1 **Online supplement**

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3 **Percent low attenuation volume and fractal dimension of low attenuation clusters**

4 **on computed tomography predict different long-term outcomes in COPD**

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23 **Supplementary Results**

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

25 **cohorts**

26 CONSORT-style diagrams for the Hokkaido COPD and the Kyoto University cohorts

27 are shown in Supplementary Figure E1 and E2, respectively.

28 As shown in Supplementary Figure E1, 121 of the 279 patients in the original Hokkaido

29 COPD Cohort study were recruited at Hokkaido University Hospital and underwent CT

30 scans at the baseline evaluation (visit 1). However, CT data of 30 patients at visit 1 had

31 not been preserved as DICOM files, and we could not perform the fractal analysis of

32 emphysematous clusters for these patients in this study. In the initial evaluation of CT

33 scans at visit 1 for the remaining 91 patients, 21 patients were excluded because their

34 CT scans were not reconstructed with the standard reconstruction kernel (n=19) or

35 abnormal chest shadows such as giant bullae or pleural thickening were found (n=2). In

36 addition, further 26 patients who underwent CT scans at visit 3 were also included.

37 Therefore, a total of 96 patients were included for the present analyses.

38 As shown in Supplementary Figure E2, 154 male patients with COPD were screened at

39 Kyoto University Hospital. Among them, 24 patients were excluded because of

40 interstitial pneumonia (n=4), bronchial asthma (n=2), bronchiectasis (n=11), abnormal

41 shadows on chest CT scans (n=11), a history of malignancy within the past 5 years

42 (n=5), and a history of lobectomy (n=1). Therefore, a total 130 male patients were

43 included in the Kyoto University cohort study.

44

45 There were no significant differences in the anthropomorphometric data and pulmonary

46 function test results between the 96 patients included in the present study and the 279

47   patients considered eligible for the original cohort (Supplementary Table E1).

48

49   **Additional analysis regarding associations of baseline %LAV and fractal *D* with**

50   **FEV$_1$ decline, exacerbation, and survival in the Hokkaido COPD cohort**

51   Time to first eExacerbations wasere shortermore common in the low *D* group than in

52   the high *D* group (p<0.01 using the antibiotic definition, p=0.01 using the prescription

53   definition) (Figure 2A and Supplementary Figure E4). There was no significant

54   difference in the frequency oftime to first exacerbations between the high and

55   low %LAV groups (p=0.60 using antibiotic definition, p=0.75 using the prescription

56   definition; (Figure 2A and Supplementary Figure E4). The prognosis was poorer in the

57   high %LAV group than in the low %LAV group (p<0.01) but did not differ between the

58   low and high *D* groups (p=0.30; Figure 2B). The univariable Cox proportional hazards

59   analyses showed that lower *D*, but not %LAV, was associated with shorter time to first

60   exacerbation (hazard ratio [HR] 0.04 [95% CI 0.00–0.85], p=0.04, and HR 1.03 [95%

61   CI 0.99–1.06], p=0.12), whereas higher %LAV, but not *D*, is associated with mortality

62   (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,

63   Supplementary Table E2). The results of the multivariable Cox proportional hazards

64   analysis in the Hokkaido COPD cohort (Supplementary Table E2) did not show an

65   association between lower *D* or high %LAV and time to first exacerbation or mortality.

66   The results of multivariable Cox proportional hazards analysis in the Hokkaido COPD

67   cohort (Table E2) did not show an association between lower *D* or high %LAV and

68   exacerbation frequency or mortality.

69   **Supplementary Tables**

70

71   **[Supplementary](#) Table E1. The characteristics in 96 patients included for the**

72   **present study and the whole participants of 279 patients in the Hokkaido COPD**

73   **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
%FEV_1, %	66.2 ± 19.4	64.5 ± 21.9	0.51
FEV_1/FVC, %	52.1 ± 12.6	51.2 ± 12.7	0.53

74   Data are shown as the means ± standard deviations. FEV_1/FVC is an absolute % value.

75   Abbreviations: FVC, forced vital capacity, FEV_1, forced expiratory volume in 1 s

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77

78   **Supplementary Table E2. Univariable and multivariable Cox proportional hazards**

79   **analysis of exacerbation and all-cause mortality in the Hokkaido COPD cohort**

80   **(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
FEV$_1$	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
FEV$_1$	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

81   Abbreviations: FEV$_1$, forced expiratory volume in 1 s, %LAV, percent low attenuation

82   volume

83 **FIGURE CAPTIONS**

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

85 **COPD cohort**

86 121 patients were recruited at Hokkaido University Hospital. Of 121 patients, 70

87 patients had CT data at Visit 1 suitable for VIDA analysis and other 26 patients had

88 suitable CT data on Visit 3. Finally, a total of 96 patients were included for the further

89 analysis.

90

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

92 **University cohort**

93 One hundred fifty-four male patients with COPD were screened at Kyoto University

94 Hospital. Among them, 24 patients were excluded because of interstitial pneumonia

95 (n=4), bronchial asthma (n=2), bronchiectasis (n=11), abnormal shadows on chest CT

96 scans (n=11), a history of malignancy within the past 5 years (n=5), and a history of

97 lobectomy (n=1). A total 130 male patients were included in the Kyoto University

98 cohort study.

99

100 **Supplementary Figure E3. Correlation between fractal *D* and %LAV in the**

101 **Hokkaido COPD cohort (N=96)**

102 There was a significant negative correlation between fractal *D* and percent lung

103 attenuation volume.

104

105 Supplementary **Figure E4**. Time to first e**E**xacerbation frequency **in prescription**

106 **definition categorized by baseline fractal *D* or %LAV in the Hokkaido COPD**

107   **cohort**

108   Patients were divided into those with mild and severe emphysematous changes based on

109   either median of D or median of %LAV. Patients with D <median value of 1.47 were

110   categorized into D low category (n=48) and patients with %LAV<median value of 18.95

111   were categorized into %LAV low category (n=48). Time to first exacerbation requiring

112   the change in their prescriptions was shorter ~~More subjects~~ in the low D group

113   ~~experienced exacerbations requiring the change in their prescriptions~~ than ~~those~~ in the

114   high D group (p=0.01), while the time to first exacerbation~~frequency of those~~

115   ~~exacerbations~~ did not differ between the high and low %LAV groups (p=0.75).

116

117   **Supplementary Figure E5. Histogram of %FEV$_1$ in the Hokkaido COPD cohort**

118   **and the Kyoto University cohort**

119   The median percent forced expiratory in 1 second (%FEV$_1$) in the Hokkaido COPD

120   cohort is equivalent to the 68th percentile of %FEV$_1$ in the Kyoto University cohort.

121

122   **Supplementary Figure E6. Comparisons of time to first exacerbation ~~frequency~~**

123   **and mortality between mild and severe emphysematous change on CT using the**

124   **68th percentile-based categorization. in the Kyoto University cohort**

125   The 68th percentile of D and the 32th percentile of percent low attenuation volume

126   (%LAV) were used to divide patients into mild and severe emphysema groups, Time to

127   first exacerbation was ~~Exacerbations were more common~~ shorter in subjects with the

128   low D group than in those with the high D group but did not differ ~~in frequency~~ between

129   those with the low %LAV and those with high %LAV groups. The mortality rate was

130   higher in subjects with the high %LAV group than in those with the low %LAV group

131   but did not differ between those with the low D and those with high D groups.

132