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Update of prognosis and characteristics of chronic obstructive pulmonary disease in a real-world setting: a 5-year follow-up analysis of a multi-institutional registry

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Abstract

Background We conducted a prospective observational study to elucidate the long-term prognosis and management of chronic obstructive pulmonary disease (COPD) in clinical practice in Japan in the mid-2010s.

Methods This prospective cohort study included 29 facilities. Data from 427 patients clinically diagnosed with COPD, enrolled between September 2013 and April 2016, were analyzed. Interstitial pneumonia was excluded through a central multidisciplinary discussion. Follow-up data were collected for up to 5 years after patient registration.

Results At the time of registration, 53 patients clinically diagnosed with COPD did not have airflow limitation (AFL). In the cohort with AFL ($n=374$), 232 patients completed a 5-year follow-up, while 49 patients died during the 1576.6 person-years of observation. The mean age was 71.7 years with an overall 5-year survival rate of 85.4%. Stratified by % forced expiratory volume in one second (FEV1), survival rates were 93.6% in the mild and moderate AFL group, 82.5% in the severe AFL group, and 66.1% in the very severe AFL group. The prognosis of the subpopulation without AFL was poor with a 5-year survival of 81.6%. This subpopulation exhibited respiratory symptoms, low vital capacity and total lung capacity, and emphysematous changes.

Conclusions Our study presents the 5-year survival and real-world clinical practice scenario of a prospective cohort of patients clinically diagnosed with COPD in Japan in the mid-2010s. The survival rates of our cohort were numerically better than the Japanese cohort in the 1990s, regardless of the high median age of this cohort. Overall, 12.4% of the patients in this cohort with no AFL at registration exhibited respiratory symptoms and distinct spirometric patterns, and had a poor prognosis.

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Keywords COPD, 5-year survival rate, Normal spirometry, Real-world registry

Background

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, and its incidence is expected to increase [1]. The background characteristics of patients with COPD can evolve over time as a result of shifts in social structures. In particular, aging influences prognosis. The prognosis of COPD has improved with treatment such as long-term oxygen therapy for patients with resting hypoxemia, noninvasive ventilation, and inhaled long-acting muscarinic antagonists (LAMAs), long-acting β_2-agonists (LABAs), and corticosteroids (ICSs) for patients with low pulmonary function and frequent exacerbations [2–5]. Consequently, the prognosis of COPD may change over time, influenced by both changes in patient demographics and advancements in therapeutic strategies. A comparison of two independent cohorts in the 1990s and the mid-2000s revealed that patients with severe COPD in the latter group had a better prognosis [6, 7]. However, there are no data on the prognosis of COPD in real-world settings after 2010 in Japan. Currently, Japan is experiencing the most advanced population aging worldwide, and other countries are predicted to follow soon [8]. Therefore, the Japanese data on COPD prognosis and management can act as a reference for other countries with aging populations, particularly in East Asia.

The diagnosis of COPD requires a forced expiratory volume in one second (FEV1) / forced vital capacity (FVC) < 0.7 post-bronchodilation, signifying airflow limitation (AFL). However, several smokers reportedly experience respiratory symptoms without AFL. Preserved ratio impaired spirometry (PRISm) refers to a decreased FEV1 in patients who do not meet the definition of an obstructive airflow pattern. Patients with PRISm reportedly have a higher mortality than individuals with normal lung function and even mild COPD in community-based observational studies [9–11]. While PRISm has an estimated global prevalence of approximately 10% and is gaining recognition, it is often overlooked in real-world practice [12]. These data highlight the importance of focusing on populations that do not meet the COPD criteria. In this group, which includes smokers with no obstructive impairment, interstitial lung abnormalities have been reported in 8–10% of individuals; previous reports may have included patients with interstitial shadows on CT imaging, which are associated with poor prognosis [13, 14].

This study analyzed data from a multi-center prospective cohort to elucidate the prognosis and treatment of COPD in a real-world setting in the mid-2010s. We also investigated the prognosis and clinical characteristics of patients without AFL clinically diagnosed with COPD, excluding those with comorbid interstitial lung disease.

Methods

Study design

This was a prospective and multi-center observational study of patients with COPD and idiopathic interstitial pneumonia (IIP) from 29 centers who were followed up longitudinally for 5 years. The aim of this study was to investigate the current state of tobacco-related lung disease (COPD and IIP) [15].

Study patients

The main inclusion criteria were age > 20 years and diagnosis of COPD or IIP. The diagnosis of COPD was made by clinicians based on the symptoms and clinical data according to international guidelines [16]. However, no exclusion criteria for pulmonary function tests were established at enrolment and the evaluation of airway reversibility was not mandatory. Patients (regardless of whether newly or previously diagnosed) were sequentially enrolled after a diagnosis of COPD or IIP by a respiratory specialist at the participating facilities. The total planned enrolment number was set at 1000 without sample size calculations. A total of 1024 patients were recruited between September 1, 2013, and April 30, 2016. Of these, eight were subsequently excluded on the basis of patient refusal ($n=4$), missing test results ($n=2$), failure to meet the inclusion criteria ($n=1$), or an unknown reason ($n=1$). The remaining 1016 patients were enrolled in the study. All diagnoses of the enrolled patients were re-evaluated by a central diagnosis committee comprising pulmonologists, subspecialist radiologists, and histopathologists. Cases with combined pulmonary fibrosis and emphysema and interstitial lung abnormality were classified as IIP [17]. After central diagnosis, 461 patients were diagnosed with COPD and 543 patients were diagnosed with IIP [17]. Follow-up surveillance was conducted annually for 5 years to evaluate exacerbation and death. Exacerbation was defined as an increase in shortness of breath, cough, or sputum production, or the onset or worsening of chest discomfort, requiring changes to treatment during the stable phase, as determined by a clinician and based on international criteria [16]. Patients with worsening dyspnea determined by a clinician to be due to other causes, such as bacterial pneumonia, and not associated with a COPD exacerbation, were excluded. The moderate to severe exacerbations of COPD were defined as events requiring the use of systemic steroids or antibiotics. All examinations and investigations were performed as part of routine care for each patient at the

physician's discretion and no additional visits or investigations were mandated for this study.

Pulmonary function tests and CT

Predicted FEV1 and VC were calculated using a reference equation reported by the Japanese Respiratory Society (JRS) in 2001 [18]. Among participants with AFL the severity of air flow obstruction was defined using the predicted FEV1 value, as follows: mild and moderate, FEV1 ≥ 50% of predicted; severe, 30% ≤ FEV1 < 50% of predicted; very severe, FEV1 < 30% of predicted. The predicted total lung capacity (TLC) and residual volume (RV) were calculated using the JRS prediction formula as standard values. To determine the volume of emphysema, the volume of low-attenuation areas (LAA) on 5-mm collimation computed tomography (CT) scans was calculated with a threshold of −910 Hounsfield units as previously described [19]. Dedicated software programs (3DSlicer; http://www.slicer.org) were used to quantify LAA. Total lung capacity by CT (TLCct) was calculated using inspiratory CT, and TLCct–VC was obtained as a surrogate value for RV; the ratio of TLCct–VC to predicted RV was calculated as %RV.

Informed consent

This prospective, multi-center, observational study was approved by the Institutional Review Board of Kyushu University (#25–135, August 23, 2013; #555-00, August 27, 2013) and by the institutional review boards of all participating hospitals. Written informed consent was obtained from all patients.

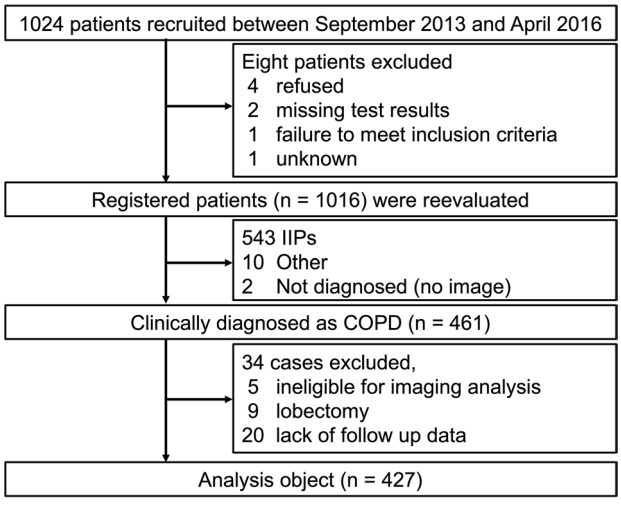

Fig. 1 Flow diagram for the study. COPD, chronic obstructive pulmonary disease

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical analysis

The cumulative survival rate was estimated using the Kaplan–Meier analysis. Hazard ratios (HR) were estimated using a Cox regression model to evaluate the association between background characteristics and survival. In the analysis of 374 patients with AFL, statistical comparisons between groups were made using the mild and moderate AFL group as the reference group. The clinical characteristics of the 53 patients without AFL were evaluated by statistical comparison with mild and moderate AFL group. A backward stepwise method was adopted with the significance level for removal set at 0.05 to select a model to predict survival. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the SAS version 9.4 (SAS Institute, Cary, NC, USA). Explanatory variables that had a long right tail and were suitable for regression on percentage change were logarithmically transformed in the regression analysis.

Results

Study subjects

Between September 2013 and April 2016, 461 patients were diagnosed with COPD by pulmonologists based on clinical data and symptoms and were enrolled in this study. Of these, five with inadequate imaging, nine who underwent lobectomy, and 20 with missing follow-up data after initial enrolment were excluded from the analysis; finally, the data from the remaining 427 patients were analyzed (Fig. 1). The median age of the total population was 72 years, with 87.1% being male, 97.4% having a history of smoking, and 99.5% presenting with more than 5% low attenuation areas (LAAs) on CT imaging. In total, 374 patients (87.6%) in the COPD cohort showed AFL (defined as FEV1/FVC < 70%), while 53 (12.4%) had no AFL. The 374 patients with AFL were categorized into three groups according to %FEV1. The numbers of patients with mild and moderate AFL, severe AFL, and very severe AFL were 197, 112, and 65, respectively (Table 1).

Characteristics of the FEV1/FVC < 70% population

Among the 374 patients with AFL, the most common comorbidity was hypertension, which accounted for 40.4% of all patients. Past history of bronchial asthma accounted for 17.4% of patients with AFL and was more frequent in the severe AFL group. Dyspnea, assessed using the modified Medical Research Council (mMRC) score, was significantly higher in patients with severe and very severe AFL (Table 1). Sputum and weight loss were

Table 1 Baseline characteristics of participants, according to pulmonary function categories at registration

	FEV1/FVC < 70% (AFL)				FEV1/FVC ≥ 70%		Total
	mild and moderate (*N* = 197)	severe (*N* = 112)	very severe (*N* = 65)	Dunnett test*	(*N* = 53)	*P*-value†	
Age (year.), median (IQR)	72 (67–76)	73 (67–78)	71 (65–75)	0.338/0.165	71 (65–78)	0.849	72 (66–77)
Sex, n (%)							
Male	173 (87.8)	94 (83.9)	59 (90.8)	0.536/0.778	46 (86.8)	0.841	372 (87.1)
Female	24 (12.2)	18 (16.1)	6 (9.2)		7 (13.2)		55 (12.9)
BMI(kg/m^2), median (IQR)	22.4 (20.0-24.4)	22.1 (19.7–24.0)	19.6 (17.1–22.2) §	0.399/ < 0.001	21.7 (17.8–24.2)	0.052	21.9 (19.2–24.1)
Smoking (pack-years), median (IQR) ‡	48.0 (30.0–80.0)	50.0 (40.0-72.5)	57.5 (40.0–80.0)	0.985/0.105	48.0 (31.0–80.0)	0.589	50 (36.5–70)
Never, n (%)	4 (2.0)	2 (1.8)	2 (3.1)	0.419/0.616	3 (5.7)	0.174	11 (2.6)
Former, n (%)	138 (70.1)	86 (76.8)	48 (73.8)		39 (73.6)		72.8 (72.8)
Current, n (%)	55 (27.9)	24 (21.4)	15 (23.1)		11 (20.8)		24.5 (24.6)
Past history of Bronchial asthma	27 (13.7)	28 (25.0) §	11 (16.9)	0.020/0.793	5 (9.4)	0.409	71 (16.6)
Comorbidity, n (%)							
Diabetes	27 (13.7)	12 (10.7)	10 (15.4)	0.693/0.923	7 (13.2)	0.925	56 (13.1)
Dyslipidaemia	33 (16.8)	14 (12.5)	5 (7.7)	0.498/0.127	9 (17.0)	0.968	61 (14.3)
Hypertension	81 (41.1)	45 (40.2)	25 (38.5)	0.982/0.909	28 (52.8)	0.127	179 (41.9)
Heart disease	35 (17.8)	18 (16.1)	6 (9.2)	0.902/0.189	11 (20.8)	0.618	70 (16.4)
GERD	13 (6.6)	9 (8.0)	6 (9.2)	0.860/0.726	4 (7.5)	0.808	32 (7.5)

FVC, Forced vital capacity; FEV1, Forced expiratory volume in one second; IQR, Interquartile range; BMI, Body mass index; GERD, Gastroesophageal reflux disease

*: Reference: mild and moderate AFL

†: Chi-square test for nominal scale variables, Wilcoxon rank sum test for continuous variables

‡: Numbers of patients (mild and moderate AFL, severe AFL, very severe AFL, and FEV1/FVC ≥ 70%, respectively) were as follows: Smoking (*N* = 196, 110, 64, 53)

§: $P < 0.05$ with Dunnett's test, Chi-square, or Wilcoxon rank sum test

more frequent in the very severe AFL group, and body mass index was also lower in the very severe AFL group (Table 2). The %VC at registration was preserved in the mild and moderate AFL and severe AFL groups, while it decreased in the very severe AFL group. Additionally, RV/TLC, %RV, and LAA increased with increasing severity of AFL (Table 3). Blood test results showed no significant differences between the groups except for the white blood cell count (Table S1).

Regarding treatment, 86.3% of patients in the mild and moderate AFL group, 96.4% in the severe AFL group, and 98.5% in the very severe AFL group used inhaled drugs. The most commonly used medication were LAMAs. ICSs were used by 37.5% patients in the mild and moderate AFL group, 66.9% patients in the severe AFL group, and 76.9% patients in the very severe AFL group. Home oxygen therapy was used in 58.5% of the very severe AFL. Phosphodiesterase inhibitors are not approved for use in Japan and their usage was not recorded (Table 4).

5-year survival and exacerbation among the FEV1/FVC < 70% population

Among 374 patients with AFL, 232 completed the 5-year follow-up while 49 died during the 1576.6 person-year observation period (Figure S1). The 5-year survival rate of all patients with AFL was 85.4% and specifically, 93.6% in the mild and moderate AFL group, 82.5% in the severe AFL group, and 66.1% in the very severe AFL group (Fig. 2). The HR for mortality adjusted for age, sex, body mass index (BMI), and smoking (pack-year) was 2.43 (95%CI: 1.10–5.37) in the severe AFL group and 7.73 (95%CI: 3.51–17.02) in the very severe AFL group considering the mild and moderate AFL group as a reference (Table S2). The prognosis of the AFL group was evaluated based on the ADO index, which is a simple and validated prognostic assessment established in 2009 [20]. The point estimates for 3-year survival were better than the original report, with 100% for those with an ADO score of 0–2 points, 98.2% for those with 3–4 points, 89.3% for those with 5–6 points, and 63.6% for those with 7–10 points (Figure S2 and Table S3). The most common cause of death was respiratory disease other than lung cancer, accounting for 46.9% of all deaths, with the frequency increasing in the groups with lower %FEV1. Deaths associated with lung and non-lung cancer malignancies each accounted for 8.2% of all deaths. In contrast, cardiovascular death occurred in only two cases (Table 5). A total of 283 events were moderate to severe exacerbations. The percentages of patients with at least one moderate to severe exacerbation and more than two exacerbations in five years were as follows: 8.6% and 4.0% in the mild and moderate AFL group, 30.4% and 11.6% in the severe

Table 2 Baseline symptom and performance status according to pulmonary function categories at registration

	FEV1/FVC < 70%				FEV1/FVC ≥ 70%	
	mild and moderate (*n* = 197)	severe (*n* = 112)	very severe (*n* = 65)	Dunnett test*	(*n* = 53)	*P*-value†
mMRC score, n (%) ‡		§	§	< 0.001/ < 0.001		0.686
0	22 (15.1)	6 (5.8)	1 (1.8)		6 (14.3)	
1	71 (48.6)	32 (31.1)	13 (22.8)		21 (50.0)	
2	38 (26.0)	36 (35.0)	12 (21.1)		6 (14.3)	
3	13 (8.9)	18 (17.5)	20 (35.1)		9 (21.4)	
4	2 (1.4)	11 (10.7)	11 (19.3)		0 (0.0)	
Symptom, n (%)						
Cough	92 (46.7)	59 (52.7)	39 (60.0)	0.516/0.119	34 (64.2)	0.024
Sputum	83 (42.1)	47 (42.0)	39 (60.0) §	0.999/0.023	28 (52.8)	0.164
Body weight loss	5 (2.5)	9 (8.0)	18 (27.7) §	0.150/<0.001	4 (7.5)	0.098
Wheeze	11 (5.6)	8 (7.1)	9 (13.8)	0.846/0.054	2 (3.8)	1.000
Clubbed fingers	20 (10.2)	11 (9.8)	4 (6.2)	0.993/0.552	3 (5.7)	0.427
PS, n (%)		§	§	< 0.001/ < 0.001		0.316
0	90 (45.7)	24 (21.4)	13 (20.0)		22 (41.5)	
1	96 (48.7)	68 (60.7)	28 (43.1)		24 (45.3)	
2	10 (5.1)	15 (13.4)	16 (24.6)		7 (13.2)	
3	1 (0.5)	5 (4.5)	7 (10.8)		0 (0.0)	
4	0 (0.0)	0 (0.0)	1 (1.5)		0 (0.0)	

FVC, Forced vital capacity; FEV1, Forced expiratory volume in one second; IQR, Interquartile range; mMRC, Modified Medical Research Council; PS, Performance Status

*: Reference: mild and moderate AFL group

†: Chi-square test for nominal scale variables, Wilcoxon rank sum test for ordered categorical variables

‡: Numbers of patients (mild and moderate AFL, severe AFL, very severe AFL, and FEV1/FVC ≥ 70%, respectively) were as follows: mMRC (*N* = 146, 103, 57, 42)

§: $P < 0.05$ with Dunnett's test, Chi-square or Wilcoxon rank sum test

AFL group, and 63.1% and 35.4% in the very severe AFL group, respectively (Table S4).

Prognostic factors for mortality of FEV1/FVC < 70% population

The predictors of mortality in patients with FEV1/FVC < 70% were examined using a simple Cox regression analysis of baseline factors (Table S5). In multivariate Cox regression analysis (stepwise variable selection), age, number of comorbidities, performance status, weight loss, C-reactive protein level, and % RV were independently associated with mortality (Table S6).

Characteristics of patients without airflow limitation

In the present cohort, 53 patients (12.4%) had a FEV1/FVC ≥ 70% at the time of enrolment. This population was also analyzed retrospectively for mortality and clinical characteristics. The 5-year survival rate in this population was 81.6%, which was significantly lower than that of the mild and moderate AFL group (adjusted HR of 2.94 with a 95% CI of 1.16–7.42) and similar to that of the severe AFL group (Fig. 2 and Table S2).

No differences in age, sex, smoking prevalence, and respiratory symptoms were found between patients with an FEV1/FVC ≥ 70% and the mild and moderate AFL group. The group with FEV1/FVC ≥ 70% had a lower VC and TLC, and certain area of LAAs. Treatment in the group with FEV1/FVC ≥ 70% was similar to that of the mild and moderate AFL group, with 84.9% of patients using an inhaler at registration (Tables 1, 2, 3 and 4). In the group with FEV1/FVC ≥ 70%, 43.5% showed obstructive impairment after one year. Conversely, 17 out of 339 patients (5.0%) in the AFL group had an FEV1/FVC ≥ 70% (Table S7).

Discussion

We conducted a 5-year survival analysis of a cohort of patients with a clinical diagnosis of COPD. Our study demonstrated that, despite the progressively aging population in Japan, the prognosis of patients with COPD has improved over time. Moreover, 12.4% of the patients clinically diagnosed with COPD had no AFL, and their prognosis was poorer than that of patients with mild and moderate AFL.

This prospective study included 374 patients with AFL at registration and elucidated the management of COPD in clinical practice and its prognosis in Japan in the mid-2010s. Our cohort exhibited a high prevalence of male

Table 3 Baseline CT and pulmonary function test of participants, according to pulmonary function categories at registration

	FEV1/FVC < 70%				FEV1/FVC ≥ 70%	
	mild and moderate (*n* = 197)	severe (*n* = 112)	very severe (*n* = 65)	Dunnett test*	(*n* = 53)	*P*-value†
LAA (%), median (IQR)	43.5 (33.7–53.1)	49.2 (40.5–57.7) §	62.8 (55.6–69.0) §	0.004/<0.001	34.9 (27.8–51.0)	0.014
TLC (L), median (IQR)	5.21 (4.43–5.89)	5.13 (4.30–5.98)	5.66 (5.24–6.56) §	0.751/<0.001	4.68 (3.86–5.38)	0.006
%TLC (%), median (IQR)	97.4 (85.5-108.5)	98.9 (88.3-109.9)	109 (99.2-120.3) §	0.951/<0.001	87.5 (77.6-102.2)	0.001
VC (L), median (IQR) ‡	3.40 (2.85–3.88)	2.64 (2.10–3.07) §	2.13 (1.88–2.60) §	< 0.001/<0.001	3.02 (2.35–3.40)	< 0.001
%VC (%), median (IQR)‡	100.6 (89.0-111.1)	80.5 (70.7–89.5) §	65.8 (55.9–75.4) §	< 0.001/<0.001	86.8 (72.2–95.0)	< 0.001
FVC (L), median (IQR)	3.25 (2.75–3.81)	2.39 (1.98–2.95) §	1.80 (1.43–2.22) §	< 0.001/<0.001	2.82 (2.12–3.19)	< 0.001
FEV1 (L), median (IQR)	1.79 (1.51–2.16)	1.00 (0.85–1.17) §	0.61 (0.51–0.69) §	< 0.001/<0.001	2.10 (1.81–2.45)	< 0.001
%FEV1 (%), median (IQR)	68.3 (58.6–81.1)	40.5 (35.3–45.0) §	23.0 (19.9–25.5) §	< 0.001/<0.001	82.8 (71.3–92.7)	< 0.001
RV/TLC (%), median (IQR) ‡	35.9 (27.3–42.3)	46.6 (41.7–55.1) §	61.8 (56.9–67.8) §	< 0.001/<0.001	36.9 (27.0–48.0)	0.182
%RV (%), median (IQR) ‡	100.2 (76.8-119.7)	132.7 (116.5-151.5) §	177.9 (163.3-191.6) §	< 0.001/<0.001	108.2 (77.5-128.9)	0.132

FVC, Forced vital capacity; FEV1, Forced expiratory volume in one second; IQR, Interquartile range; VC, Vital capacity; TLC, Total lung capacity; RV, Residual volume; LAA, Low attenuation area

*: Reference: mild and moderate AFL group

†: Wilcoxon rank sum test

‡: Numbers of patients (mild and moderate AFL, severe AFL, very severe AFL, and FEV1/FVC ≥ 70%, respectively) were as follows: VC, %VC, RV/TLC and %RV/TLC (*N* = 197, 111, 64, 53)

§: $P < 0.05$ with Dunnett's test or Wilcoxon rank sum test

Table 4 Baseline treatment of participants, according to pulmonary function categories at registration

	FEV1/FVC < 70%			FEV1/FVC ≥ 70%		
	mild and moderate (*n* = 197)	severe (*n* = 112)	very severe (*n* = 65)	Dunnett test *	(*n* = 53)	*P*-value †
Medication, n (%)						
No	18 (9.1)	4 (3.6)	1 (1.5)	0.159/0.080	7 (13.2)	0.097
Yes	179 (90.9)	108 (96.4)	64 (98.5)		46 (86.8)	
Inhaler treatment				< 0.001/<0.001		0.478
No inhaler, n (%)	27 (13.7)	4 (3.6)	3 (4.6)		8 (15.1)	
ICS, n (%)	1 (0.5)	0 (0.0)	1 (1.5)		0 (0.0)	
LABA or LAMA, n (%)	58 (29.4)	13 (11.6)	4 (6.2)		13 (24.5)	
ICS + LABA or LAMA, n (%)	25(12.7)	25(22.3)	8(12.3)		11(20.8)	
LABA/LAMA, n (%)	39 (19.8)	22 (19.6)	8 (12.3)		12 (22.6)	
Treatment other than inhaler						
Theophylline, n (%)	25 (12.7)	26 (23.2)	31 (47.7) §	0.058/<0.001	5 (9.4)	0.393
Macrolide, n (%)	11 (5.6)	10 (8.9)	8 (12.3)	0.500/0.162	3 (5.7)	1.000
LTRA, n (%)	9 (4.6)	19 (17.0) §	10 (15.4) §	0.001/0.020	7 (13.2)	0.0504
Tulobuterol tape, n (%)	1 (0.5)	3 (2.7)	0 (0.0)	0.147/0.921	1 (1.9)	0.380
HOT, n (%)	7 (3.6)	20 (17.9) §	38 (58.5) §	< 0.001/<0.001	3 (5.7)	0.446

FVC, Forced vital capacity; FEV1, Forced expiratory volume in one second; IQR, Interquartile range; ICS, Inhaled corticosteroid; LABA, Long-acting beta-antagonist; LAMA, Long-acting muscarinic antagonist; LTRA, Leukotriene receptor antagonist; HOT, Home oxygen therapy

*: Reference: mild and moderate AFL group

†: Chi-square test or Fisher's exact test for nominal scale variables, Wilcoxon rank sum test for ordered categorial variables and continuous variables

§: $P < 0.05$ with Dunnett's test, or Chi-square test

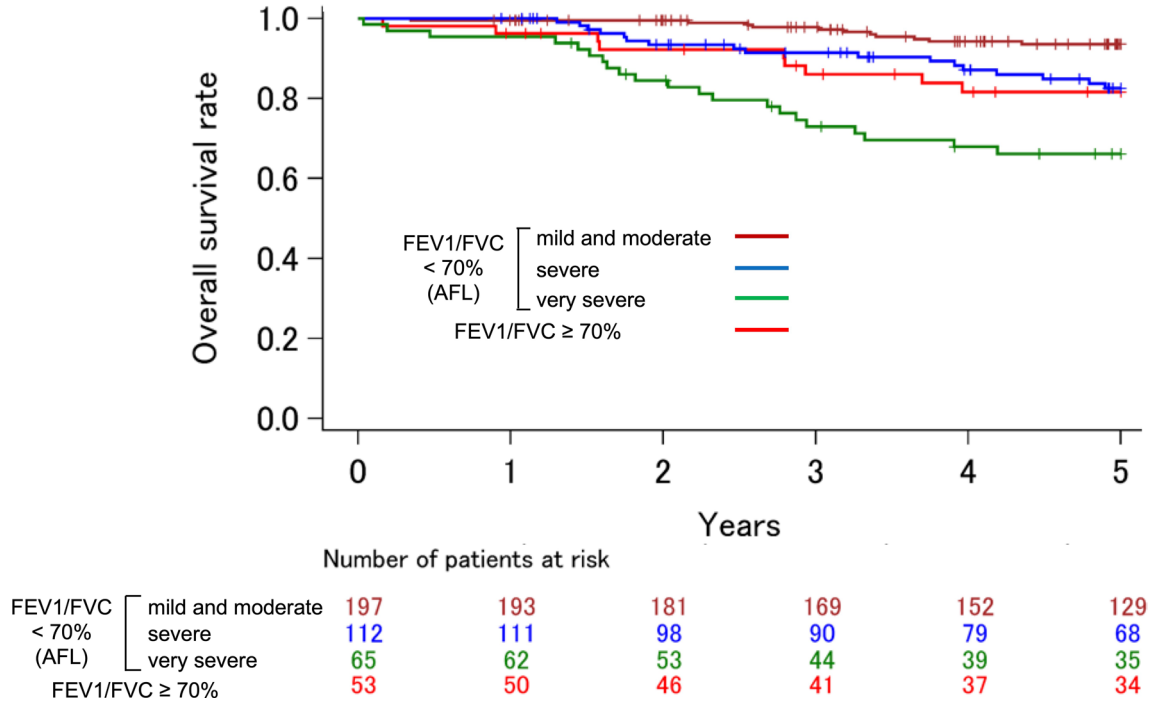

Fig. 2 Kaplan–Meier plots of survival probability according to baseline lung function categories. FVC, forced vital capacity; FEV1, forced expiratory volume in one second

Table 5 Cause of death of participants, according to pulmonary function categories at registration

	FEV1/FVC < 70%			FEV1/FVC ≥ 70%	Total
Cause of death	**mild and moderate (*n* = 197)**	**severe (*n* = 112)**	**very severe (*n* = 65)**	**(*n* = 53)**	**(*n* = 427)**
All-cause, n (%)	11	17	21	9	58
Respiratory disease, n (%)	4 (36.4)	7 (41.2)	12 (57.1)	2 (22.2)	25 (43.1)
Lung cancer, n (%)	2 (18.2)	2 (11.8)	0 (0.0)	2 (22.2)	6 (10.3)
Cancer other than lung cancer, n (%)	0 (0.0)	2 (11.8)	2 (9.5)	2 (22.2)	6 (10.3)
Non-respiratory infection, n (%)	1 (9.1)	1 (5.9)	0 (0.0)	1 (11.1)	3 (5.2)
Cardiovascular disease, n (%)	1 (9.1)	1 (5.9)	0 (0.0)	0 (0.0)	2 (3.4)
Others, n (%)	0 (0.0)	2 (11.8)	3 (14.3)	0 (0.0)	5 (8.6)
Unknown, n (%)	3 (27.3)	2 (11.8)	4 (19.0)	2 (22.2)	11 (19.0)

FVC, Forced vital capacity; FEV1, Forced expiratory volume in one second

patients and low BMI, consistent with previous Japanese reports [21–23]. Life expectancy in Japan increased from 79.6 to 83.9 years in the 20 years between 1995 and 2015, as observed in other countries [8]. Thus, the mean age of our cohort was 71.7 years, with approximately 20% being over 80 years of age, representing the real-world scenario in Japan, which is characterized by a super-aging society. In the 1990s, a prospective study in Japan with a mean age of 68.7 years reported 5-year survival rates of approximately 90% for patients with 50 ≤ %FEV1, 80% for patients with 30 ≤ %FEV1 < 50, and 60% for patients with %FEV1 < 30 [24]. The 5-year survival rates of the severe AFL group (82.5%) and very severe AFL groups (66.1%) in our cohort were numerically better than the Japanese cohort in the 1990s, regardless of the high median age, and the survival rates evaluated using the ADO score were also favorable. The improved prognosis of this cohort may be attributed to advancements in treatment and healthcare. In our study, 90.9% of patients AFL used an inhaler and 53.2% of patients with AFL used ICS. The high prevalence of ICS use may be attributed to the recommendations set out in the 2013 guidelines for patients with COPD. These guidelines recommend the concurrent use of ICS in patients with %FEV1 below 50 or those experiencing frequent exacerbations [16]. Furthermore, this cohort included patients with a history of bronchial asthma. Nonetheless, the exacerbation rate was low in our cohort. Lower exacerbation rates have been reported

in the Japanese population, suggesting potential ethnic differences in exacerbation frequencies [25]. The most common causes of death were respiratory disease, followed by lung cancer and other malignancies, which is consistent with to previous reports in Japan [26]. Notably, there were only two cases of cardiovascular death. In western countries, cardiovascular deaths are reported to account for 20–30% of total deaths [27], while in Japan, cardiovascular deaths have been reported to be as low as 11% [26]. Racial differences may contribute to the lower incidence of exacerbations and cardiovascular deaths in this cohort.

In this cohort, 12.4% patients did not have AFL but were treated as having COPD and had a poor prognosis. In addition to respiratory-related deaths, cancer-related deaths were also frequently observed. The majority of this population had a history of heavy smoking, 35.7% had dyspnea on exertion with an mMRC≥2, and 52.8% had a wet cough. On examination, VC and TLCct were low and FEV1 was preserved with a certain extent of emphysema. At the time of registration, 86.8% of this population underwent respiratory treatment. In the SPIROMICS and COPDGene studies, two large longitudinal observational studies, 23–50% of current and former smokers with normal spirometry had respiratory symptoms, and 20–42% underwent treatment interventions [28, 29]. Similarly, a meta-analysis showed that approximately one-fourth of patients treated for COPD in primary healthcare settings did not show obstructive impairment on spirometry [30]. Consistent with these studies, our study highlights the presence of a population with respiratory symptoms that clinicians treat as COPD, even without AFL, in the real-world setting. Patient with PRISm reportedly have a higher mortality than those with normal lung function and even mild COPD in community-based observational studies [9–11]. However, these studies did not exclude interstitial pneumonia. It has been reported that approximately 8–10% of smokers exhibit interstitial lung abnormalities, with a higher prevalence observed particularly in cases without airflow limitation [13, 14]. A unique aspect of this cohort is that we demonstrated poor prognosis in cases clinically diagnosed with COPD after excluding interstitial pneumonia. Respiratory symptoms and the extent of emphysema are associated with poor prognosis, even in smokers without AFL [31–34]. Populations with restrictive spirometric patterns have higher mortality rates [31, 35, 36]. Therefore, the poor prognosis in the FEV1/FVC≥70% group may be attributed to the considerable rate of respiratory symptoms, imaging abnormalities, and low VC, all of which are reportedly associated with mortality. Therefore, our study suggests the importance of multidimensional evaluation of patients with respiratory symptoms, including pulmonary function tests and imaging.

Some longitudinal observational studies have reported that approximately 10% of patients with obstructive patterns in pulmonary function tests become free of obstructive patterns after annual follow-up [9–11]. Therefore, it is possible that some patients in the FEV1/FVC≥70% group in this cohort met the definition of COPD at the time of diagnosis. Interestingly, in the one-year follow-up of lung function, 43.5% of patients in the FEV1/FVC≥70% group exhibited obstructive impairment, while 17 out of 339 cases (5.0%) in the AFL group had an FEV1/FVC≥70%. Although it has been reported that lung function can change over long-term observation, the significant variability observed in a short period of time is instructive. Further investigation is needed to determine whether individuals with phenotypes characterized by fluctuations in lung function have a poor prognosis [9, 10, 37].

The following limitations of this study should be acknowledged: some of the enrolled patients were not newly diagnosed with COPD, lung function was not confirmed at the time of diagnosis, and the time of diagnosis was not recorded. Airway reversibility assessment, six-minute walk tests and DLCO measurements were optional, and as a result, indices such as the BODE index could not be calculated. Additionally, the health-related quality of life and physical activity were not assessed. Moreover, only patients who provided informed consent, and not consecutive patients, were enrolled. Finally, despite the execution of annual protocolized assessments, some data were missing.

Conclusions

This study presents the 5-year survival and real-world clinical practice data of a prospective cohort of patients clinically diagnosed with COPD in Japan in the mid-2010s. The high survival rates in our cohort were numerically better than the Japanese cohort in the 1990s, regardless of the high median age of the participants. Overall, 12.4% of the patients in this cohort did not show AFL at registration and exhibited respiratory symptoms and distinct spirometric patterns, and had a poor prognosis.

Abbreviations

COPD	Chronic obstructive pulmonary disease
MDD	Multidisciplinary discussion
FEV1	Forced expiratory volume 1 s
FVC	Forced vital capacity
AFL	Airflow limitation
PRISm	Preserved ratio impaired spirometry
IIPs	Idiopathic interstitial pneumonias
JRS	Japanese Respiratory Society
TLC	Total lung capacity
RV	Residual volume
LAA	Low attenuation areas
CT	Computed tomography
TLCct	Total lung capacity by CT
HR	Hazard ratio

mMRC	Modified Medical Research Council
LAMA	Long-acting muscarinic antagonist
ICS	Inhaled corticosteroids
HOT	Home oxygen therapy
PS	Performance status
BMI	Body mass index

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

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Author contributions
TT and KT equally contributed to this work. TT, KTsubouchi and IO contributed to the literature search, figures, the study design, data collection, data analysis, data interpretation, and writing approved the final version of the review. NH and YN contributed to the literature search, study design, data collection, and data interpretation and approved the final version of the review. FK and STokunaga contributed to the literature search, figures, data analysis, and writing and approved the final version of the review. KI, RT, STakata, SK, NN, MY, YK, KTobino, EH, HI, HW, TM, MF, KY and MO contributed to the literature search, data collection, and data interpretation and approved the final version of the review. HY contributed to the literature search, data analysis, and writing, and approved the final version of the review. IO accepts full responsibility for the work and/or conduct of the study, has access to the data and controls the decision to publish.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study involves human participants and this prospective, multi-center observational study was approved by the Institutional Review Board of Kyushu University (#25–135, August 23, 2013; #555-00, August 27, 2013) and by the institutional review boards of all participating hospitals. Participants provided informed consent before participating in the study.

Consent for publication
Not applicable since there are no details on individuals reported within the manuscript.

Competing interests
STakata has received personal fees from AstraZeneca, Nippon Boehringer Ingelheim, Novartis, GSK, and Teijin Pharma. KY has received personal fees from Nippon Boehringer Ingelheim, GSK and Teijin Pharma. MO has received personal fees from Nippon Boehringer Ingelheim. IO has received personal fees from AstraZeneca, Nippon Boehringer Ingelheim and Novartis.

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References

1. World Health Organization. The top 10 causes of death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
2. Lipson DA, Crim C, Criner GJ, Day NC, Dransfield MT, Halpin DMG, 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;201:1508–16.
3. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. N Engl J Med. 2020;383:35–48.
4. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. JAMA. 2017;317:2177–86.

5. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005;2005:CD001744.
6. Almagro P, Salvadó M, Garcia-Vidal C, Rodriguez-Carballeira M, Delgado M, Barreiro B, et al. Recent improvement in long-term survival after a COPD hospitalisation. Thorax. 2010;65:298–302.
7. Sato S, Oga T, Muro S, Tanimura K, Tanabe N, Nishimura K, et al. Changes in mortality among patients with chronic obstructive pulmonary disease from the 1990s to the 2000s: a pooled analysis of two prospective cohort studies. BMJ Open. 2023;13:e065896.
8. Health status. https://stats.oecd.org/index.aspx?queryid=24879#. Accessed 6 Nov 2023.
9. Wijnant SRA, De Roos E, Kavousi M, Stricker BH, Terzikhan N, Lahousse L, et al. Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam Study. Eur Respir J. 2020;55:1901217.
10. Wan ES, Hokanson JE, Regan EA, Young KA, Make BJ, DeMeo DL, et al. Significant spirometric transitions and preserved ratio impaired spirometry among ever smokers. Chest. 2022;161:651–61.
11. Washio Y, Sakata S, Fukuyama S, Honda T, Kan-o K, Shibata M, et al. Risks of mortality and airflow limitation in Japanese individuals with preserved ratio impaired spirometry. Am J Respir Crit Care Med. 2022;206:563–72.
12. Huang J, Li W, Sun Y, Huang Z, Cong R, Yu C, et al. Preserved ratio impaired spirometry (PRISM): a global epidemiological overview, radiographic characteristics, comorbid associations, and differentiation from chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2024;19:753–64.
13. Kim SS, Yagihashi K, Stinson DS, Zach JA, McKenzie AS, Curran-Everett D, et al. Visual assessment of CT findings in smokers with nonobstructed spirometric abnormalities in the COPDGene® study. Chronic Obstr Pulm Dis. 2014;1:88–96.
14. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. 2011;364:897–906.
15. Ogata-Suetsugu S, Hamada N, Tsuda T, Takata S, Kitasato Y, Inoue N, et al. Characteristics of tobacco-related lung diseases in Fukuoka Prefecture, Japan: a prospective, multi-institutional, observational study. Respir Investig. 2020;58:74–80.
16. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187:347–65.
17. Tsubouchi K, Hamada N, Tokunaga S, Ichiki K, Takata S, Ishii H, et al. Survival and acute exacerbation for patients with idiopathic pulmonary fibrosis (IPF) or non-IPF idiopathic interstitial pneumonias: 5-year follow-up analysis of a prospective multi-institutional patient registry. BMJ Open Respir Res. 2023;10:e001864.
18. Special Committee of Pulmonary Physiology, the Japanese Respiratory Society. Standard values of spirogram and arterial blood gas in normal Japanese subjects. J Jpn Respir Soc. 2001;39:S1–17.
19. Müller NL, Staples CA, Miller RR, Abboud RT. Density mask. An objective method to quantitate emphysema using computed tomography. Chest. 1988;94:782–7.
20. Puhan MA, Garcia-Aymerich J, Frey M, ter Riet G, Antó JM, Agustí AG, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet. 2009;374:704–11.
21. Ichinose M, Taniguchi H, Takizawa A, Grönke L, Loaiza L, Voß F, et al. The efficacy and safety of combined tiotropium and olodaterol via the Respimat(®) inhaler in patients with COPD: results from the Japanese sub-population of the Tonado(®) studies. Int J Chron Obstruct Pulmon Dis. 2016;11:2017–27.
22. Ichinose M, Nishimura M, Akimoto M, Kurotori Y, Zhao Y, de la Hoz A, et al. Tiotropium/olodaterol versus tiotropium in Japanese patients with COPD: results from the DYNAGITO study. Int J Chron Obstruct Pulmon Dis. 2018;13:2147–56.
23. Fukuchi Y, Fernandez L, Kuo H-P, Mahayiddin A, Celli B, Decramer M, et al. Efficacy of tiotropium in COPD patients from Asia: a subgroup analysis from the UPLIFT trial. Respirology. 2011;16:825–35.
24. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. Am J Respir Crit Care Med. 2003;167:544–9.
25. Ishii T, Nishimura M, Akimoto A, James MH, Jones P. Understanding low COPD exacerbation rates in Japan: a review and comparison with other countries. Int J Chron Obstruct Pulmon Dis. 2018;13:3459–71.
26. Makita H, Suzuki M, Konno S, Shimizu K, Nasuhara Y, Nagai K, et al. Unique mortality profile in Japanese patients with COPD: an analysis from the Hokkaido COPD cohort study. Int J Chron Obstruct Pulmon Dis. 2020;15:2081–90.
27. Williams MC, Murchison JT, Edwards LD, Agustí A, Bakke P, Calverley PMA, et al. Coronary artery calcification is increased in patients with COPD and associated with increased morbidity and mortality. Thorax. 2014;69:718–23.
28. Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JHM, Grenier PA, et al. Clinical and radiologic disease in smokers with normal spirometry. JAMA Intern Med. 2015;175:1539–49.
29. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. N Engl J Med. 2016;374:1811–21.
30. Perret J, Yip SWS, Idrose NS, Hancock K, Abramson MJ, Dharmage SC, et al. Undiagnosed and 'overdiagnosed' COPD using postbronchodilator spirometry in primary healthcare settings: a systematic review and meta-analysis. BMJ Open Respir Res. 2023;10:e001478.
31. Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (gold) classification of lung disease and mortality: findings from the atherosclerosis risk in communities (ARIC) study. Respir Med. 2006;100:115–22.
32. Stavem K, Sandvik L, Erikssen J. Can Global Initiative for Chronic Obstructive Lung Disease Stage 0 provide prognostic information on long-term mortality in men? Chest. 2006;130:318–25.
33. Johannessen A, Skorge TD, Bottai M, Grydeland TB, Nilsen RM, Coxson H, et al. Mortality by level of emphysema and airway wall thickness. Am J Respir Crit Care Med. 2013;187:602–8.
34. Oelsner EC, Hoffman EA, Folsom AR, Carr JJ, Enright PL, Kawut SM, et al. Association between emphysema-like lung on cardiac computed tomography and mortality in persons without airflow obstruction: a cohort study. Ann Intern Med. 2014;161:863–73.
35. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. Thorax. 2010;65:499–504.
36. Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. Thorax. 2003;58:388–93.
37. Wan ES, Fortis S, Regan EA, Hokanson J, Han MK, Casaburi R, et al. Longitudinal phenotypes and mortality in preserved ratio impaired spirometry in the COPDGene study. Am J Respir Crit Care Med. 2018;198:1397–405.

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