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Graduate School of Medicine

Lessons from the Hokkaido COPD cohort study

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COI disclosure

Masaharu Nishimura

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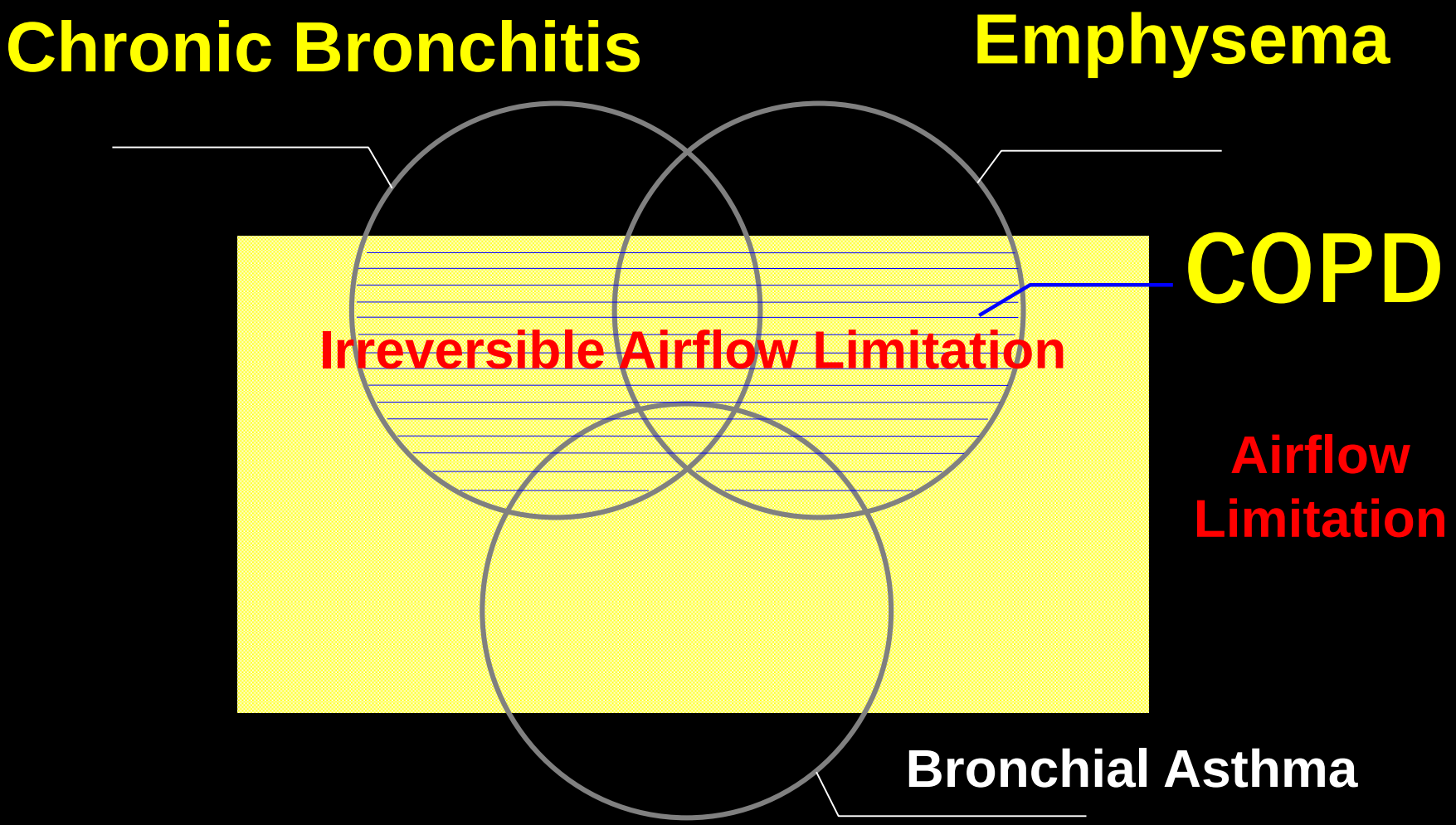
Classic Venn Diagram of COPD



Global Initiative for Chronic Obstructive Lung Disease

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE NHLBI/WHO WORKSHOP REPORT

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Definition of COPD

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

The chronic airflow limitation characteristics of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person

Hokkaido COPD cohort study

Study design: Multi-site, observational cohort study

Subjects: 279 patients with COPD

Institutions: Hokkaido University Hospital and 10 affiliate hospitals

Study period: 10 years (entry: 2003-2005, completed in 2015)

Hokkaido COPD Cohort Study

since 2003

Primary Objective

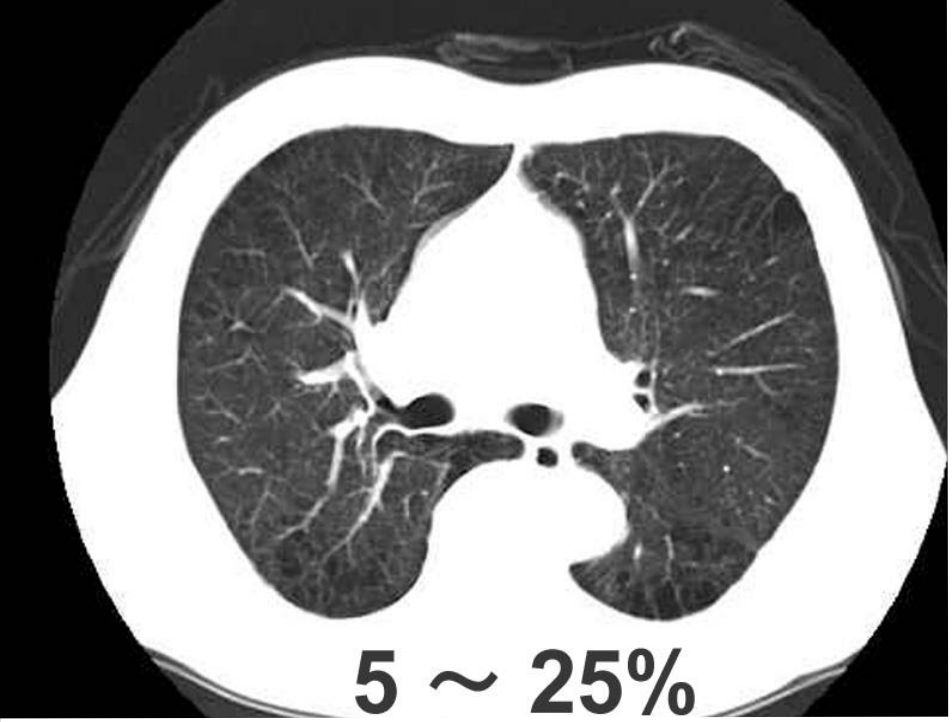
To examine the natural history and the prognosis of COPD according to the phenotype, based on HRCT findings, the reversibility of airflow limitation, and/or other clinical features.

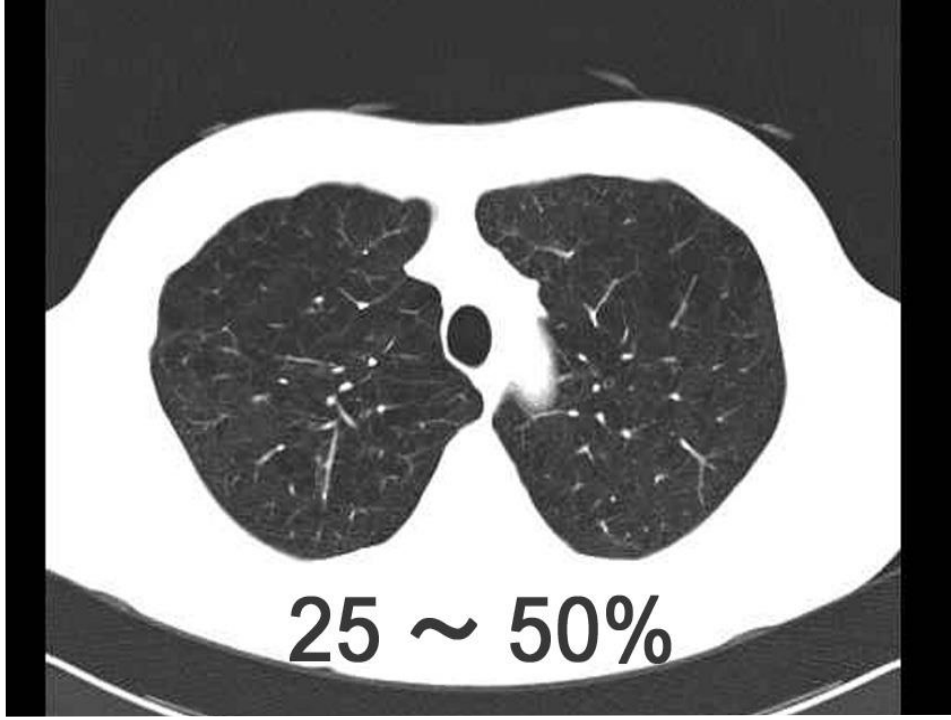
Subjects

- Entry criteria
  - Diagnosis of COPD re-confirmed by respiratory physicians on the basis of GOLD guideline at entry
  - Age 40 years old or older smokers
- Exclusion criteria
  - Patients with clinically diagnosed bronchial asthma
  - Use of supplemental oxygen therapy for >12 hours/day
  - History of lung resection, cancer, tuberculosis, cystic fibrosis, interstitial pneumonitis, or pulmonary fibrosis

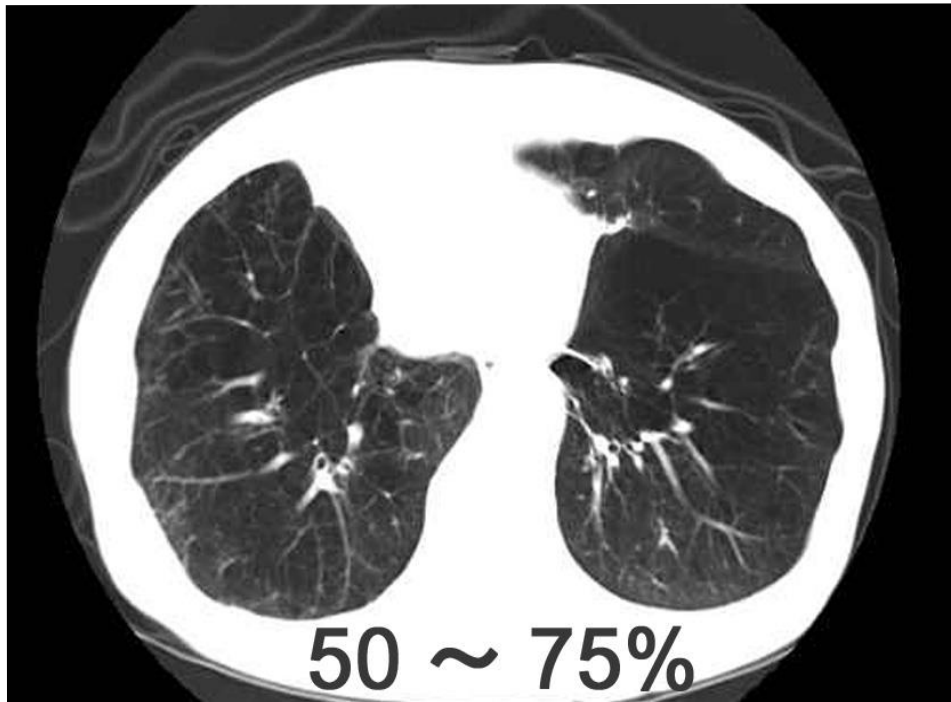
Data Collection

- Demographic information
- Pulmonary function tests
  - Spirometry before and 30 min after inhalation of bronchodilator (salbutamol, 400μg)
  - DLco, lung volumes
- HRCT
- Blood tests: α_1 anti-trypsin, CBC, ESR, CRP, IgE (RIST, RAST)
- Blood for genetic analysis
- Quality of life (SGRQ)
- Exacerbation information

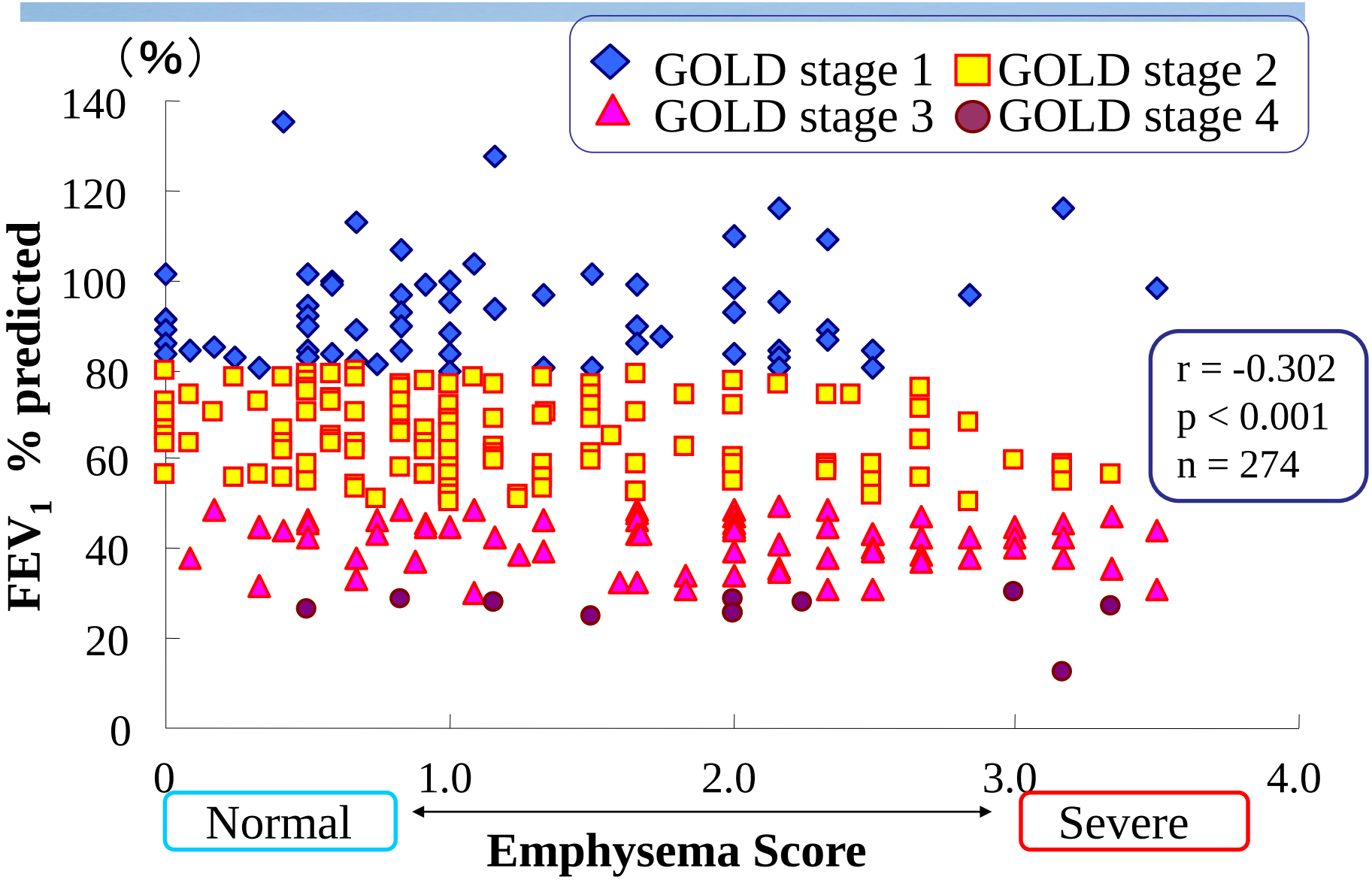




Score	Amount of LAA Involvement
0	0%
0.5	<5%
1	5-25%
2	25-50%
3	50-75%
4	75-100%



Relationship between emphysema and FEV_1



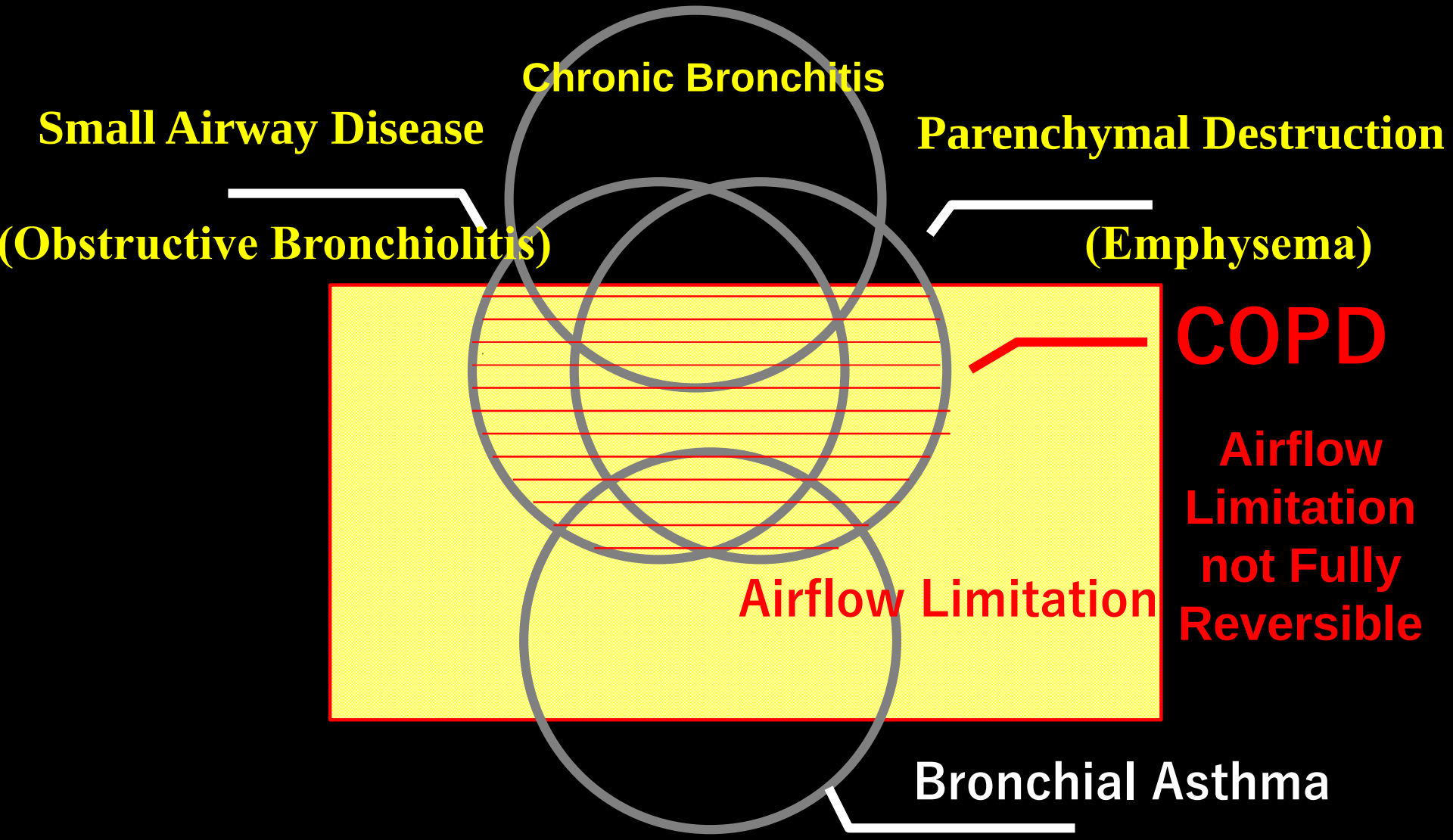
(Makita et al, Thorax 2007)

Chronic Bronchitis Symptoms and Emphysema Severity

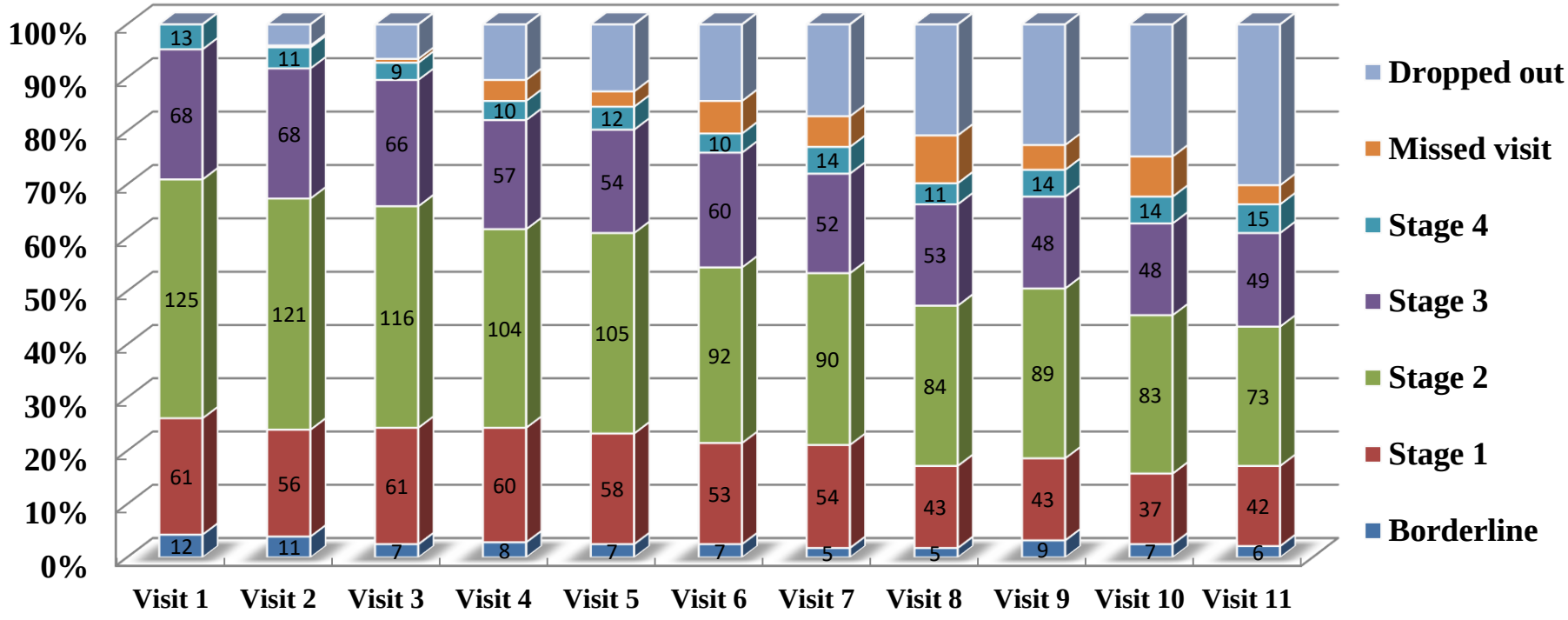
Emphysema Score	Score<1	1≦Score<2.5	Score≧2.5	Total
Chronic Sputum or Cough	19 (28%)	21 (26%)	6 (19%)	46 (26%)
Chronic Sputum and Cough	7 (9%)	12 (13%)	4 (12%)	23 (11%)

Presence of sputum is defined as more than 10 cc/day

New Venn Diagram of COPD

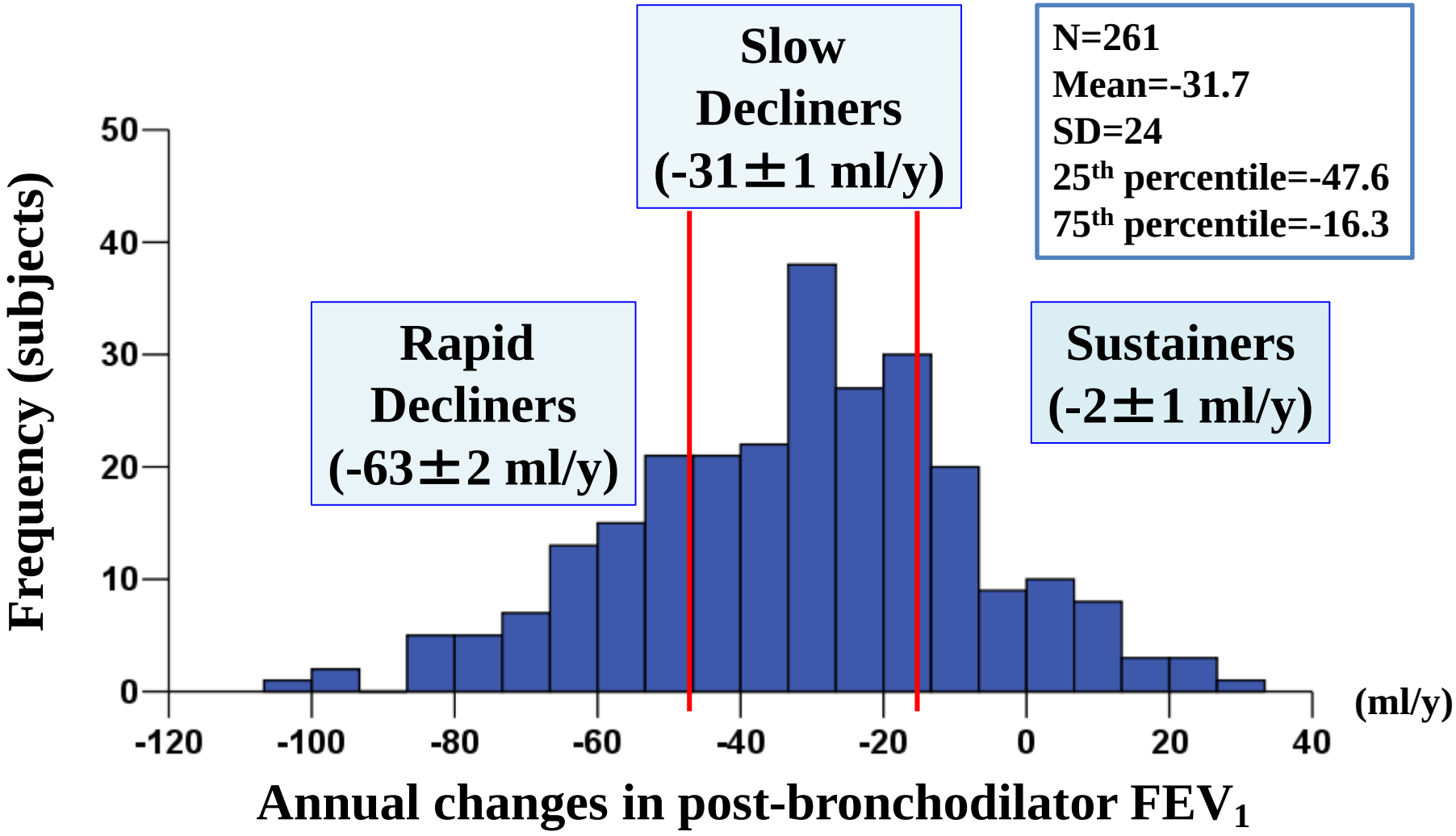


Five-year follow-up rate of the Hokkaido COPD Cohort Study



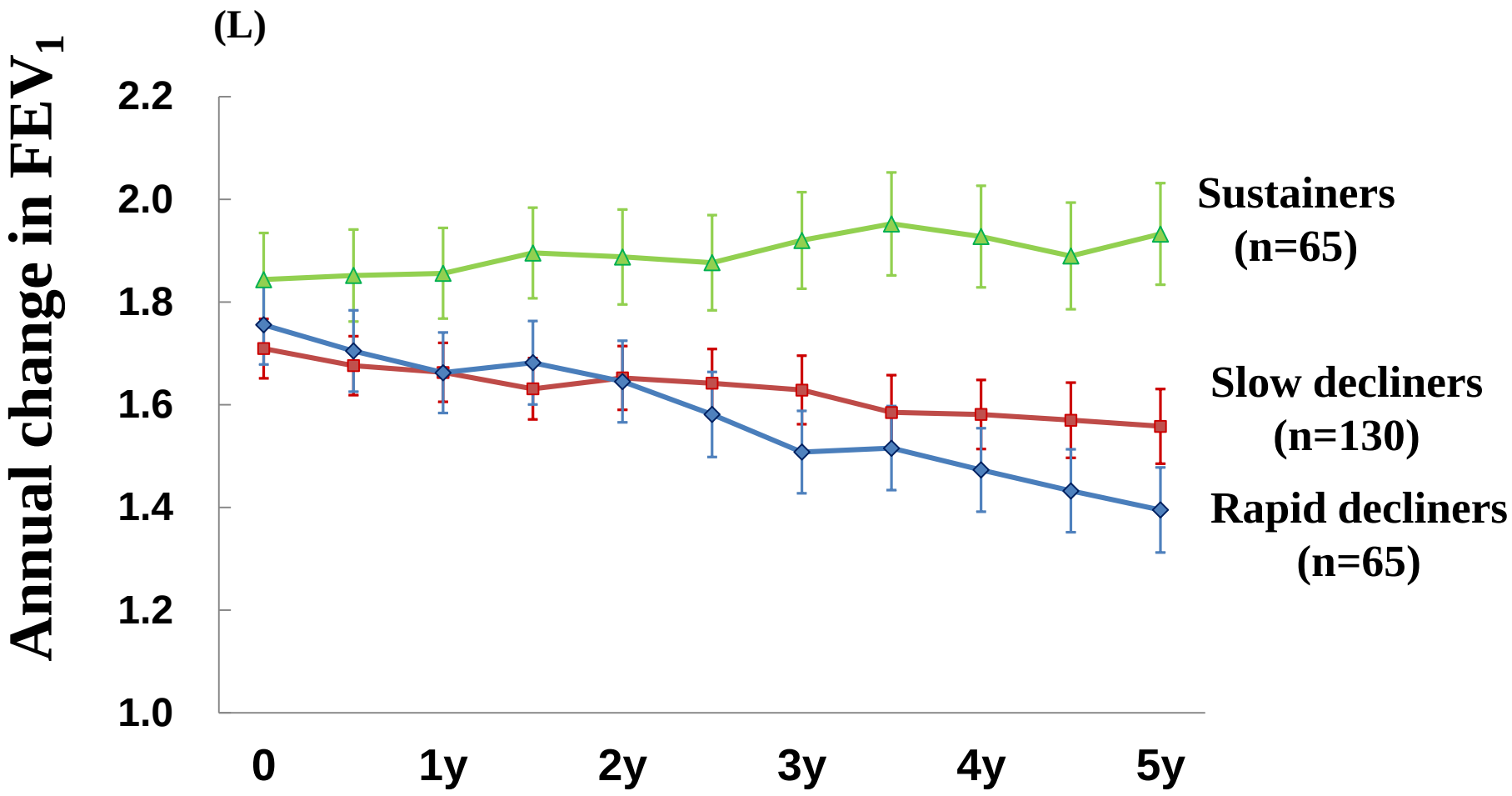
Subjects	279	267	259	239	236	222	215	196	203	189	185
Dropped out	0	11	18	29	35	40	48	58	63	69	84
Died	0	0	5	5	7	10	13	17	23	28	34

Frequency distribution of annual changes in FEV_1 using mixed effects model



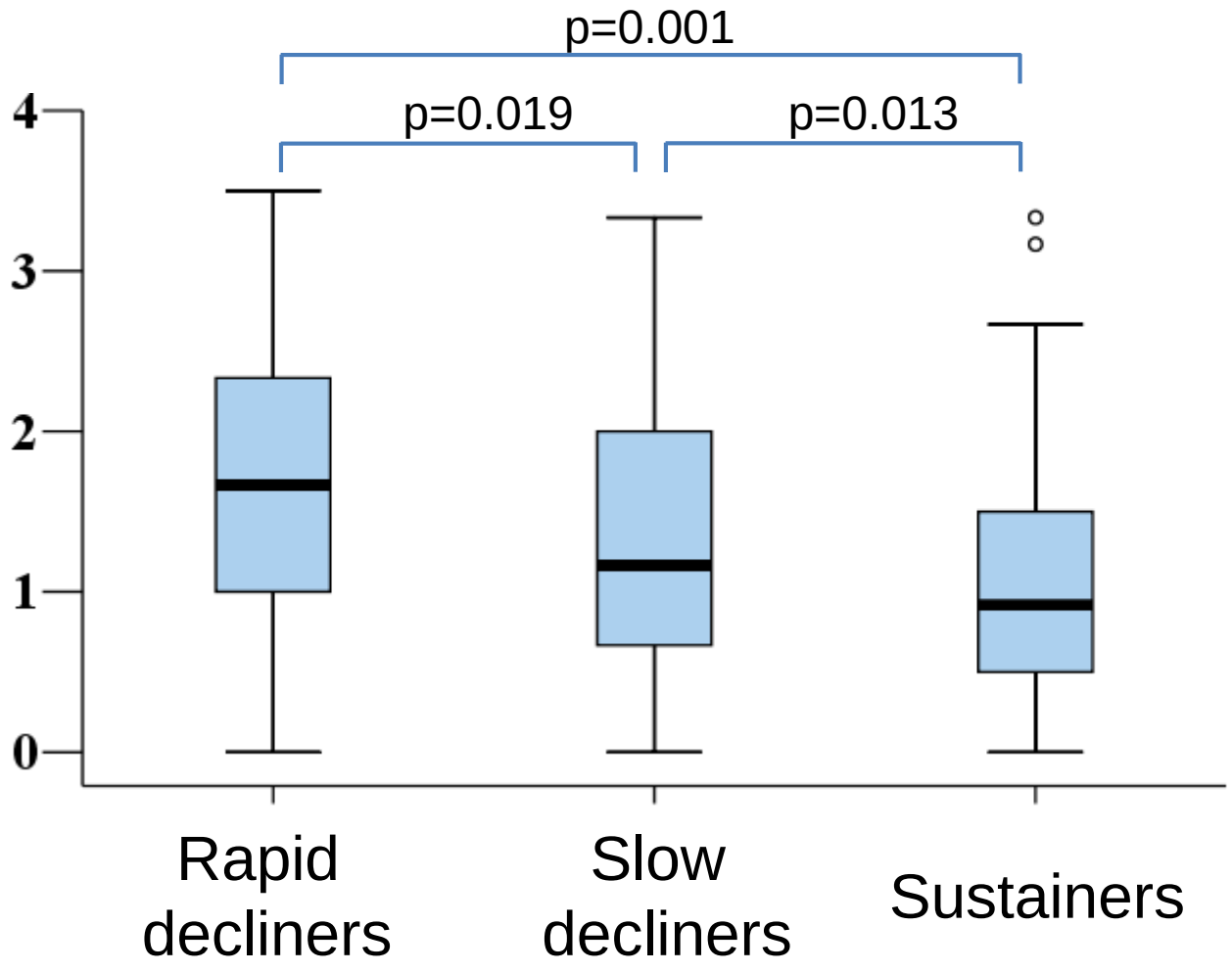
Nishimura M et al, Am J Respir Crit Care Med. 2012

Annual change in FEV_1

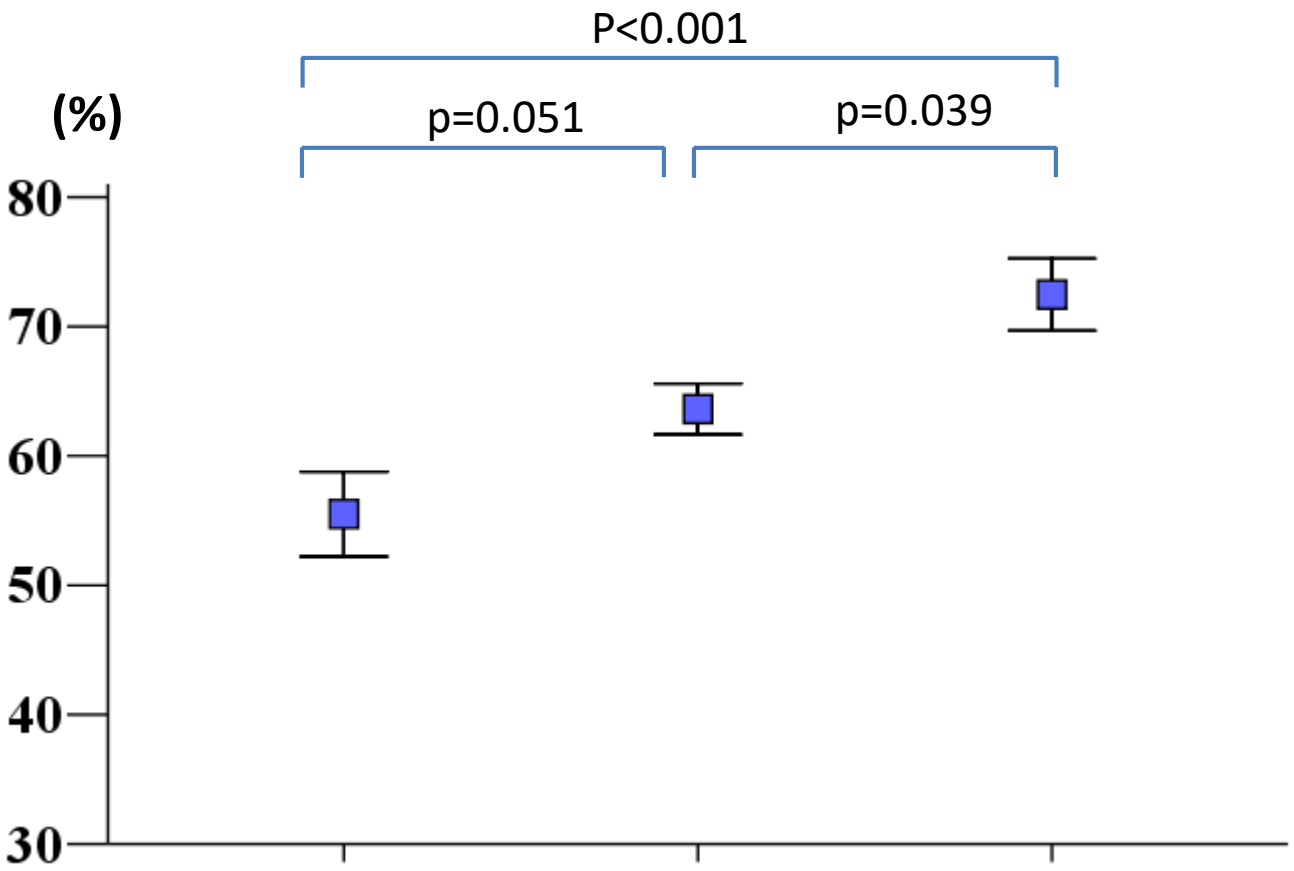


Nishimura M, et al: Am J Respir Crit Care 2012

Emphysema Scores assessed visually



%Kco (DLco/VA)



(mean±SEM, ANOVA with Tukey's test)

Multivariate logistic regression analysis for FEV_1 decline

Rapid decliners vs. Slow decliners

Variable	Odd Ratio	95%CI	P-value
DLco/VA (%)	0.98	0.73 - 0.96	0.014
Blood neutrophils (1×10^3 cells/μL)	1.04	1.01 - 1.07	0.021
Blood eosinophils (1×10^2 cells/μL)	0.98	0.95 - 1.01	0.12
Smoking status	0.70	0.30 - 1.76	0.42
Chronic bronchitis	1.34	0.44 - 4.11	0.61
Age	0.98	0.94 -1.03	0.39
Sex	0.22	0.03 - 1.85	0.16

FEV_1, Reversibility of FEV_1, MRC dyspnea scale, Exacerbation frequency were also included in this model as dependent factors

Multivariate logistic regression analysis for FEV_1 decline
Sustainers vs. Decliners

Variable	Odd Ratio	95%CI	P-value
DLco/VA (%)	1.21	1.06 – 1.38	0.004
Blood neutrophils (1×10^3 cells/μL)	1.01	0.98 - 1.04	0.71
Blood eosinophils (1×10^2 cells/μL)	1.03	1.01 - 1.06	0.013
Smoking status	1.23	0.30 - 1.76	0.42
Chronic bronchitis	2.97	1.24 – 7.12	0.014
Age	0.98	0.94 -1.02	0.29
Sex	1.01	0.27 – 3.72	0.99

FEV_1, Reversibility of FEV_1, MRC dyspnea scale, Exacerbation frequency were also included in this model as dependent factors

Summary

- Annual changes of FEV_1 were varied widely in individuals.
- The subjects with emphysema or the subjects who have low diffusing capacity would be linked with more rapid decline of FEV_1.
- We should pay more attention to those subjects whose FEV_1 is well preserved over years. They may have eosinophilic component in airway inflammation.

Publications from the first 5-year data

- 3D-CT analysis of airways: Hasegawa M, et al. AJRCCM 2006
- Baseline characteristics: Makita H, Thorax 2007
- Significance of gene polymorphisms (ADBR2, CCL5):

  Hizawa N, Chest 2007

  Hizawa N, Eur Respir J 2008

  Konno S, et al. Pharmacogenet Genomics 2011
- Annual FEV_1 change (5 years): Nishimura M, et al. AJRCCM 2012
- Exacerbation: Suzuki M, et al. Eur Respir J 2014
- Blood biomarkers: Suzuki M, et al. Annals ATS 2014
- Health-related QOL: Nagai K, et al. Int J COPD 2015
- Bronchodilator reversibility: Konno S, et al. Respir Med 2016

Hokkaido COPD cohort study

Collecting data for the first 5 years

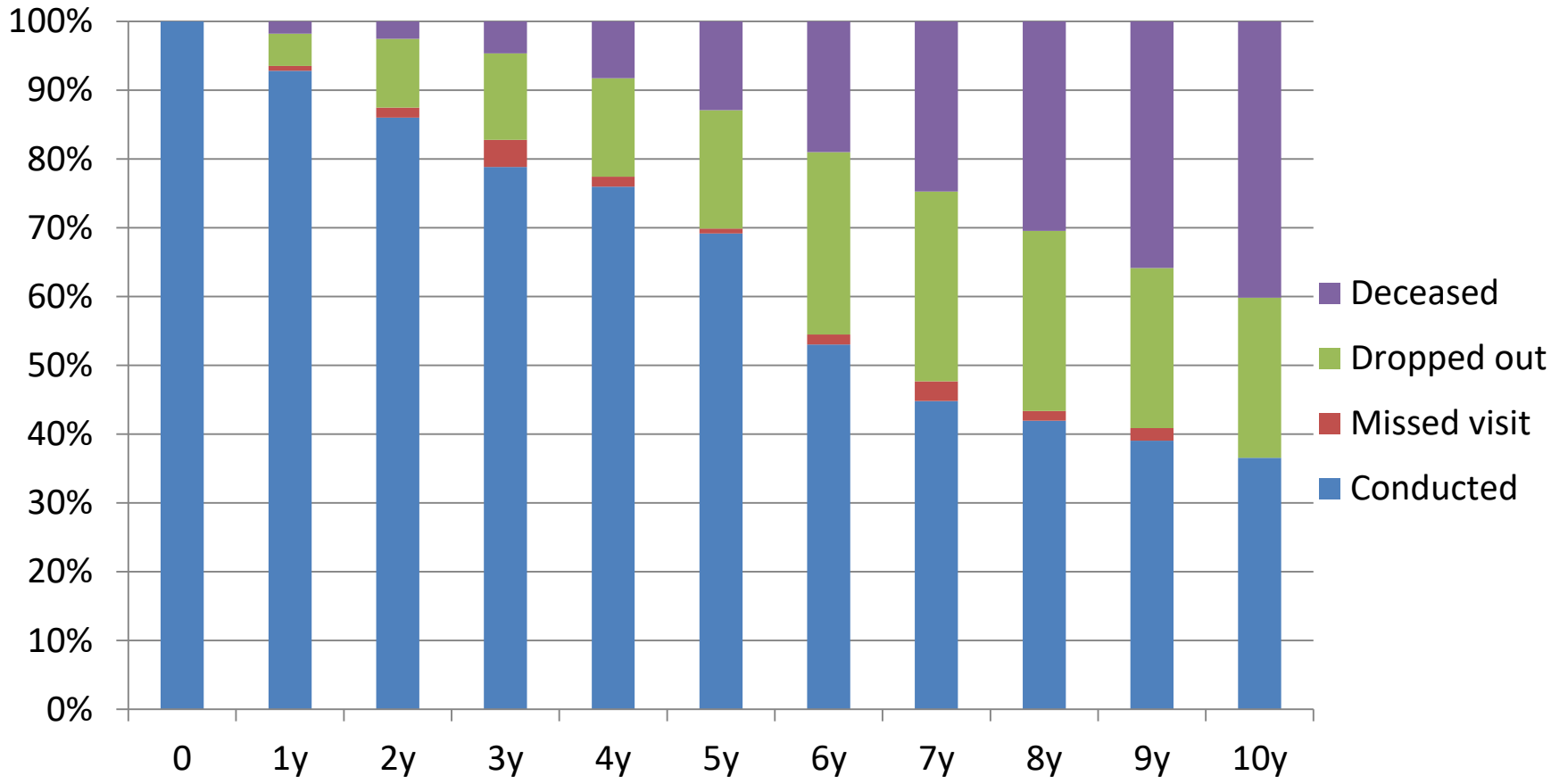
- Pre- and post-bronchodilator spirometry (every 6 months)
- Diffusing capacity (every year)
- Blood test (every year)
- CT scan (every year)
- Health related QOL assessed by SGRQ (every year)
- Exacerbation information (every month by reply postcards)

Collecting data for the last 5 years

- Pre- and post-bronchodilator spirometry (every year)
- Diffusion capacity (every year)
- CT scan (every year) if subjects gave informed consent

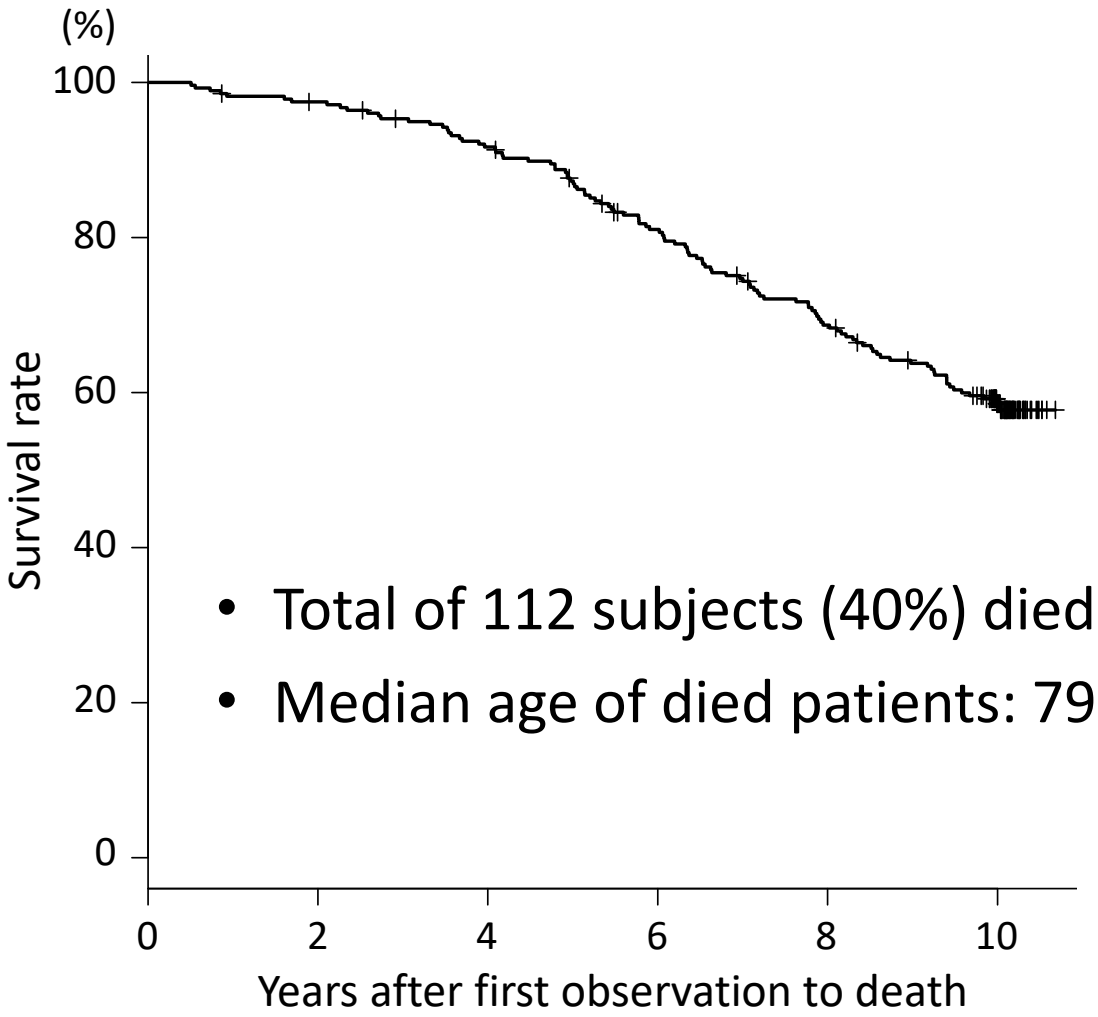
Accurate mortality data: 95% of subjects after 10 years

Follow-up status for 10 years



- About Hokkaido COPD cohort study
- Results from 10-years' follow-up data
  - Mortality
  - Lung cancer development
  - Significance of asthma-like features
  - Annual change in lung function

Survival curve of COPD patients

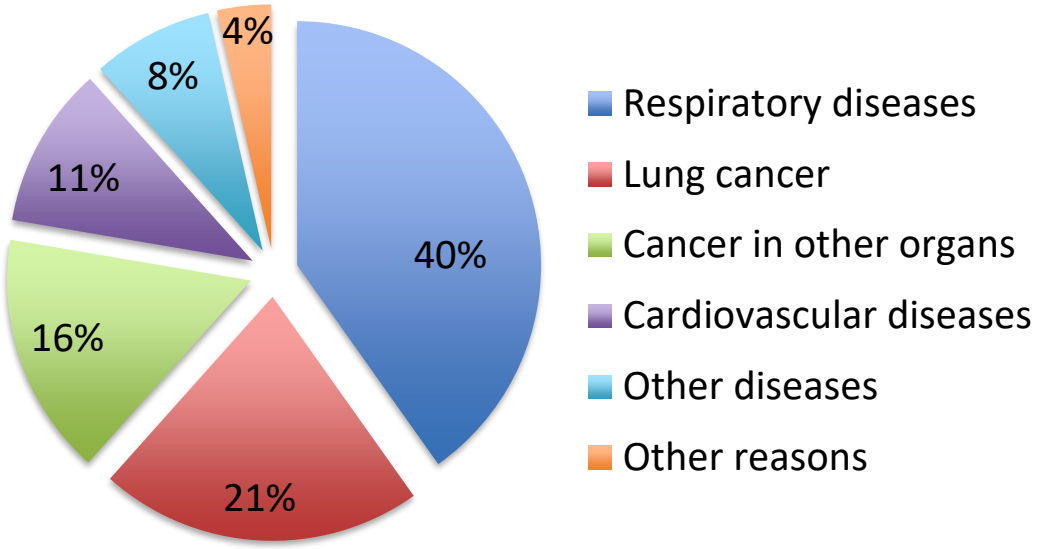


- Total of 112 subjects (40%) died
- Median age of died patients: 79 years old

Almost the same as the average life expectancy for Japanese men
(80.79 years old in 2015)

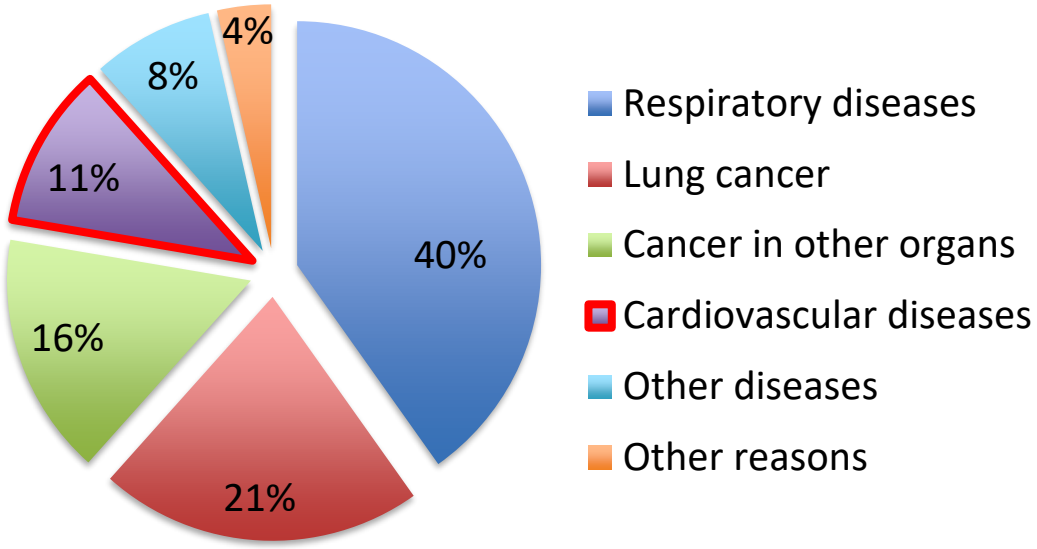
Cause of death

All subjects
(N=112)



Cause of death

All subjects
(N=112)



Death from cardiovascular diseases

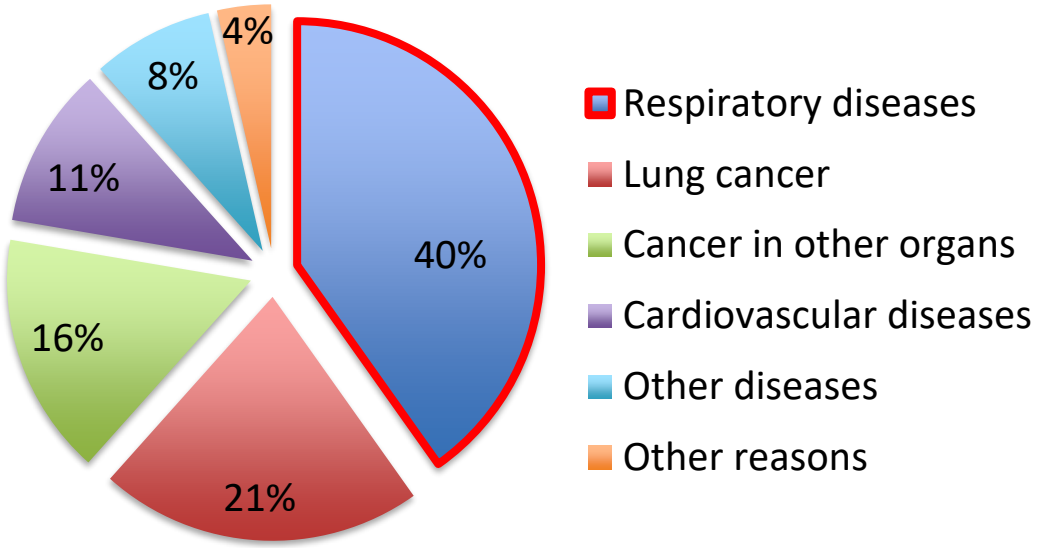
TORCH: 27%

UPLIFT: 19%

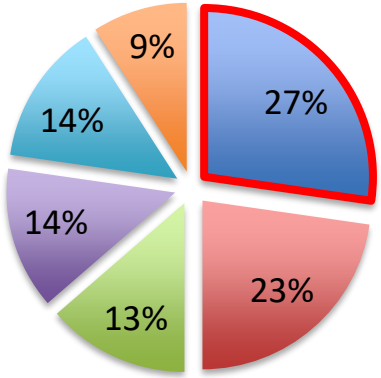
TIOSPIR: 26%

Cause of death

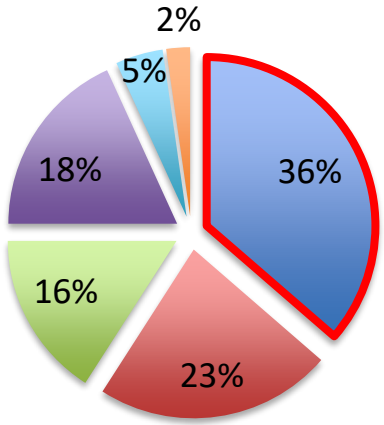
All subjects (N=112)



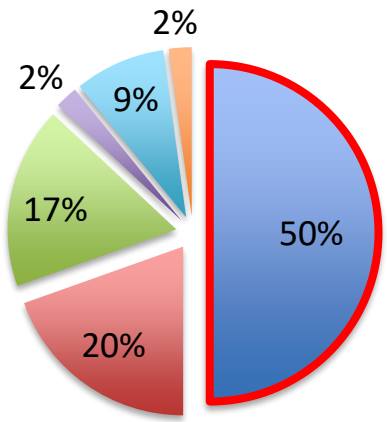
GOLD 1 (N=22)



GOLD 2 (N=44)

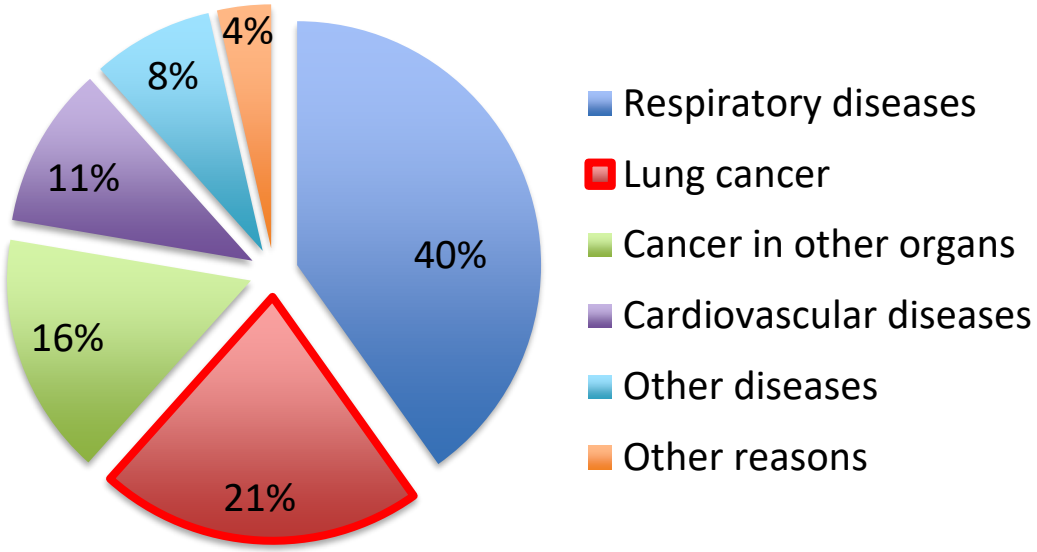


GOLD 3/4 (N=46)

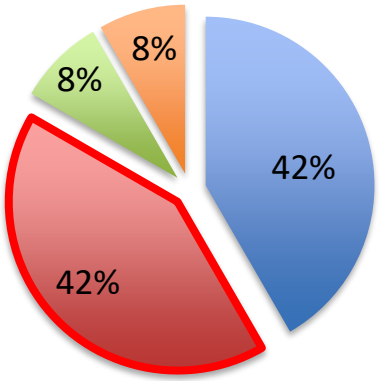


Cause of death

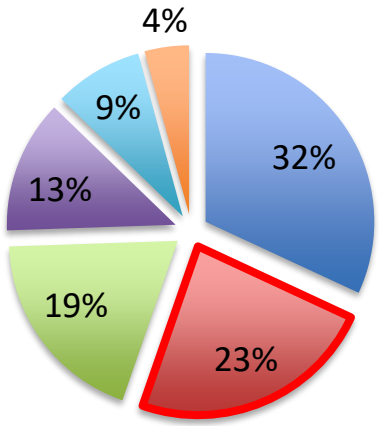
All subjects (N=112)



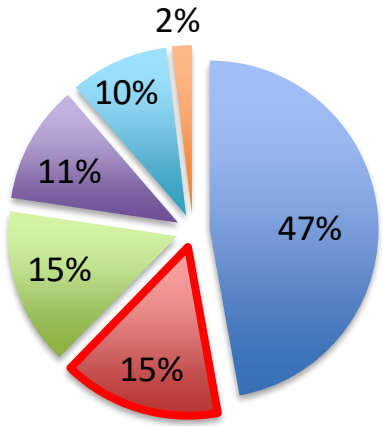
Age ≤64 (N=12)



Age 65-74 (N=47)



Age ≥75 (N=53)



Risk factors for all-cause mortality

	Kco excluded		CT emphysema score excluded	
Baseline variables	Hazard ratio (95%CI)	p value	Hazard ratio (95%CI)	p value
Age (10 years older)	2.99 (2.20-4.08)	<0.001	2.86 (2.11-3.88)	<0.001
BMI (1 kg/m^2 increase)	0.92 (0.86-0.99)	0.02	0.94 (0.87-1.01)	0.09
Pack-years (10 pack-years increase)	0.94 (0.88-1.01)	0.10	0.94 (0.88-1.01)	0.08
Post-BD FEV_1 %predicted (10% increase)			0.93 (0.85-1.02)	0.12
Kco %predicted (10% increase)			0.89 (0.81-0.98)	0.02
CT emphysema score (1 point increase)	1.38 (1.10-1.73)	0.005		

Multivariate stepwise Cox proportional hazards models

Mortality in COPD

- 40% of subjects died during 10 years
- The most frequent cause of death was respiratory diseases followed by lung cancer, whereas cardiovascular diseases were less frequent
- More emphysema and body weight loss were significant risk factors for all-cause mortality

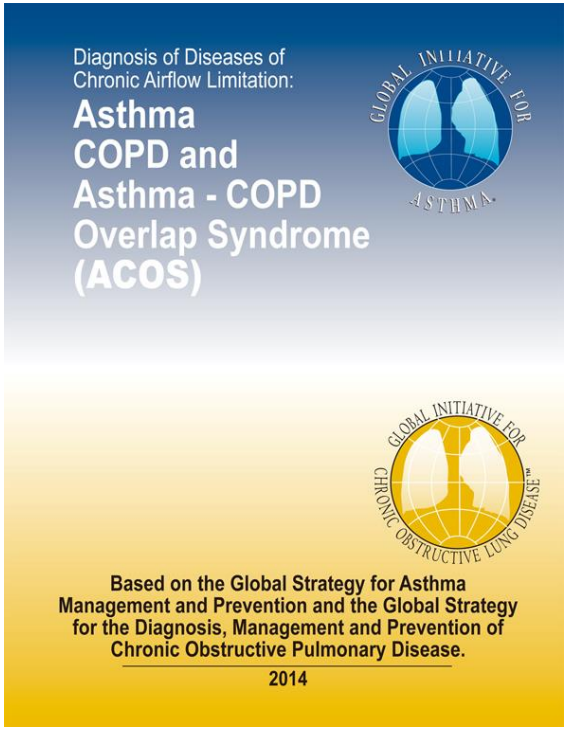
(Unpublished data)

Today's talk

- About Hokkaido COPD cohort study
- Results from 10-years' follow-up data
  - Mortality
  - Lung cancer development
  - Significance of asthma-like features
  - Annual change in lung function

Overlap of COPD and asthma: ACO(S)

- Recently, the term “Asthma–COPD overlap syndrome (ACOS)” has been proposed by a joint project of the GINA and GOLD; however, a formal definition of ACOS has not been established



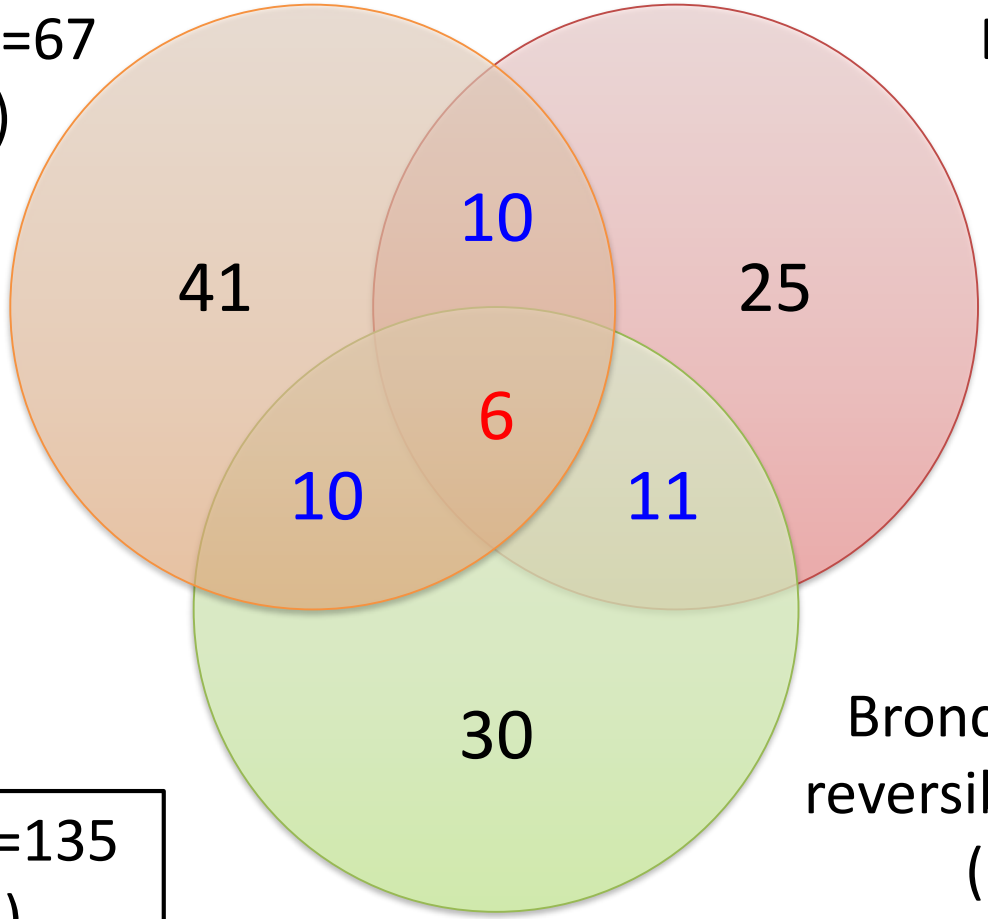
“Patients with features of both asthma and COPD experience...”

- Frequent exacerbations
- Poor QOL
- Rapid decline in lung function
- High mortality

Asthma-like features in COPD

Bronchodilator reversibility	ΔFEV_1 ≥200 mL & ≥12% by SABA (average values from visits 1-3)
Blood eosinophilia	Blood eosinophil count ≥300 /μL at baseline
Atopy	The presence of serum specific IgE to at least one of the 14 common inhaled antigens (MAST-26 assay)

Venn diagram of the three asthma-like features

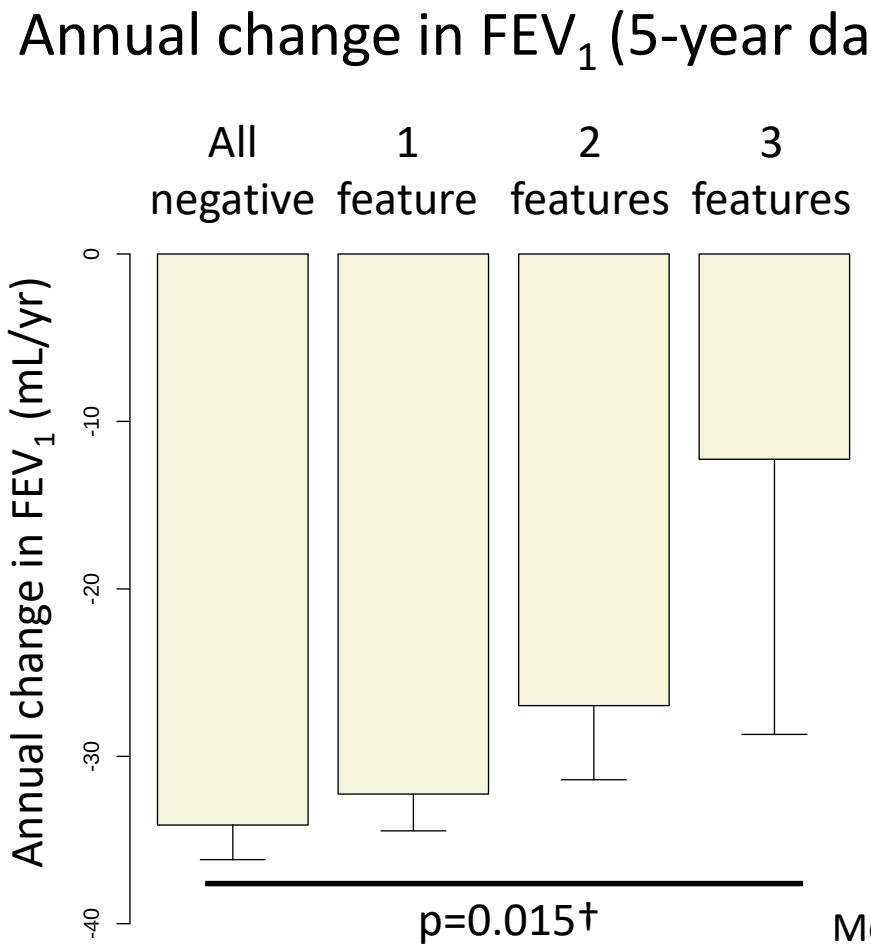


1 feature: N=96
2 features: N=31
3 features: N=6

None: N=135
(50%)

(Suzuki M, et al. Am J Respir Crit Care Med 2016)

Asthma-like features and lung function decline

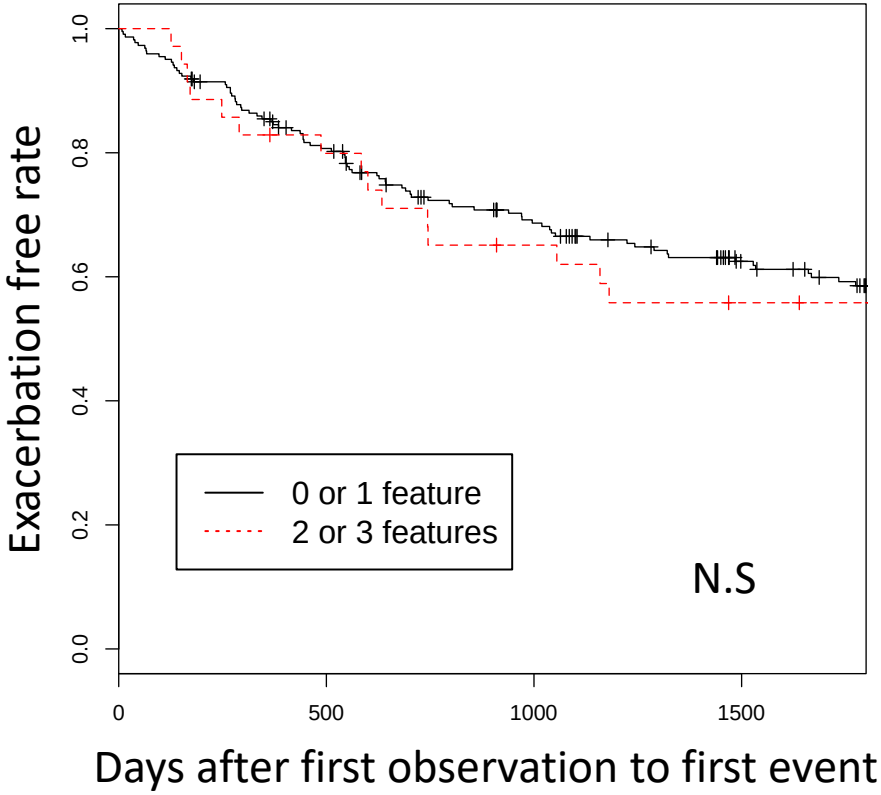


Mean ± SEM
†Jonckheere-Terpstra trend test

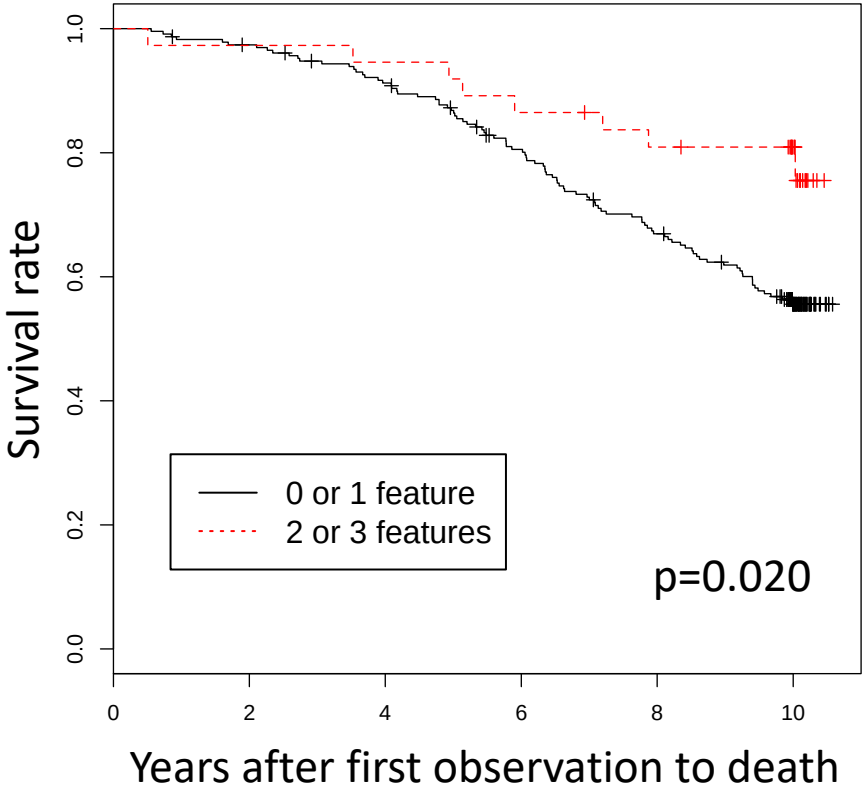
(Suzuki M, et al. Am J Respir Crit Care Med 2016)

Asthma-like features and exacerbation or mortality

COPD exacerbation
(prescription change, 5-year data)



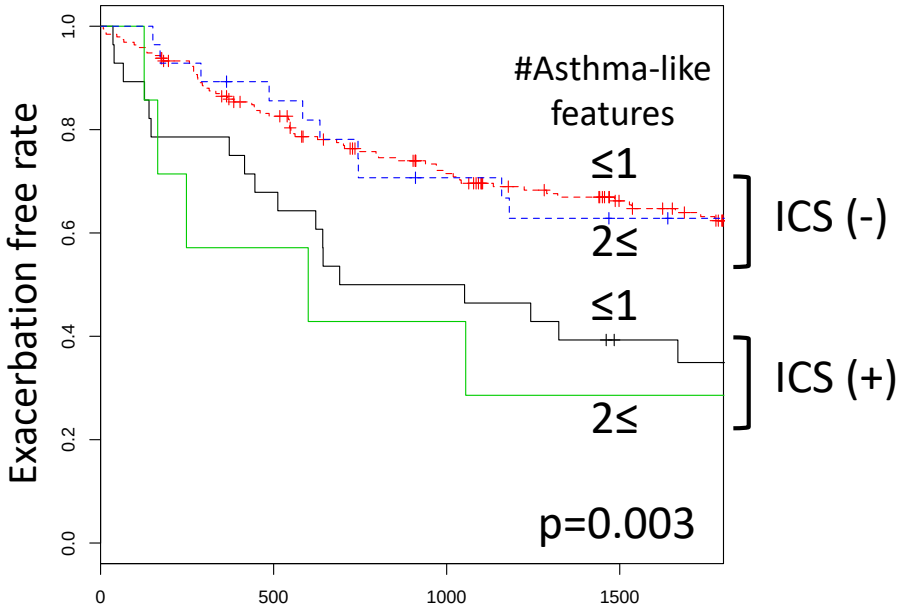
10-year mortality



(Suzuki M, et al. Am J Respir Crit Care Med 2016)

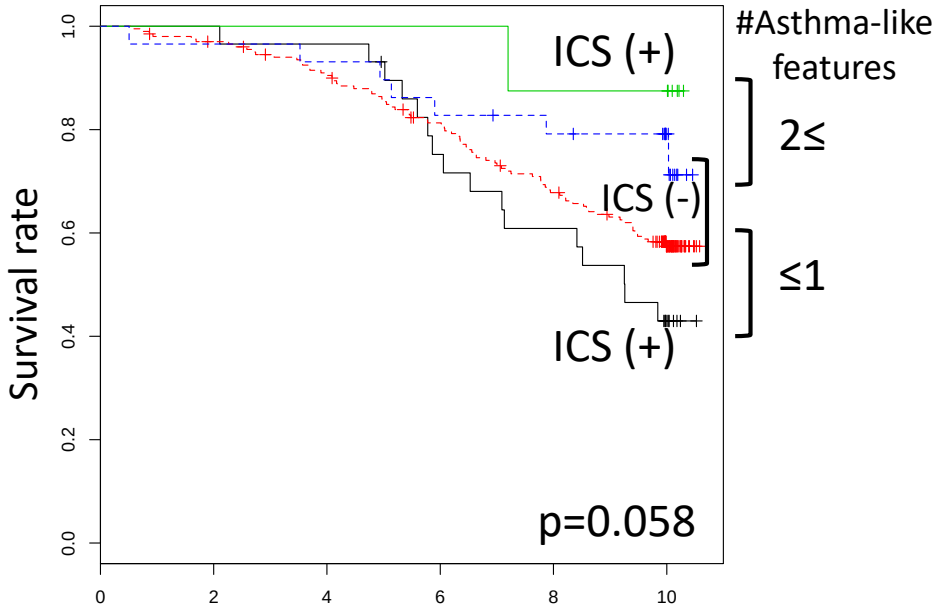
ICS use and exacerbation or mortality

COPD exacerbation
(prescription change, 5-year data)



Days after first observation to first event

10-year mortality



Years after first observation to death

(Suzuki M, et al. Am J Respir Crit Care Med 2016)

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Asthma-like features in COPD

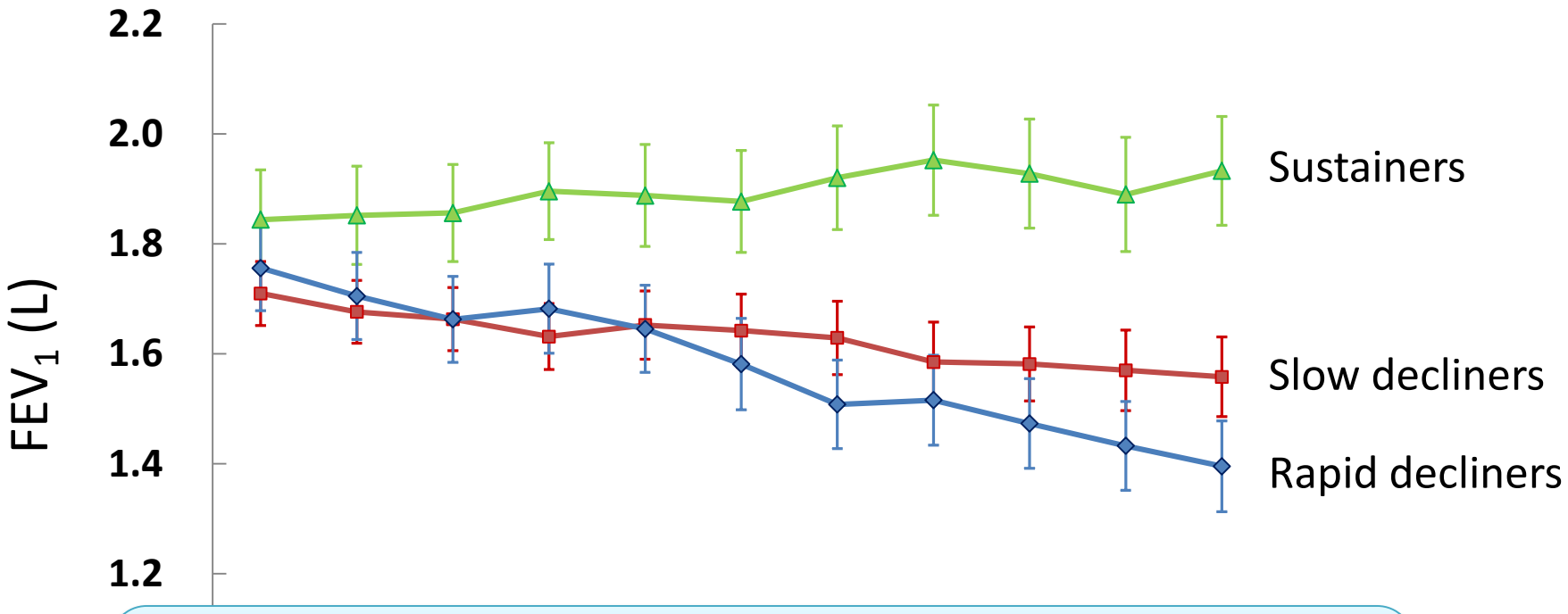
- 50% of subjects had at least one asthma-like feature
- Subjects with multiple asthma-like features had lower 10-year mortality
- Treatment with ICS was associated with lower mortality in subjects with multiple asthma-like features

(Suzuki M, et al. Am J Respir Crit Care Med 2016)

Today's talk

- About Hokkaido COPD cohort study
- Results from 10-years' follow-up data
  - Significance of asthma-like features
  - Lung cancer development
  - Mortality
  - Annual change in lung function

Annual changes in FEV_1



How does the rate of lung function decline become beyond 5 years?

(Nishimura M, et al. Am J Respir Crit Care Med 2012)

Lung function change beyond 5 years

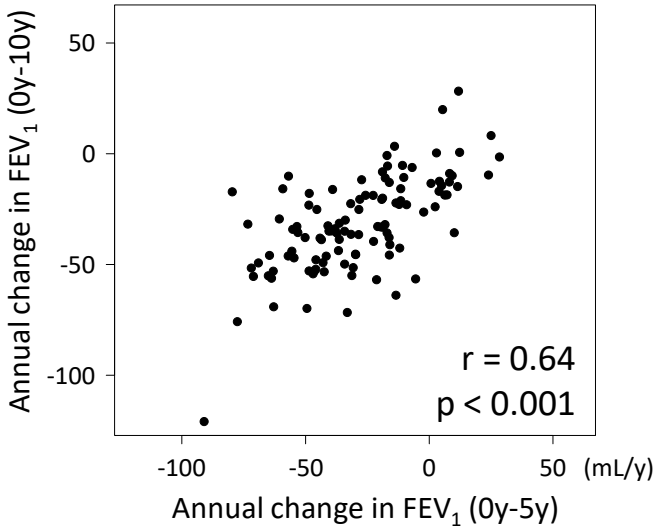
All subjects who had at least 3 spirometric measurements during the first 5 years: N=261

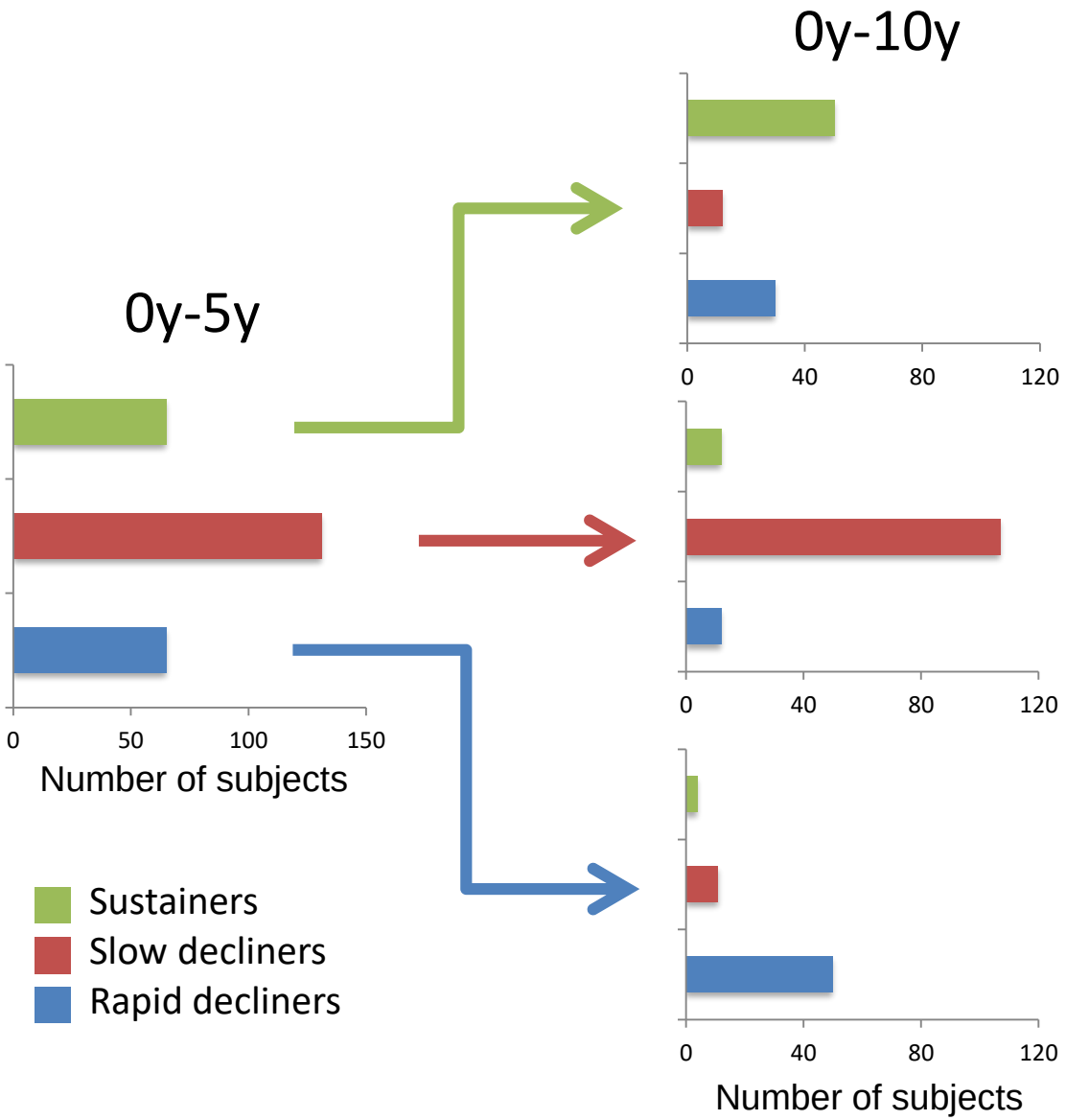
Annual change in FEV_1 during the first 5 years (0y-5y)

Annual change in FEV_1 during the entire 10 years (0y-10y)

*Each annual change in FEV_1 value was calculated by a linear mixed-effects model

Annual change in FEV_1: 0y-5y vs. 0y-10y





(Suzuki M, et al. Scientific Report 2018)

Lung function change beyond 5 years

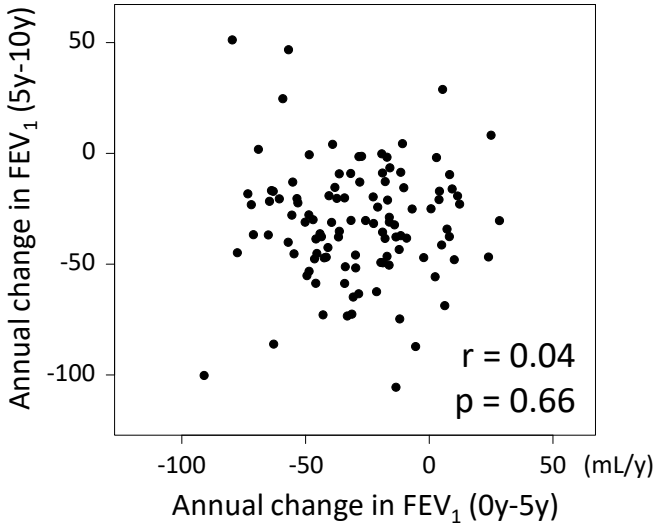
10-year survivors who had at least 3 spirometric measurements during the last 5 years: N=110

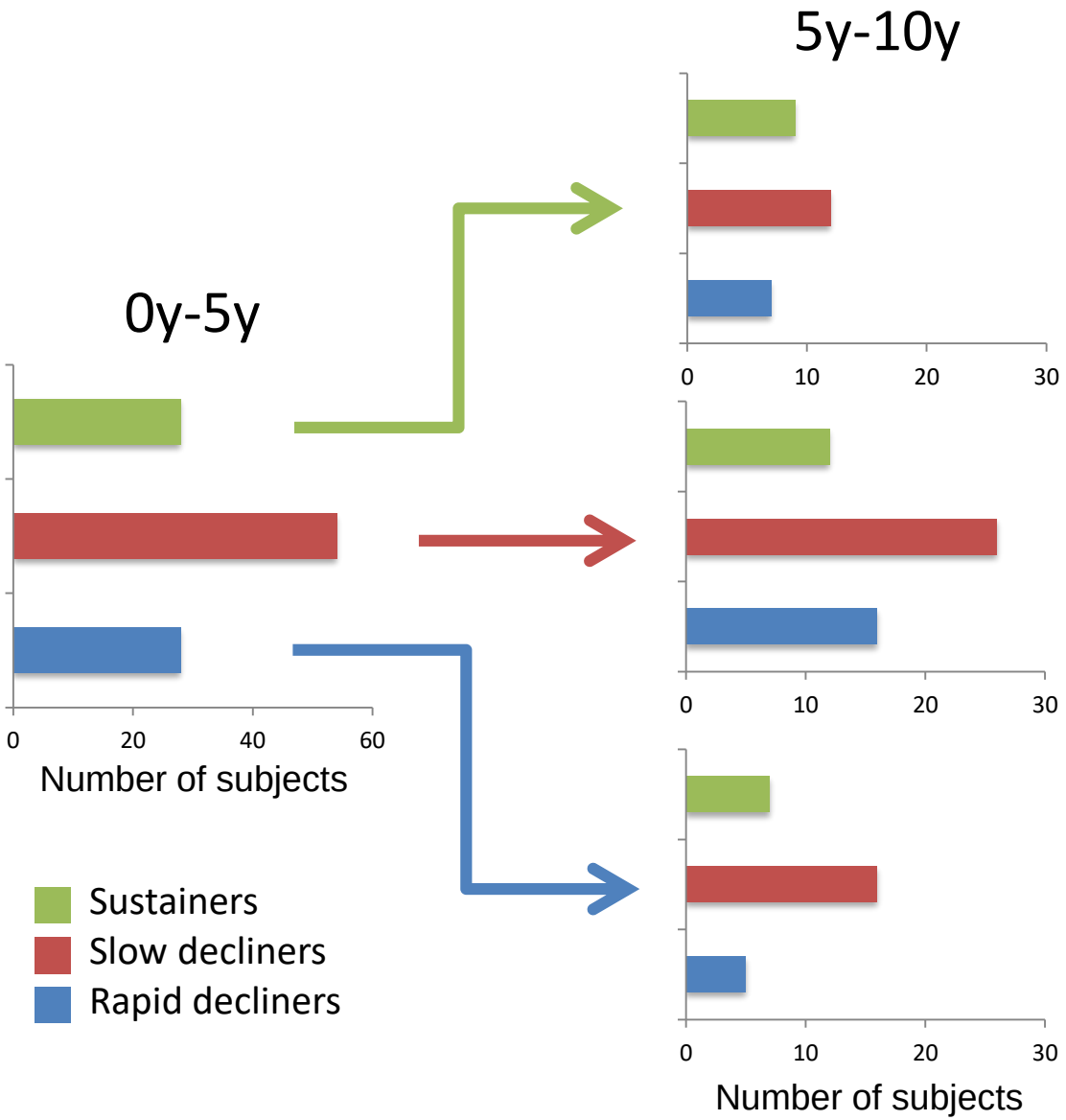
Annual change in FEV_1 during the first 5 years (0y-5y)

Annual change in FEV_1 during the last 5 years (5y-10y)

*Each annual change in FEV_1 value was calculated by a linear mixed-effects model

Annual change in FEV_1: 0y-5y vs. 5y-10y (10y survivors)





(Suzuki M, et al. Scientific Report 2018)

Lung function change in COPD

- The rate of FEV_1 decline calculated from the first 5 years and the entire 10 years well-correlated each other
- The rate of FEV_1 decline calculated from the first 5 years and the last 5 years did not correlate each other among 10-year survivors
- The subjects of each FEV_1 decline group during the first 5 years did not necessarily continue to belong the same FEV_1 decline group during the last 5 years

  → Disease activity of COPD is definitely changeable in each individual

- Such changeable disease activity existed in each GOLD grade (i.e. disease severity)

(Unpublished data)

Lessons from the Hokkaido COPD cohort study

- More emphysema and body weight loss were strong risk factors for mortality and the most frequent cause of death was respiratory diseases
- The prevalence of lung cancer development was high in COPD patients especially with apparent emphysema
- The presence of multiple asthma-like features was associated with better prognosis in COPD, and such patients might have the benefit from ICS
- The rate of FEV_1 decline (disease activity) was not necessarily the same in the natural course of long-term survivors with COPD under appropriate treatment

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