**Online supplement**

**Percent low attenuation volume and fractal dimension of low attenuation clusters on computed tomography predict different long-term outcomes in COPD**

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**Supplementary Results**

**Detail of study population in the the Hokkaido COPD and the Kyoto University cohorts**

CONSORT-style diagrams for the Hokkaido COPD and the Kyoto University cohorts are shown in Supplementary Figure E1 and E2, respectively.

As shown in Supplementary Figure E1, 121 of the 279 patients in the original Hokkaido COPD Cohort study were recruited at Hokkaido University Hospital and underwent CT scans at the baseline evaluation (visit 1). However, CT data of 30 patients at visit 1 had not been preserved as DICOM files, and we could not perform the fractal analysis of emphysematous clusters for these patients in this study. In the initial evaluation of CT scans at visit 1 for the remaining 91 patients, 21 patients were excluded because their CT scans were not reconstructed with the standard reconstruction kernel (n=19) or abnormal chest shadows such as giant bullae or pleural thickening were found (n=2). In addition, further 26 patients who underwent CT scans at visit 3 were also included. Therefore, a total of 96 patients were included for the present analyses.

As shown in Supplementary Figure E2, 154 male patients with COPD were screened at Kyoto University Hospital. Among them, 24 patients were excluded because of interstitial pneumonia (n=4), bronchial asthma (n=2), bronchiectasis (n=11), abnormal shadows on chest CT scans (n=11), a history of malignancy within the past 5 years (n=5), and a history of lobectomy (n=1). Therefore, a total 130 male patients were included in the Kyoto University cohort study.

There were no significant differences in the anthropomorphometric data and pulmonary function test results between the 96 patients included in the present study and the 279 patients considered eligible for the original cohort (Supplementary Table E1).

**Additional analysis regarding associations of baseline %LAV and fractal *D* with FEV1 decline, exacerbation, and survival in the Hokkaido COPD cohort**

Time to first exacerbation was shorterin the low *D* group than in the high *D* group (p<0.01 using the antibiotic definition, p=0.01 using the prescription definition) (Figure 2A and Supplementary Figure E4). There was no significant difference in the time to first exacerbation between the high and low %LAV groups (p=0.60 using antibiotic definition, p=0.75 using the prescription definition; (Figure 2A and Supplementary Figure E4). The prognosis was poorer in the high %LAV group than in the low %LAV group (p<0.01) but did not differ between the low and high *D* groups (p=0.30; Figure 2B). The univariable Cox proportional hazards analyses showed that lower *D*, but not %LAV, was associated with shorter time to first exacerbation (hazard ratio [HR] 0.04 [95% CI 0.00–0.85], p=0.04, and HR 1.03 [95% CI 0.99–1.06], p=0.12), whereas higher %LAV, but not *D*, is associated with mortality (HR 0.14 [95% CI 1.02–1.07], p<0.01, and HR 0.11 [95% CI 0.01–1.35], p=0.08, Supplementary Table E2). The results of the multivariable Cox proportional hazards analysis in the Hokkaido COPD cohort (Supplementary Table E2) did not show an association between lower *D* or high %LAV and time to first exacerbation or mortality.

**Supplementary Tables**

**Supplementary Table E1. The characteristics in 96 patients included for the present study and the whole participants of 279 patients in the Hokkaido COPD cohort.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | 96 patients in the present study | 279 patients in the original cohort | p |
| Sex, male/female | 89/7 | 262/17 | 0.68 |
| Age, years | 69.8 ± 8.0 | 69.4 ± 7.9 | 0.74 |
| Height, m | 1.63±0.07 | 1.63 ± 6.7 | 0.82 |
| Weight, kg | 60.0±10.5 | 59.3±10.3 | 0.54 |
| Body mass index | 22.7 ± 3.1 | 22.3±3.2 | 0.33 |
| GOLD stage 1/2/3/4 | 29/45/19/3 | 72/126/68/13 | 0.65 |
| %FVC, % | 101.6± 14.6 | 100.5 ± 18.9 | 0.60 |
| %FEV1, % | 66.2 ± 19.4 | 64.5 ± 21.9 | 0.51 |
| FEV1/FVC, % | 52.1 ± 12.6 | 51.2 ± 12.7 | 0.53 |

Data are shown as the means ± standard deviations. FEV1/FVC is an absolute % value.

Abbreviations: FVC, forced vital capacity, FEV1, forced expiratory volume in 1 s

**Supplementary Table E2. Univariable and multivariable Cox proportional hazards analysis of exacerbation and all-cause mortality in the Hokkaido COPD cohort (n=96)**

|  |  |  |
| --- | --- | --- |
|  | **Exacerbation** | **Mortality** |
|  | **HR** | **95% CI** | **P value** | **HR** | **95% CI** | **P value** |
| **Model 1** |  |  |  |  |  |  |
| %LAV | 1.03 | 0.99-1.06 | 0.12 | 0.14 | 1.02-1.07 | <0.01 |
| **Model 2** |  |  |  |  |  |  |
| D | 0.04 | 0.00-0.85 | 0.04 | 0.11 | 0.01-1.35 | 0.08 |
| **Model 3** |  |  |  |  |  |  |
| **%LAV** | 1.01 | 0.96-1.05 | 0.76 | 1.03 | 1.00-1.07 | 0.08 |
| **Age** | 0.98 | 0.93-1.04 | 0.50 | 1.15 | 1.07-1.23 | <0.01 |
| **Height** | 1.01 | 0.91-1.11 | 0.47 | 1.04 | 0.94-1.14 | 0.46 |
| **Weight** | 0.97 | 0.91-1.04 | 0.47 | 0.97 | 0.91-1.03 | 0.35 |
| **FEV1** | 0.48 | 0.16-1.36 | 0.17 | 1.56 | 0.65-3.71 | 0.32 |
| **Smoking status** | 0.54 | 0.15-1.53 | 0.36 | 1.04 | 0.39-2.44 | 0.94 |
| **Model 4** |  |  |  |  |  |  |
| **D** | 0.51 | 0.00-4.60 | 0.25 | 0.29 | 0.02-5.18 | 0.40 |
| **Age** | 0.98 | 0.92-1.04 | 0.07 | 1.15 | 1.08-1.23 | <0.01 |
| **Height** | 1.00 | 0.92-1.09 | 0.66 | 1.08 | 1.00-1.17 | 0.06 |
| **Weight** | 0.98 | 0.92-1.04 | 0.19 | 0.95 | 0.90-1.00 | 0.03 |
| **FEV1** | 0.52 | 0.19-1.43 | 0.93 | 1.27 | 0.55-2.94 | 0.57 |
| **Smoking status**  | 0.53 | 0.15-1.49 | 0.37 | 0.89 | 0.34-2.02 | 0.78 |

Abbreviations: FEV1, forced expiratory volume in 1 s, %LAV, percent low attenuation volume

**FIGURE CAPTIONS**

**Supplementary Figure E1. Selection of patients with COPD in the Hokkaido COPD cohort**

121 patients were recruited at Hokkaido University Hospital. Of 121 patients, 70 patients had CT data at Visit 1 suitable for VIDA analysis and other 26 patients had suitable CT data on Visit 3. Finally, a total of 96 patients were included for the further analysis.

**Supplementary Figure E2. Selection of patients with COPD in the Kyoto University cohort**

One hundred fifty-four male patients with COPD were screened at Kyoto University Hospital. Among them, 24 patients were excluded because of interstitial pneumonia (n=4), bronchial asthma (n=2), bronchiectasis (n=11), abnormal shadows on chest CT scans (n=11), a history of malignancy within the past 5 years (n=5), and a history of lobectomy (n=1). A total 130 male patients were included in the Kyoto University cohort study.

**Supplementary Figure E3. Correlation between fractal *D* and %LAV in the Hokkaido COPD cohort (N=96)**

There was a significant negative correlation between fractal *D* and percent lung attenuation volume.

Supplementary **Figure E4**. Time to first **exacerbation in prescription definition categorized by baseline fractal *D* or %LAV in the Hokkaido COPD cohort**

Patients were divided into those with mild and severe emphysematous changes based on either median of *D* or median of %LAV. Patients with *D* <median value of 1.47 were categorized into *D* low category (n=48) and patients with %LAV<median value of 18.95 were categorized into %LAV low category (n=48). Time to first exacerbation requiring the change in their prescriptions was shorter in the low *D* group than in the high *D* group (p=0.01), while the time to first exacerbation did not differ between the high and low %LAV groups (p=0.75).

**Supplementary Figure E5. Histogram of %FEV1 in the Hokkaido COPD cohort and the Kyoto University cohort**

The median percent forced expiratory in 1 second (%FEV1) in the Hokkaido COPD cohort is equivalent to the 68th percentile of %FEV1 in the Kyoto University cohort.

**Supplementary Figure E6. Comparisons of time to first exacerbation and mortality between mild and severe emphysematous change on CT using the 68th percentile-based categorization. in the Kyoto University cohort**

The 68th percentile of *D* and the 32th percentile of percent low attenuation volume (%LAV) were used to divide patients into mild and severe emphysema groups, Time to first exacerbation was shorter in subjects with the low D group than in those with the high D group but did not differ between those with the low %LAV and those with high %LAV groups. The mortality rate was higher in subjects with the high %LAV group than in those with the low %LAV group but did not differ between those with the low D and those with high D groups.