Available online at www.sciencedirect.com

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Fractal dimension in CT low attenuation areas is predictive of long-term oxygen therapy initiation in COPD patients: Results from two observational cohort studies

Takahiro Ibaraki [a,b], *Koich Tomoda* [c], *Nobuhiro Fujioka* [a], *Kazuhiro Sakaguchi* [a], *Yukio Fujita* [a], *Yoshifumi Yamamoto* [a], *Shigeto Hontsu* [a], *Motoo Yamauchi* [a], *Masanori Yoshikawa* [a], *Naoya Tanabe* [d], *Kazuya Tanimura* [d], *Susumu Sato* [d], *Keigo Saeki* [e], *Shigeo Muro* [a,*]

[a] *Department of Respiratory Medicine, Nara Medical University, Nara, Japan*
[b] *Saiseikai Suita Hospital, Osaka, Japan*
[c] *Department of General Internal Medicine 1, Kawasaki Medical School, Okayama, Japan*
[d] *Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[e] *Department of Epidemiology, Nara Medical University, Nara, Japan*

ARTICLE INFO

Article history:
Received 27 April 2021
Received in revised form
18 August 2021
Accepted 1 September 2021
Available online 25 September 2021

Keywords:
COPD
Computed tomography
Fractal property
Long term oxygen therapy (LTOT)
Pulmonary function test

ABSTRACT

Background: Some chronic obstructive pulmonary disease (COPD) patients develop hypoxemia with disease progression, with some even requiring long-term oxygen therapy (LTOT). Lung function, especially diffusing capacity, and the annual decline in PaO_2, are reported to be predictive factors of chronic respiratory failure. However, the association between lung morphometry evaluated using computed tomography (CT) images and LTOT initiation is unknown.

Methods: We retrospectively evaluated the relationship between clinical indices, including pulmonary function, body mass index (BMI), and CT parameters, at baseline and LTOT initiation in two prospective COPD cohorts. In the Nara Medical University cohort (n = 76), the low attenuation area (LAA) and its fractal dimension (fractal D) were adapted as the indices for parenchymal destruction in CT images. The association between these CT measurements and LTOT initiation was replicated in the Kyoto University cohort (n = 130).

Abbreviations: COPD, Chronic obstructive pulmonary disease; LTOT, Long term oxygen therapy; LAA, Low attenuation area; COVID-19, Coronavirus disease 2019.

* Corresponding author. Department of Respiratory Medicine, Nara Medical University. 840 Shijo-cho, Kashihara, Nara, 634-8522, Japan.
E-mail address: smuro@naramed-u.ac.jp (S. Muro).

https://doi.org/10.1016/j.resinv.2021.09.001

Results: In the Nara Medical University cohort, lower BMI (hazard ratio [HR]:0.70, p = 0.006), lower % diffusing capacity (%DLCO) (HR: 0.92, p = 0.006), lower %DLCO/VA (HR, 0.90, p = 0.008), higher RV/TLC (HR, 1.26, p = 0.012), higher LAA% (HR: 1.18, p = 0.001), and lower fractal D (HR: 3.27×10^{-8}, p < 0.001) were associated with LTOT initiation. Multivariate analysis in the Kyoto University cohort confirmed that lower %DLCO and lower fractal D were independently associated with LTOT initiation, whereas LAA% was not.

Conclusion: Fractal D, which is the index for morphometric complexity of LAA in CT analysis, is predictive of LTOT initiation in COPD patients.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities [1].

Some COPD patients have accompanying hypoxemia along with disease progression. Hypoxemia in COPD is assumed to result from pathological and physiological derangements, such as loss of lung parenchyma, remodeling and destruction of the bronchioles, pulmonary vasculature, and ventilation-perfusion imbalance [2]. Uemasu et al. reported that mild hypoxemia, a low diffusing capacity (DLCO/VA) at baseline, and a further decline in PaO_2 [3] are predictive of future hypoxemia progression resulting in long-term oxygen therapy (LTOT) initiation.

For patients with hypoxemia, LTOT has been shown to reduce overall mortality and improve cognitive function and emotional status [4,5]. In addition to COPD patients who are chronically hypoxic at rest, conditions such as severe hypoxemia during exercise, severe hypoxemia during sleep, or merged pulmonary hypertension can also cause LTOT initiation in clinical practice [6].

However, few studies have investigated the factors predictive of LTOT initiation in COPD patients. It is well known that computed tomography (CT) emphysema severity, as indicated by a low attenuation area (LAA)%, correlates well with DLCO and hypoxemia [7,8], which is the major cause of LTOT initiation. In addition to LAA%, Mishima et al. showed that lung morphometric complexity, expressed as the exponent D derived by the fractal analysis of the size distribution of the CT-emphysema clusters (fractal D), can reveal the fine parenchymal destructive change that the conventional CT-emphysema index (LAA%) could not indicate [9]. Moreover, compared with LAA%, the change in fractal D was shown to be more sensitive in detecting parenchymal destruction caused by COPD exacerbation [10], which is a major cause of COPD clinical deterioration [1]. Furthermore, Shimizu and Tanabe et al. showed that fractal D and LAA% are differently associated with important clinical outcomes of COPD, such as prognosis and COPD exacerbation [10,11].

In this study, we hypothesized that fractal D is associated with clinical deterioration in COPD patients, especially with regards to LTOT initiation. The aims of this study were to (1) explore the associations between baseline pulmonary function, LAA%, fractal D in chest CT, and LTOT initiation in the Nara Medical University cohort, as well as (2) confirm the results in another cohort from Kyoto University.

2. Material and methods

Patients with stable COPD who regularly visited Nara Medical University Hospital between May 2008 and September 2013 agreed to participate in this observational study.

All patients were diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [1] and treated according to the Japanese Respiratory Society guidelines at that time [12]. All the participants provided written informed consent before the start of the study.

Patients who had other pulmonary diseases, such as bronchial asthma, pulmonary fibrosis, congestive heart failure, as well as those who were already receiving LTOT at the time of entry, were excluded.

Patient characteristics, such as age, sex, body mass index (BMI), and smoking history, were recorded at enrollment. The patients' most recent CT scans and spirometry test data were collected from the electronic medical record within 1 year or 90 days after enrollment after they had provided written informed consent to participate in the cohort study.

All participants underwent multi-detector row CT. The conventional whole-lung CT data obtained from 5-mm thick slice were preserved for the Nara Medical University cohort. However, because of storage capacity curtailment, thin slices of 1-mm thickness were preserved for every five slices.

Using all images of the entire lung (slice thickness, 5 mm), we calculated the values of LAA%, exponent fractal D, and CT-derived lung volume. The cumulative frequency distribution of the LAA sizes, Y, can be derived using the power law of LAA size X of the form X of the form $Y = K \times X^{-D}$. All CT data were analyzed using SYNAPSE VINCENT v.5.1.001 (FUJIFILM Inc., Tokyo, Japan) in the Nara cohort. The equation is the same for the analysis in Kyoto cohort, although the CT thickness is different as shown below.

2.1. LTOT initiation criteria

LTOT was indicated for patients who developed chronic respiratory failure ($PaO_2 \leq 55$ Torr, or SpO_2 was less than 90% in ambient air) and/or pulmonary hypertension. For patients with borderline cases, such as those with exertional

hypoxemia and/or hypoxemia during sleep, the indication for LTOT was determined by the physician in charge, considering the patient's general status.

2.2. Kyoto University cohort

The Kyoto University cohort has been described elsewhere [13]. Briefly, 130 male stable COPD patients who regularly visited the outpatient clinic were recruited. Clinical data, such as chest inspiratory CT scan with 0.5 mm slices, pulmonary function test results, and patient characteristics were recorded at the entry point. The LTOT initiation data were obtained through a review of the electronic clinical data.

The protocol for the Nara Medical University cohort study was approved by the Health Authority Research Ethics Committee of Nara Medical University (No.345–7), which adhered to the principles of the amended Declaration of Helsinki. The protocol for the Kyoto University cohort was also approved by the local ethics committee (No.R1660-2). All participants provided written informed consent.

2.3. Statistical analysis

To investigate the longitudinal association between fractal D at baseline and the initiation of LTOT, we performed univariate Cox hazard analysis for both cohorts. For the Kyoto cohort, multivariable Cox hazard analyses were also performed. For the selection of independent variables, we applied a forced entry method to create multiple models with a probability greater than 0.05, removing insignificant predictors so that the coefficients were one-tenth of the LTOT initiation. Data are presented as medians, with p-values and a 95% confidence interval (95%CI). The cut-off value for categorization was the median of each. All statistical analyses were performed using R statistical software (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria), and the EZR package was used [14].

3. Results

3.1. Study population

Seventy-six patients agreed to participate in the Nara Medical University cohort. Among them, 7 patients had already initiated LTOT at enrollment, and 17 patients had insufficient data for CT scan or spirometry tests. Finally, a total of 52 patients were recruited from the Nara Medical University cohort. The median follow-up period was 36 months. The validation cohort was comprised of 130 male patients from the Kyoto University cohort. LTOT was initiated in nine patients at enrollment, and 121 patients were investigated. The median follow-up duration was 84.7 months. Table 1 shows the characteristics of the participants in the Nara Medical University cohort and their comparison with those of the Kyoto University cohort. The spirometric data of the two cohorts

Table 1 – Characteristics of participants in the Nara Medical University and Kyoto University cohorts.

Characteristics	Nara Medical University cohort	Kyoto University cohort	p-value
Age, years	72.0 ± 8.1	72.7 ± 8.4	0.845
Sex (Male, Female)	51, 1	121, 0	
Smoking history, pack-year	66.5 ± 34.5	59.0 ± 38.9	0.286
BMI, kg/m^2	21.4 ± 3.0	21.3 ± 2.9	0.800
GOLD	I: 12, II: 26, III: 14, IV: 0	I:22, II:61, III:33, IV:5	
FEV_1, L	1.51 ± 0.54	1.55 ± 0.65	0.326
%FEV_1, %	63.7 ± 19.0	57.4 ± 19.4	0.099
VC, L	3.31 ± 0.67	3.25 ± 0.73	0.772
%VC, %	101.0 ± 17.8	93.7 ± 16.9	0.012*
FVC, L	3.28 ± 0.70	3.30 ± 0.80	0.370
%FVC, %	98.4 ± 18.7	98.3 ± 18.8	0.993
FEV1/FVC, %	48.9 ± 11.8	47.1 ± 12.4	0.634
DLCO, mL/min/mmHg	10.2 ± 6.0 (n = 32)	12.5 ± 4.6	0.056
%DLCO,%	41.3 ± 24.0 (n = 32)	52.1 ± 17.8	0.028*
DLCO/VA, mL/min/mmHg/L	1.64 ± 0.94 (n = 32)	2.75 ± 1.02	<0.001*
%DLCO/VA, %	37.4 ± 21.9 (n = 32)	63.0 ± 22.8	<0.001*
FRC, L	3.89 ± 0.88 (n = 32)	3.56 ± 0.66	0.008*
RV, L	2.60 ± 0.73 (n = 32)	2.34 ± 0.57	0.028*
RV/TLC, %	45.0 ± 7.6 (n = 32)	41.5 ± 8.0	0.068
LAA%, %	27.0 ± 13.4	32.7 ± 8.5	0.015*
fractal D	1.88 ± 0.38	1.55 ± 0.43	<0.001*
follow up period, days	1095 ± 312	2542 ± 735	<0.001*
LTOT period, days	411 ± 327	1448 ± 906	0.019*

Notes. The data are presented as median ± SD.
DLCO, diffusing capacity of the lung for carbon monoxide; fractal D, fractal dimension; LAA%, percent low attenuation area; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity.
*p < 0.05.

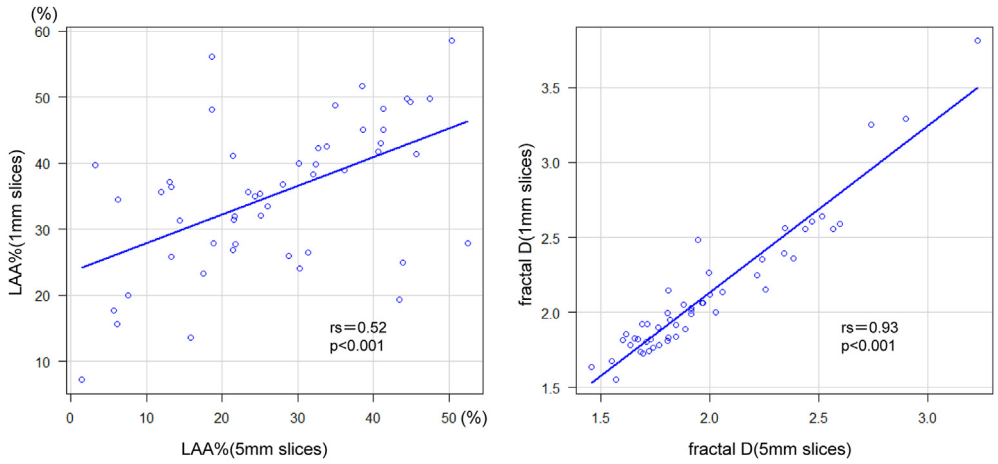

Fig. 1 – Association between LAA% and fractal D of thick slices (5 mm) and incompletely thin slices (1 mm) (Spearman's rank correlation coefficient).

were similar; however, diffusion function and hyperinflation were more impaired in the Nara Medical University cohort. The values of LAA% and fractal D were different in these groups, probably due to methodological differences.

3.1.1. *Comparison of CT indices between conventional CT slices (5 mm) and high-resolution CT slices (1 mm) in the Nara Medical University cohort*

The data taken from conventional whole-lung CT with 5 mm thick slices and incomplete thin slices (1 mm) were preserved in the Nara Medical University cohort, whereas the Kyoto University cohort contained the data from whole-lung CT with thin slices (0.5 mm), as previously described in the method. Therefore, we evaluated the relationship between the CT indices of conventional CT slices and thin CT slices (1 mm) for every 5 slices in the Nara Medical University cohort. We found a higher correlation of fractal D of the 5 mm slices with that of the 1-mm slices than with LAA% (Fig. 1). Moreover, it was found that the LAA% for the 5 mm slice thickness was underestimated for the 1 mm slice thickness by approximately 20%.

3.1.2. *Relationships between LAA%, fractal D, pulmonary function indices, and LTOT initiation in the Nara Medical University cohort*

The baseline characteristics of the patients who needed LTOT initiation and those who did not in the Nara Medical University cohort are shown in Table 2. During the follow-up, LTOT was initiated in 8 patients in the Nara Medical University cohort, with the median initiation period being 13.7 months. For the Kaplan-Meier analysis, we graded the BMI, LAA%,

Table 2 – Comparison of participants receiving and those not receiving LTOT in the Nara Medical University and Kyoto University cohorts.

	Nara Medical University cohort			Kyoto University cohort		
	LTOT (n = 8)	no LTOT (n = 44)	p-value	LTOT (n = 17)	no LTOT (n = 104)	p-value
Age, years	71.0 ± 9.6	72.0 ± 8.0	0.879	74.2 ± 5.2	72.0 ± 8.7	0.137
Sex (Male, Female)	8, 0	43, 1		17, 0	104, 0	
Smoking history, pack-year	53.5 ± 37.5	70.8 ± 34.3	0.543	73.5 ± 50.0	58.0 ± 36.5	0.173
BMI, kg/m^2	18.6 ± 2.8	22.3 ± 2.8	0.006*	22.1 ± 3.3	21.1 ± 2.8	0.715
GOLD	I: 1, II: 4, III: 3, IV: 0	I: 11, II: 22, III: 11, IV: 0		I:3, II:9, III:3, IV:2	I:19, II:52, III:30, IV:3	
FEV_1, L	1.29 ± 0.41	1.55 ± 0.54	0.200	1.43 ± 0.52	1.57 ± 0.67	0.221
%FEV_1, %	52.7 ± 16.8	66.6 ± 19.1	0.125	55.4 ± 18.8	57.7 ± 19.4	0.445
FVC, L	3.03 ± 0.82	3.33 ± 0.68	0.382	3.08 ± 0.83	3.33 ± 0.81	0.638
%FVC, %	94.5 ± 24.5	100.3 ± 17.5	0.551	102.5 ± 19.6	97.6 ± 18.8	0.734
FEV_1/FVC, %	45.3 ± 8.8	49.2 ± 12.2	0.375	41.1 ± 10.3	47.8 ± 12.6	0.087
%DLCO, %	30.7 ± 13.3 (n = 5)	44.6 ± 22.9 (n = 27)	0.003*	37.4 ± 13.9	55.9 ± 16.5	<0.001*
%DLCO/VA, %	27.6 ± 10.2 (n = 5)	38.7 ± 20.9 (n = 27)	0.002*	45.2 ± 15.2	66.1 ± 21.4	<0.001*
FRC, L	4.33 ± 0.75 (n = 5)	3.88 ± 0.91 (n = 27)	0.640	3.44 ± 0.72	3.58 ± 0.65	0.797
RV/TLC, %	50.6 ± 6.5 (n = 5)	44.4 ± 6.9 (n = 27)	0.009*	38.1 ± 10.6	41.6 ± 7.5	0.961
LAA%, %	44.0 ± 6.0	24.0 ± 12.1	<0.001*	39.0 ± 6.8	31.8 ± 8.2	<0.001*
fractal D	1.61 ± 0.09	1.93 ± 0.37	<0.001*	1.20 ± 0.20	1.68 ± 0.42	<0.001*

Notes. The data are presented as median ± SD.
DLCO, diffusing capacity of the lung for carbon monoxide; fractal D, fractal dimension; LAA%, percent low attenuation area; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity.
*p < 0.05.

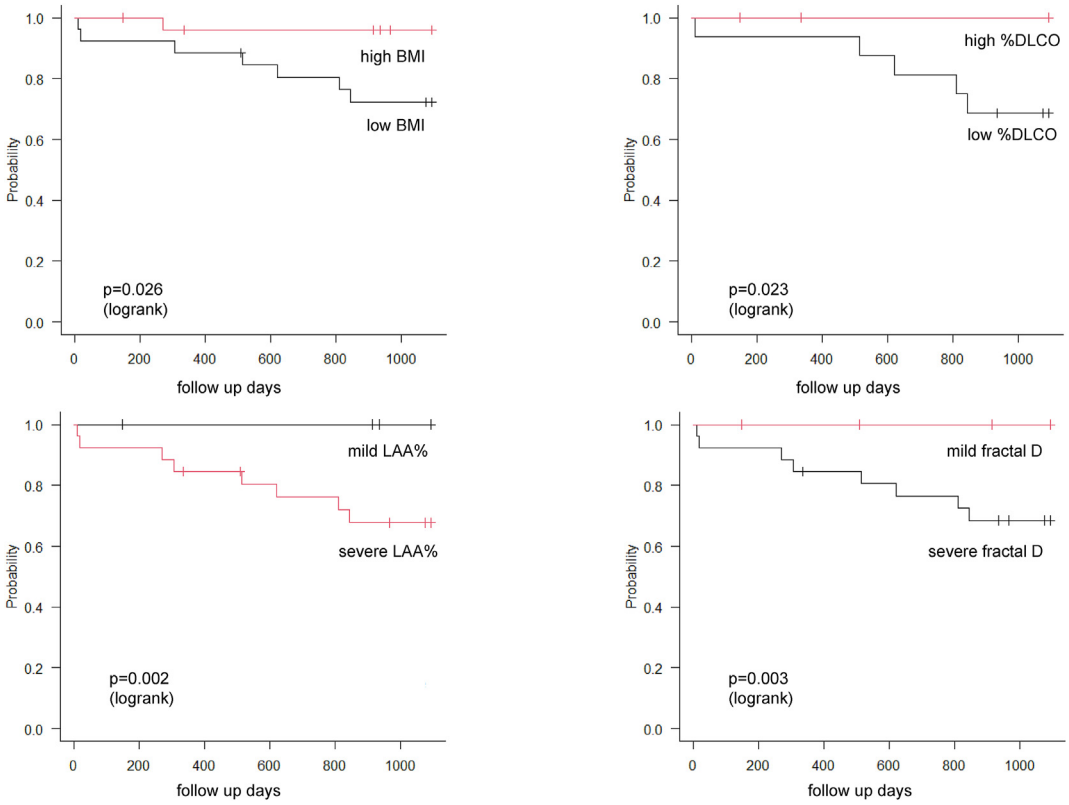

Fig. 2 – Time to LTOT initiation categorized by baseline body mass index (BMI), percent diffusing capacity for carbon monoxide (%DLCO), percent low attenuation area (LAA%), and fractal dimension (fractal D) in the Nara Medical University cohort. We graded the BMI, LAA%, fractal D, and %DLCO from median to low/high (or mild/severe). Patients with a cut-off BMI value of 21.4 were categorized into the low BMI group. Those with a cutoff %DLCO value of 41.5% were categorized as the low %DLCO group. Those with a cut-off LAA% value of 27.0 were categorized as the high LAA% group. Those with a cut-off fractal D value of 1.88 were categorized as the low fractal D group.

fractal D, and %DLCO from median to low/high (or mild/severe) for the Nara Medical University cohort. The Kaplan-Meier analysis showed that patients with severe fractal D had a significantly higher risk of LTOT initiation within 3 years than patients with mild fractal D ($p < 0.001$) (Fig. 2). Furthermore, low BMI, low %DLCO, and high LAA% were associated with a significantly higher risk of LTOT initiation within 3 years. On the other hand, the index of obstructive impairment was not a significant factor of LTOT initiation. Using a Cox proportional hazards analysis, lower BMI (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.55–0.90), lower DLCO (HR, 0.72; 95%CI, 0.57–0.92), lower %DLCO (HR, 0.92; 95%CI, 0.87–0.98), lower DLCO/VA (HR, 9.8×10^{-2}; 95%CI, 1.9×10^{-2} - 0.51), lower %DLCO/VA (HR, 0.90; 95%CI, 0.84–0.97), higher RV/TLC (HR, 1.26; 95%CI, 1.05–1.50), higher LAA% (HR, 1.18; 95%CI, 1.07–1.30), and lower fractal D (HR, 3.27×10^{-8}; 95%CI, 2.92×10^{-12} - 3.66×10^{-4}) were significantly associated with LTOT initiation. (Table 3). Multivariate analysis was not performed because of the low frequency of events.

3.1.3. *Comparison with the Kyoto University cohort*

The Kyoto University cohort was also evaluated to confirm the results of the Nara Medical University cohort. LTOT was initiated in 17 of 121 male patients with COPD in the Kyoto University cohort. The median duration for LTOT initiation was 1448 days (range, 14–2799).

Kaplan-Meier analysis for the Kyoto University cohort showed similar results, except for BMI, to those of the Nara Medical University cohort (Fig. 3). The univariate analysis showed that the predictive factors of LTOT initiation in the Kyoto University cohort were DLCO, %DLCO, DLCO/VA, %DLCO/VA, LAA%, and fractal D, which was similar to the findings in the Nara Medical University cohort (Table 4). As with the results in Nara Medical University cohort, the index of obstructive impairment was not a significant factor influencing LTOT initiation. In contrast, BMI and RV/TLC were not predictive factors of LTOT initiation in the Kyoto University cohort. Furthermore, multivariate analysis showed that while BMI, %DLCO, %DLCO/VA, and fractal D were significantly associated with LTOT initiation, LAA% was not associated with LTOT initiation (Table 5).

4. Discussion

For the Nara Medical University cohort study, univariate analysis showed that BMI, DLCO, %DLCO, DLCO/VA, %DLCO/VA, RV/TLC, LAA%, and fractal D were significant predictors of

Table 3 – Univariate Cox proportional hazard analysis for LTOT in the Nara Medical University cohort.

	HR	(95%CI)	p value
Age	1.02	(0.93–1.11)	0.695
smoking history	1.00	(0.97–1.02)	0.701
BMI	0.70	(0.55–0.90)	0.006*
FEV_1	0.35	(0.075–1.63)	0.180
$\%FEV_1$	0.97	(0.93–1.01)	0.124
VC	0.55	(0.20–1.54)	0.253
%VC	0.98	(0.94–1.01)	0.206
FVC	0.63	(0.24–1.64)	0.344
%FVC	0.98	(0.95–1.02)	0.303
FEV_1/FVC	0.97	(0.92–1.03)	0.315
DLCO	0.72	(0.57–0.92)	0.008*
%DLCO	0.92	(0.87–0.98)	0.006*
DLCO/VA	9.8×10^{-2}	$(1.9 \times 10^{-2} - 0.51)$	0.006*
%DLCO/VA	0.90	(0.84–0.97)	0.008*
LAA%	1.18	(1.07–1.30)	0.001*
fractal D	3.27×10^{-8}	$(2.92 \times 10^{-12} - 3.66 \times 10^{-4})$	<0.001*
FRC	1.40	(0.52–3.74)	0.502
RV	2.31	(0.72–7.44)	0.161
%RV	1.01	(0.99–1.04)	0.407
%TLC	1.01	(0.96–1.06)	0.833
RV/TLC	1.26	(1.05–1.50)	0.012*
Exacerbation	2.96	(0.60–14.7)	0.184
Exacerbation before 1year	1.00	(0.98–1.01)	0.687

Notes. DLCO diffusing capacity of the lung for carbon monoxide; fractal D, fractal dimension; LAA% percent low attenuation area; FRC, functional residual capacity; RV residual volume; TLC, total lung capacity.
*$p < 0.05$.

LTOT initiation. We validated our results for the Kyoto University cohort, except for the results regarding BMI. Moreover, multivariate analysis of the Kyoto University cohort revealed that fractal D, rather than LAA% and DLCO (or %DLCO, % DLCO/VA), were predictive factors of LTOT initiation in COPD clinics. To our knowledge, this is the first study to show that fractal D in chest images is useful for predicting the need for the initiation of new treatment in COPD patients independent of emphysema severity on CT or diffusion capacity.

The main reason for LTOT initiation in Japan is chronic respiratory failure (CRF). A previous study reported that DLCO/VA and mild hypoxemia are related to the development of CRF [3]. Thus, it can be assumed that DLCO/VA is a predictive factor of LTOT initiation. However, CT image parameters were not evaluated in the previous study. It is well known that diffusion capacity shows a good correlation with LAA% or fractal D [15]; thus, it is acceptable that both of these CT parameters are associated with LTOT initiation in this study. Moreover, multivariable analysis showed that fractal D, but not LAA%, was significantly predictive of LTOT initiation in the Kyoto University cohort.

Recently, it has been reported that regular treatment with single inhaler triple therapy may be beneficial for life prognosis in COPD patients [16,17] and it is possible that the treatment arm could affect our results. Therefore, we evaluated the relationship between the type of treatments (e.g. LABA, LAMA, LAMA + LABA, ICS + LABA, ICS + LAMA + LABA or on demand SABDs without LABDs) and HOT initiation. In the Kyoto cohort, patients treated with LAMA + LABA or ICS + LAMA + LABA underwent LTOT more frequently than those with non-regular treatment. However, pulmonary function impairment in these groups was significantly more severe than in patients with non-regular treatment patients (data not shown). Therefore, these results may have been influenced by the severity of the disease. We believe that a larger scale validation study is needed to clarify the impact of different treatment methods.

Table 4 – Comparison of two cohorts based on factors significantly associated with LTOT found after univariate analysis.

	HR		
	Nara Medical University cohort	Kyoto University cohort	p-value
BMI	0.70*	1.00	* 0.006
DLCO	0.72*	0.65†	* 0.008 † <0.001
%DLCO	0.92*	0.90†	* 0.006 † <0.001
DLCO/VA	0.097*	0.11†	* 0.006 † <0.001
%DLCO/VA	0.90	0.91†	* 0.008 † <0.001
RV/TLC	1.26*	1.03	* 0.012
LAA%	1.18*	1.18†	* 0.001 † <0.001
fractal D	3.3×10^{-8}*	2.9×10^{-3}†	* <0.001 † <0.001

Notes. *: Significant correlation with LTOT in the Nara Medical University cohort.
†: Significant correlation with LTOT in the Kyoto University cohort.

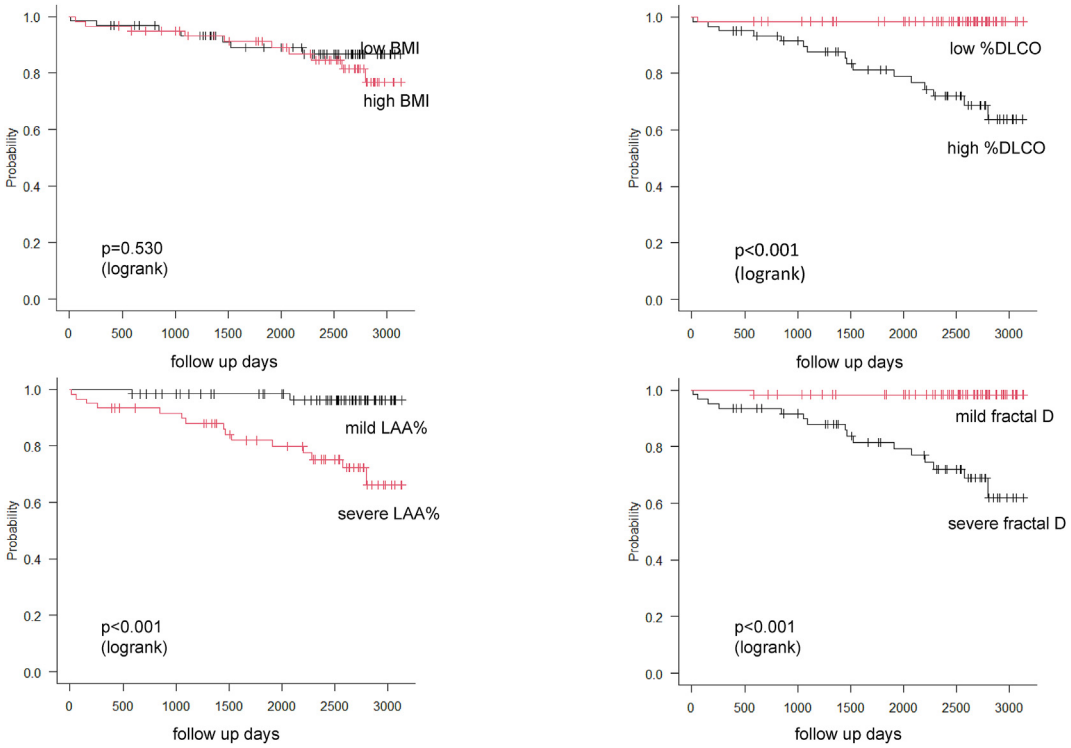

Fig. 3 – Time to LTOT categorized by baseline body mass index (BMI), percent diffusing capacity for carbon monoxide (% DLCO), percent low attenuation area (LAA%), or fractal dimension (fractal D) in the Kyoto University cohort. We graded the BMI, LAA%, fractal D, and %DLCO from median to low/high (or mild/severe). The patients with a cut-off BMI value of 21.3 were categorized into the low BMI group. Those with a cutoff %DLCO value of 52.1 were categorized into the low %DLCO group. Those with a cut-off LAA% value of 32.7 were categorized as the high LAA% group. Those with a cut-off fractal D value of 1.55 were categorized into the low D group.

The significance of the fractal property in chest CT images was originally reported by Mishima et al., who demonstrated that fractal D was related to DLCO/VA in COPD patients, as well as healthy individuals [9]. They suggested that the deterioration of fractal D reflected a slight parenchymal destruction that LAA%, a classical emphysematous parameter in image analysis, could not reflect. In addition, Tanabe et al. reported that fractal D was a more sensitive surrogate index of parenchymal destruction during exacerbation of significant emphysema compared to LAA% [10]. These findings suggest that fractal D is sensitive for detecting emphysematous progression that strongly relates to oxygen uptake impairment, resulting in an excellent association predictive of LTOT initiation compared with LAA%. Additionally, the superiority of fractal D to LAA% for LTOT initiation prediction may be attributed to its features, such as reproducibility and stability, as an image index. It has been shown that LAA% is susceptible to intra- and/or inter-subject variation at the breath-hold level on CT imaging and is possibly influenced by CT image thickness, whereas fractal D is more robust [18,19]. Gierada et al. reported that LAA% is influenced by CT thickness [20]. In our Nara Medical University cohort, LAA% and fractal D of the 5 mm slices correlated with those of the 1 mm slices. Moreover, we found that the correlation of fractal D for the 5 mm slices was higher with that for the 1 mm slices than with LAA %. Compared with LAA% of the 1 mm slices, the LAA% for the 5 mm slices seemed underestimated.

LAA in each CT slice is the number of pixels or voxels (or a figure that converts them to an area) below the threshold Housefiled Unit (HU), while LAA% is the ratio to the total lung area in that slice. It is well-known, as described above, that various factors, such as the type of CT equipment, imaging conditions, and reconstruction kernel, among others, can directly influence the CT value and LAA. Fractal D, on the other hand, is a "dimension" that measures the number and size of LAA clusters, and is calculated by displaying the size of a certain threshold cluster (X) and the cumulative frequency of clusters with a size greater than X (Y) in logarithmic form. In other words, fractal D is the value that expresses the relationship between the size and number of clusters rather than evaluating the absolute CT value in those voxels. We think, therefore, that fractal "D" is unlikely to be affected by the slice thickness as shown in this article. Moreover, Mishima et al. showed that even the LAA% is within normal range in COPD subjects, fractal D in those COPD patients are smaller than those in healthy subjects, and that the D values did not correlate with pulmonary function tests except for diffusing capacity. These findings suggest that D is a sensitive and powerful parameter for the detection of the terminal airspace enlargement that occurs in early COPD. In these situations, we

Table 5 – Multivariate Cox proportional analysis of LTOT in the Kyoto University cohort.

	Model1		Model2		Model3		Model4		Model5	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
fractal D	6.40×10^{-10} (6.37×10^{-14} – 6.45×10^{-6})	<0.001*	2.10×10^{-5} (1.87×10^{-9} - 0.24)	0.024*	0.037 (1.37×10^{-3} – 0.98)	0.049*	4.12×10^{-9} (9.48×10^{-13} – 1.79×10^{-5})	<0.001*	9.52×10^{-11} (1.40×10^{-16} - 6.46×10^{-5})	<0.001*
BMI	1.18 (1.01–1.38)	0.037*								
%DLCO			0.94 (0.89–1.00)	0.045*						
%DLCO/VA					0.95 (0.90–0.99)	0.019*				
RV/TLC							6.21×10^{-3} (3.20×10^{-6} - 12.05)	0.19		
LAA%									0.93 (0.81–1.06)	0.27

Notes. *p < 0.05.

speculate that it is possible that parenchymal destruction is so slight that it does not result in hypoxemia, because of the compensation by ventilation - perfusion re-distribution. This suggests that fractal D is a more reliable parameter to use for clinical studies on conventional CT (not in high-resolution CT). Almost all studies on lung imaging in COPD patients have been performed using thin-slice CT; however, this study suggests that fractal D may replace thin-slice CT examination for the investigation of morphometric complexity during thick-slice CT examination. If this is the case, fractal D may allow us to study the clinical significance of emphysematous lesions in detail without the need for high-resolution CT data. Further detailed validation studies are needed to confirm these speculations.

The relationship between pulmonary function impairment and respiratory failure has been well-explored. It is well known that hypoxemia is more closely related to diffusion impairment than to obstructive impairment [3]. However, pulmonary function tests are effort-dependent and sometimes impossible to perform in some patients who cannot follow instructions, because of symptoms such as cough and dyspnea, or poor comprehension. With some patients with poor pulmonary function being prone to respiratory failure. In addition, pulmonary function tests are sometimes inappropriate for patients with aneurysms. Coronavirus disease 2019 (COVID-19) has had a significant impact on clinics globally. Given that there have been many asymptomatic cases recorded, medical examinations that induce aerosol production, such as spirometry, can result in in-hospital outbreaks through aerosol transmission. In comparison with pulmonary function tests, CT images are relatively easier to obtain with less concern for aerosol transmission. Since CT examination is a common diagnostic imaging method used in Japan, the investigation of fractal D in lung CT may be an alternative to lung function tests in situations where pulmonary function tests are difficult to perform.

This study has limitations: (1) Although we believe fractal D is a good index to correlate with LTOT initiation, the fractal D may not be calculable using all CT analysis software. However, the principle of calculating fractal D is simple, with there being no particular restrictions on CT image acquisition methods. We hope that this analysis will become available in many facilities. (2) The whole-lung CT data of the Nara Medical University cohort study were analyzed using only thick-slice (5 mm) data. However, the Kyoto cohort thin-slice (0.5 mm) whole-lung data, which are assumed to be more suitable for detailed image analysis, were evaluated, and similar results were reproduced. We have also shown that fractal D in thick slices or thin slices (1 mm) captured every 5 mm for the whole-lung data was predictive of LTOT initiation. (3) In the Nara Medical University cohort study, the population was relatively small. Therefore, we could not perform multivariate analysis. However, univariate analysis showed similar results for the Nara Medical University and the Kyoto University cohorts, and multivariate analysis showed that DLCO (or % DLCO, %DLCO/VA) and fractal D were predictive of LTOT initiation. Thus, we believe that fractal property is a reliable parameter associated with LTOT initiation. (4) The reasons for LTOT initiation were not precisely evaluated in this study. A majority of patients receiving LTOT had chronic respiratory

failure; however, some may have had other conditions, such as secondary pulmonary hypertension, heart failure, and marginal hypoxia during sleep and/or exercise. A larger study is needed to clarify these issues.

In conclusion, we have shown that fractal D of LAA clusters in lung imaging is predictive of LTOT initiation in patients with COPD, and is probably independent of lung function.

Conflict of Interest

S.M. received honoraria from Boehringer Ingelheim Japan, AstraZeneca Japan, and Novartis Japan. K.S. received funding from LIXIL Corp.; KYOCERA Corp.; ENDO Lighting Corp.; and KANEKA Corp.

Acknowledgments

This study is partially supported by grants-in-aid for scientific research (C) (20K08573, 16K09536, 25461156) (no. C20K08573).

REFERENCES

[1] GOLD2020 Report. https://goldcopd.org/gold-reports/.
[2] Rodriguez-Roisin R, Drakulovic M, Rodriguez DA, Roca J, Barbera JA, Wagner PD. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. J Appl Physiol 2009;106:1902–8. https://doi.org/10.1152/japplphysiol.00085.2009.
[3] Uemasu K, Sato S, Muro S, Sato A, Tanabe N, Hasegawa K, et al. Annual decline in arterial blood oxygen predicts the development of chronic respiratory failure in COPD with mild hypoxaemia: a 6-year follow-up study. Respirology 2019;24:262–9. https://doi.org/10.1111/resp.13402.
[4] Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med 1980;93:391–8.
[5] Stuart-Harris C. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema: report of the Medical Research Council Working Party. Lancet 1981;1:681–6.
[6] Jacobs SS, Krishnan JA, Lederer DJ, Ghazipura M, Hossain T, Tan A-YM. Home oxygen therapy for adults with chronic lung disease: an official american thoracic society clinical practice guideline. Am J Respir Crit Care Med 2020;202:e121–41. https://doi.org/10.1164/rccm.202009-3608ST.
[7] Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. Am J Respir Crit Care Med 2000;162:1102–8. https://doi.org/10.1164/ajrccm.162.3.9907120.
[8] Fuseya Y, Muro S, Sato S, Tanabe N, Sato A, Tanimura K, et al. Complementary regional heterogeneity information from COPD patients obtained using oxygen-enhanced MRI and chest CT. PloS One 2018;13:e0203273. https://doi.org/10.1371/journal.pone.0203273.
[9] Mishima M. Fractal analysis of emphysema in X-ray CT and simulation. Med imaging Technol 2000;18:179–86.
[10] Tanabe N, Muro S, Hirai T, Oguma T, Terada K, Marumo S, et al. Impact of exacerbations on emphysema progression in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2011;183:1653–9. https://doi.org/10.1164/rccm.201009-1535OC.
[11] Shimizu K, Tanabe N, Tho NV, Suzuki M, Makita H, Sato S, et al. Percent low attenuation volume and fractal dimension of low attenuation clusters on CT predict different long-term outcomes in COPD. Thorax 2020:1–7. https://doi.org/10.1136/thoraxjnl-2019-213525. 0.
[12] The JRS guidelines for the management of chronic obstructive pulmonary disease. 5th ed. 2018. https://www.jrs.or.jp/modules/guidelines/index.php?content_id=112.
[13] Tanimura K, Sato S, Fuseya Y, Hasegawa K, Uemasu K, Sato A, et al. Quantitative assessment of erector spinae muscles in patients with chronic obstructive pulmonary disease. Novel chest computed tomography-derived index for prognosis. Ann Am Thorac Soc 2016;13(3):334–41.
[14] Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452–8. https://doi.org/10.1038/bmt.2012.244.
[15] Tanabe N, Muro S, Sato S, Oguma T, Sato A, Hirai T. Fractal analysis of low attenuation clusters on computed tomography in chronic obstructive pulmonary disease. BMC Pulm Med 2018;18:144. https://doi.org/10.1186/s12890-018-0714-5.
[16] Lipson DA, Crim C, Criner GJ, Day NC, Dransfield MT, Dransfield MT, et al. Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2020 Jun 15;201(12):1508–16. https://doi.org/10.1164/rccm.201911-2207OC.
[17] Martinez FJ, Rabe KF, Ferguson GT, Wedzicha JA, Singh D, Wang C, et al. Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/formoterol for chronic obstructive pulmonary disease. A randomized, double-blind, multicenter, parallel-group study. Am J Respir Crit Care Med 2021 Mar 1;203(5):553–64. https://doi.org/10.1164/rccm.202006-2618OC.
[18] Hwang J, Oh Y-M, Lee M, Choi S, Seo JB, Lee SM, et al. Low morphometric complexity of emphysematous lesions predicts survival in chronic obstructive pulmonary disease patients. Eur radiology 2019;29:176–85. https://doi.org/10.1007/s00330-018-5551-7.
[19] Tanabe N, Muro S, Sato S, Oguma T, Sato A, Hirai T. Fractal analysis of low attenuation clusters on computed tomography in chronic obstructive pulmonary disease. BMC Pulm Med 2018;18:144.
[20] Gierada DS, Bierhals AJ, Choong CK, Bartel ST, Ritter JH, Das NA, et al. Effects of CT section thickness and reconstruction kernel on emphysema quantification relationship to the magnitude of the CT emphysema index. Acad Radiol 2010;17:146–56. https://doi.org/10.1016/j.acra.2009.08.007.