expiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment); FEV_1 = forced expiratory volume in 1 second; D_{LCO} = diffusing lung capacity for carbon monoxide. * indicates a p value <0.05.

Table E19. Univariable and multivariable regression models to explore whether the CT indices, including the low attenuation volume percentage on the expiratory scan, are associated with the ventilation discordance index in the Kyoto-Himeji cohort

	Univariable	Multivariable		
		Model 1	Model 2	Model 3
eLAV%	-0.40* [-0.52, -0.28]	-0.38* [-0.50, -0.26]	-0.33* [-0.45, -0.21]	-0.29* [-0.42, -0.17]
WA%	-0.24* [-0.37, -0.11]	-0.20* [-0.32, -0.08]	-0.07 [-0.22, 0.07]	-0.09 [-0.23, 0.05]
Mucus [presence]	-0.21* [-0.34, -0.08]		-0.04 [-0.17, 0.08]	-0.02 [-0.15, 0.10]
TAC	0.36* [0.23, 0.48]		0.21* [0.07, 0.36]	0.22* [0.07, 0.36]
iLAV%$_{upper}$/iLAV%$_{lower}$	0.21* [0.08, 0.34]			0.09 [-0.03, 0.21]
Hyperventilated emphysema ratio in the upper lung	-0.23* [-0.36, -0.10]			-0.22* [-0.34, -0.10]
Hyperventilated emphysema ratio in the lower lung	-0.03 [-0.17, 0.10]			0.12 [0.00, 0.24]

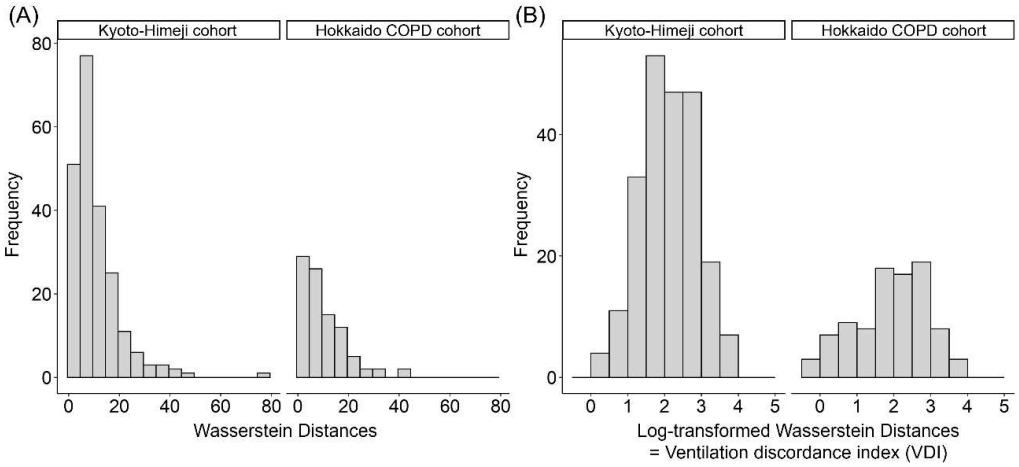
The data are expressed as standardized estimates [95% CI]. Institution was also adjusted for the model. eLAV% = low attenuation volume percentage on the expiratory scan; WA% = wall area percentage; TAC = total airway count; Mucus [presence] = mucus score ≥1 (mucus positive for at least one airway segment); iLAV% = low attenuation volume percentage on the inspiratory scan. * indicates a p value <0.05.

Figure E1. Definition of the volume change percentage



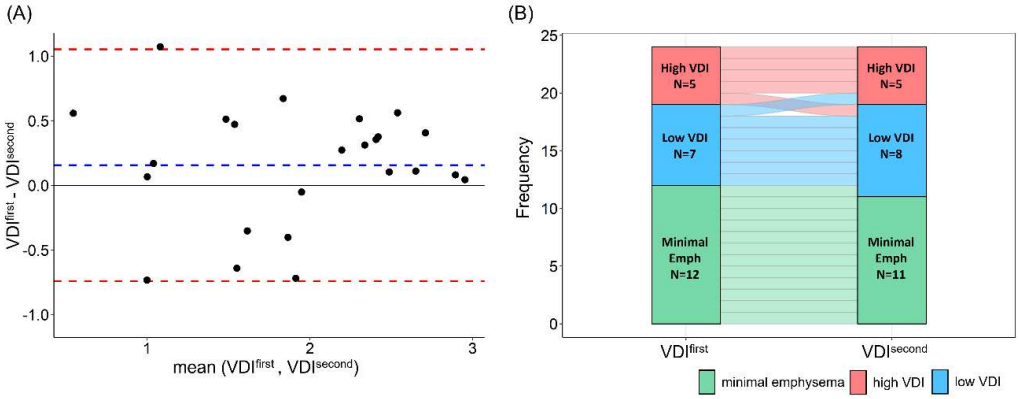
The volume change percentage indicates the change in voxel volume; <100 indicates contraction, =100 indicates no change, and >100 indicates expansion.

Figure E2. Histograms of raw (untransformed) and log-transformed Wasserstein distances



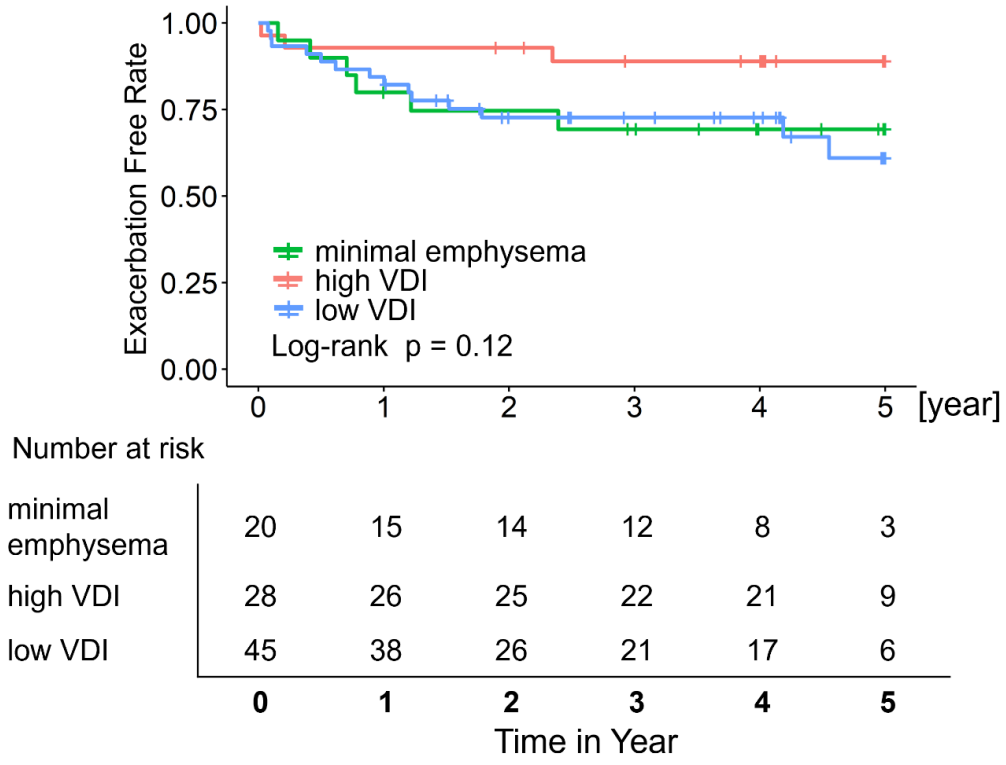
Distribution of (A) raw and (B) log-transformed Wasserstein distances in the two cohorts. The ventilation discordance index was defined as log-transformed Wasserstein distances.

Figure E3. Reproducibility of the ventilation discordance index in the Kyoto-Himeji cohort



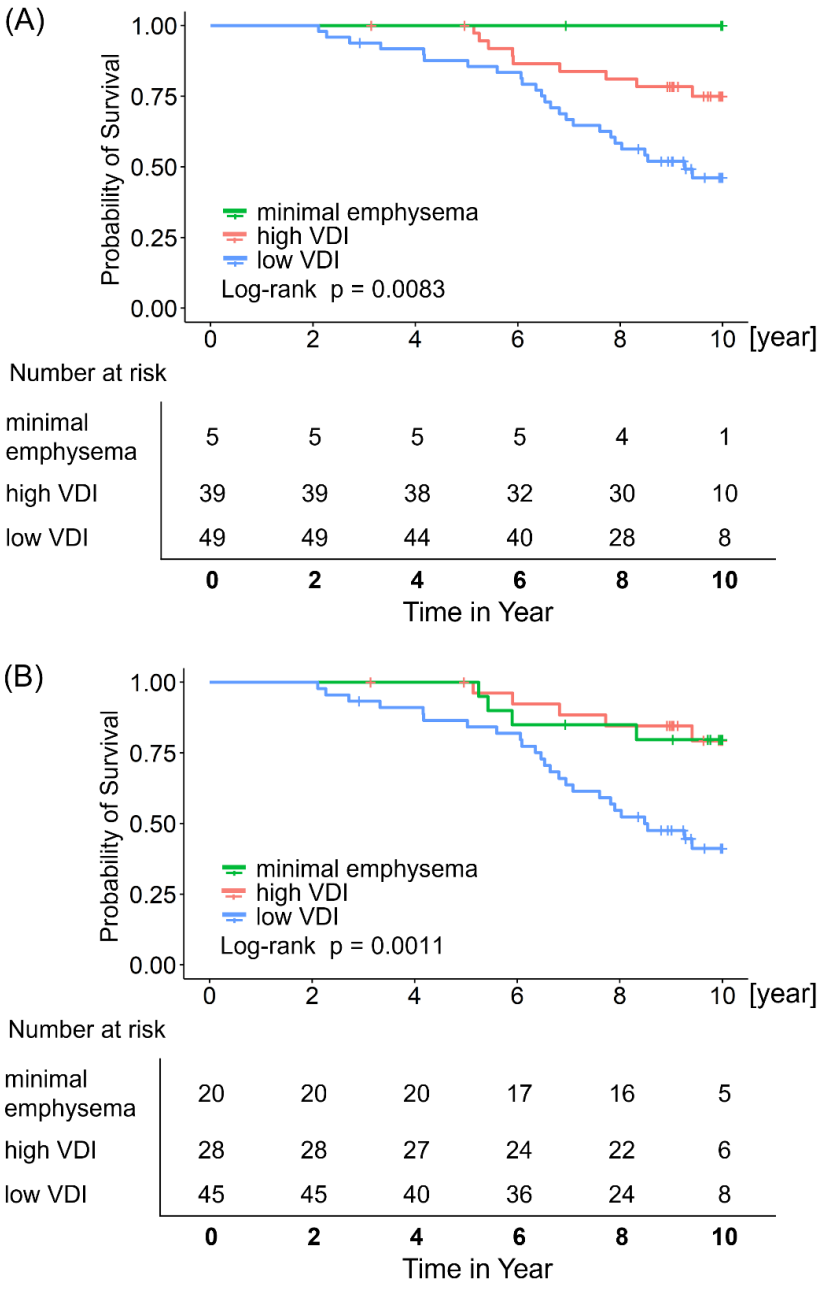
(A) Bland–Altman plots of VDI on the first and second scans. The blue and red lines represent the mean ± 1.96 SD of the difference in VDI on the first and second scans. (B) The Sankey bar graph shows the change in the VDI group on the first and second scans.

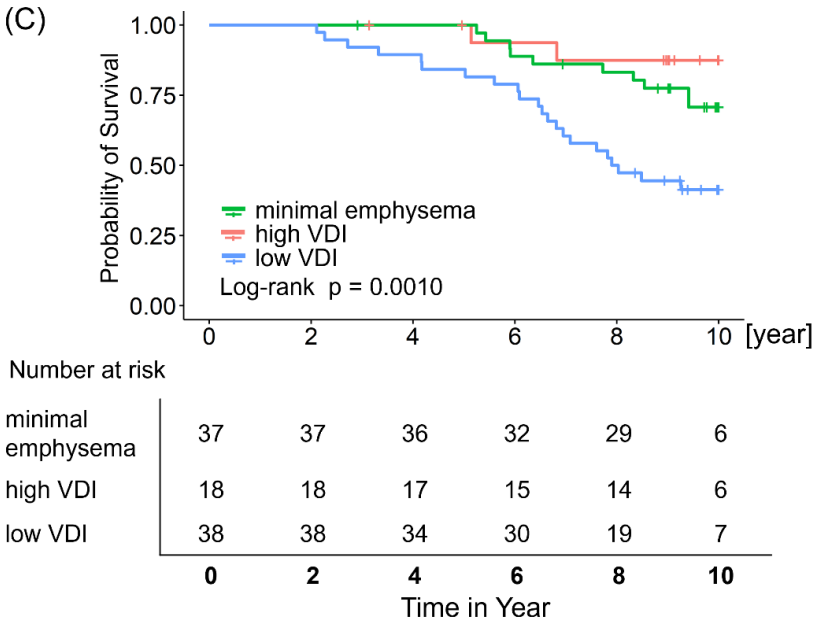
Figure E4. Kaplan–Meier curves for the time to first exacerbation in the Hokkaido COPD cohort according to the ventilation discordance index group



There was no significant difference in the time to first exacerbation among the three groups (log-rank p=0.12).

Figure E5. Association between mortality and the ventilation discordance index groups using 5%, 10%, and 15% cut-off values to define established emphysema in the Hokkaido COPD cohort





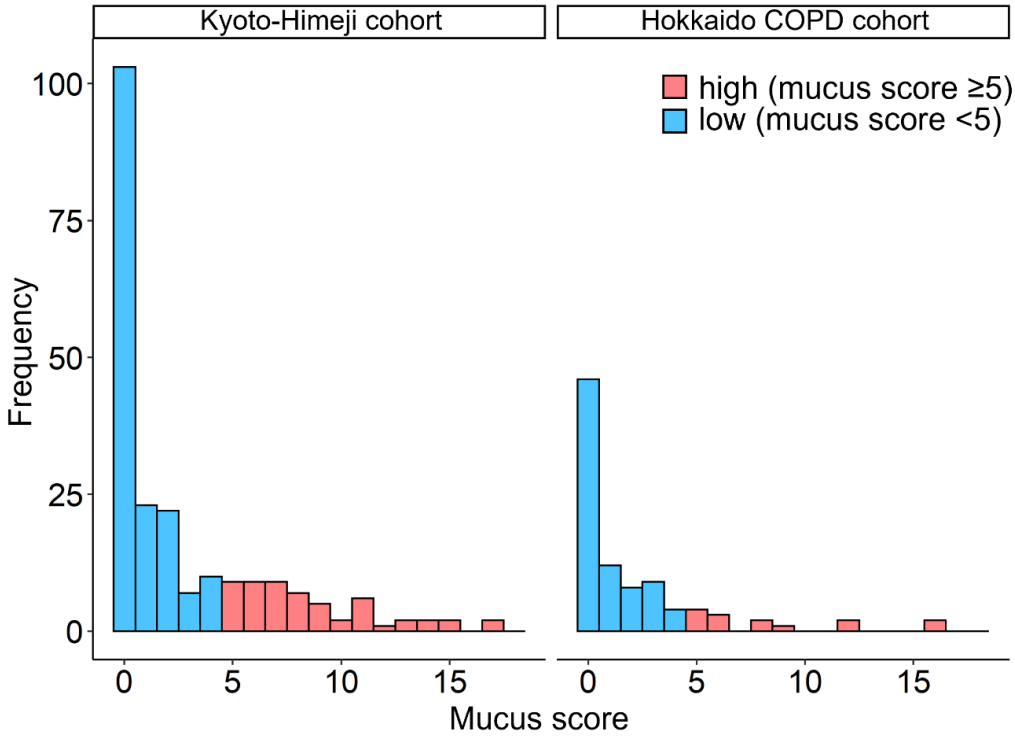
Number at risk

minimal emphysema	37	37	36	32	29	6
high VDI	18	18	17	15	14	6
low VDI	38	38	34	30	19	7
	0	**2**	**4**	**6**	**8**	**10**

Time in Year

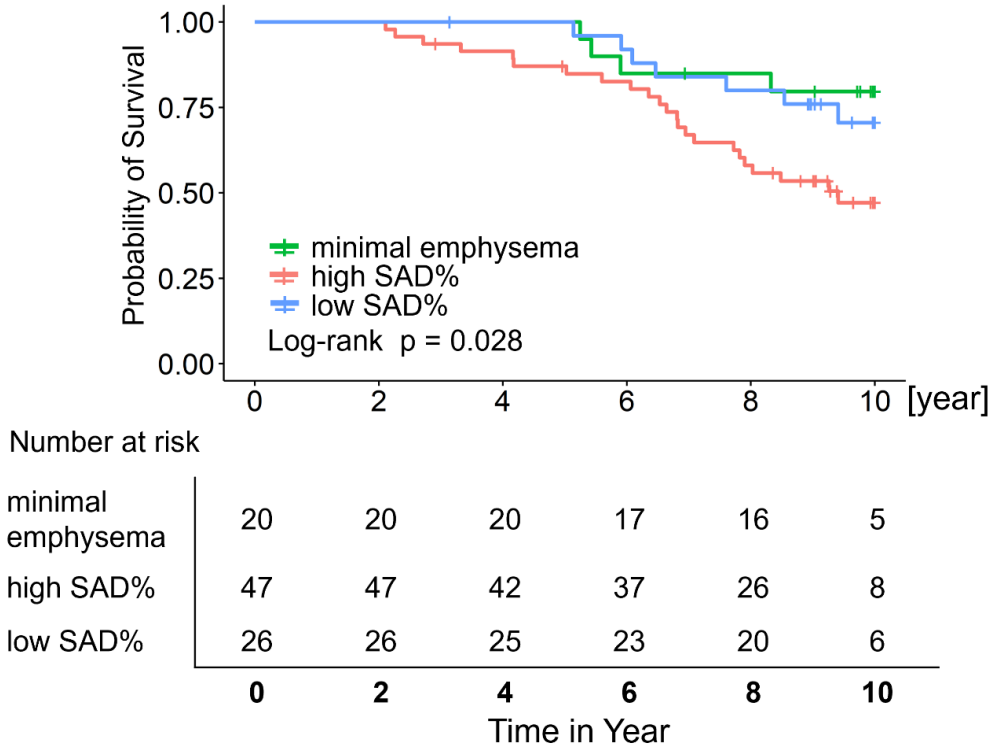
The Kaplan–Meier curves of all-cause mortality in the Hokkaido COPD cohort using the cut-off values of (A) iLAV% ≥5%, (B) iLAV% ≥10%, and (C) iLAV% ≥15% to define the established emphysema. (A) All-cause mortality significantly differed among the three groups using an iLAV% cut-off value of 5% (p = 0.008), and the multivariable Cox proportional hazards model showed that compared with the high VDI group, all-cause mortality was significantly higher in the low VDI group (HR [95% CI] = 2.63 [1.01, 6.87]). (B) All-cause mortality significantly differed among the three groups using an iLAV% cut-off value of 10% (p = 0.001), and the multivariable Cox proportional hazard model showed that compared with the high VDI group, all-cause mortality was significantly higher in the low VDI group (HR [95% CI] = 4.11 [1.34, 12.60]) but not in the minimal emphysema group (HR [95% CI] = 2.54 [0.54, 12.05]). (C) All-cause mortality significantly differed among the three groups using an iLAV% cut-off value of 15% (p = 0.001), and the multivariable Cox proportional hazards model showed that compared with the high VDI group, the all-cause mortality was significantly higher in the low VDI group (HR [95% CI] = 9.00 [1.78, 45.53]) and minimal emphysema group (HR [95% CI] = 6.08 [1.12, 33.00]).

Figure E6. Distribution of mucus scores in the two cohorts



Mucus scores <5 were defined as "low" scores, and those ≥5 were defined as "high" scores.

Figure E7. Association between mortality and the small airway disease group in the Hokkaido COPD cohort



Number at risk

minimal emphysema	20	20	20	17	16	5
high SAD%	47	47	42	37	26	8
low SAD%	26	26	25	23	20	6
	0	**2**	**4**	**6**	**8**	**10**

Time in Year

Kaplan–Meier curves of all-cause mortality in the Hokkaido COPD cohort using the small airway disease (SAD) group. All-cause mortality significantly differed among the three groups (p = 0.028). The multivariable Cox proportional hazard model showed that compared with the low SAD group, the all-cause mortality was significantly higher in the high SAD group (HR [95% CI] = 3.03 [1.10, 8.31]) but not in the minimal emphysema group (HR [95% CI] = 2.42 [0.49, 11.82]).

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