Relationship of baseline or annual change of clinical parameters on mortality in patients with COPD

Hironi Makita[1,2], Masaru Suzuki[1], Katsura Nagai[1], Masaharu Nishimura[1] and Hokkaido COPD Cohort Study Group

1 First Department of Medicine, Hokkaido University School of Medicine 2 Hokkaido Medical Research Institute for Respiratory Disease

Abstract

Background: We have shown that the rate of annual change in FEV1 was varied widely among patients with COPD over 5 years (Nishimura, AJRCCM 2012).

Aim: To examine how baseline or annual changes of clinical parameters are related to mortality.

Methods: A total of 279 of clinically stable patients with COPD (GOLD 1, 26%; GOLD 2, 45%; GOLD 3/4, 29%) served as subjects. We collected BMI and spirometric data every 6 months, diffusing capacity (Kco), emphysema severity assessed by CT, and health-related QOL (SGRQ) every year, and monitored exacerbation frequency, smoking behavior, and any medications. Mortality of the subjects was continuously recorded by physicians, telephone interviews, and letters to their families. Annual changes in post-bronchodilator FEV1, BMI, Kco, and SGRQ until the 3rd year were determined by linear regression.

Results: The median follow-up time was 8.2 years. Of the 265 patients, 98 died, with 38 classified as respiratory deaths. Age, emphysema score, BMI, FEV1 (%), Kco, SGRQ, exacerbations, and usage of respiratory medications were significantly related to mortality of all causes of death. By a multivariate logistic regression analysis, age (odds ratio [OR] 1.16; 95%CI 1.11-1.22; p<0.001), Kco (OR 0.99; 95%CI, 0.97-0.998; p=0.03), and BMI (OR 0.88; 95%CI, 0.79-0.97; p=0.01) emerged as independent risk factors for mortality of all causes. Interestingly, when looking at indices of annual changes, an annual decline in Kco was significantly linked with mortality of any respiratory diseases.

Conclusion: An annual decline in Kco, besides age, BMI, Kco at baseline, is an independent risk factor of mortality of any respiratory diseases in patients with COPD.
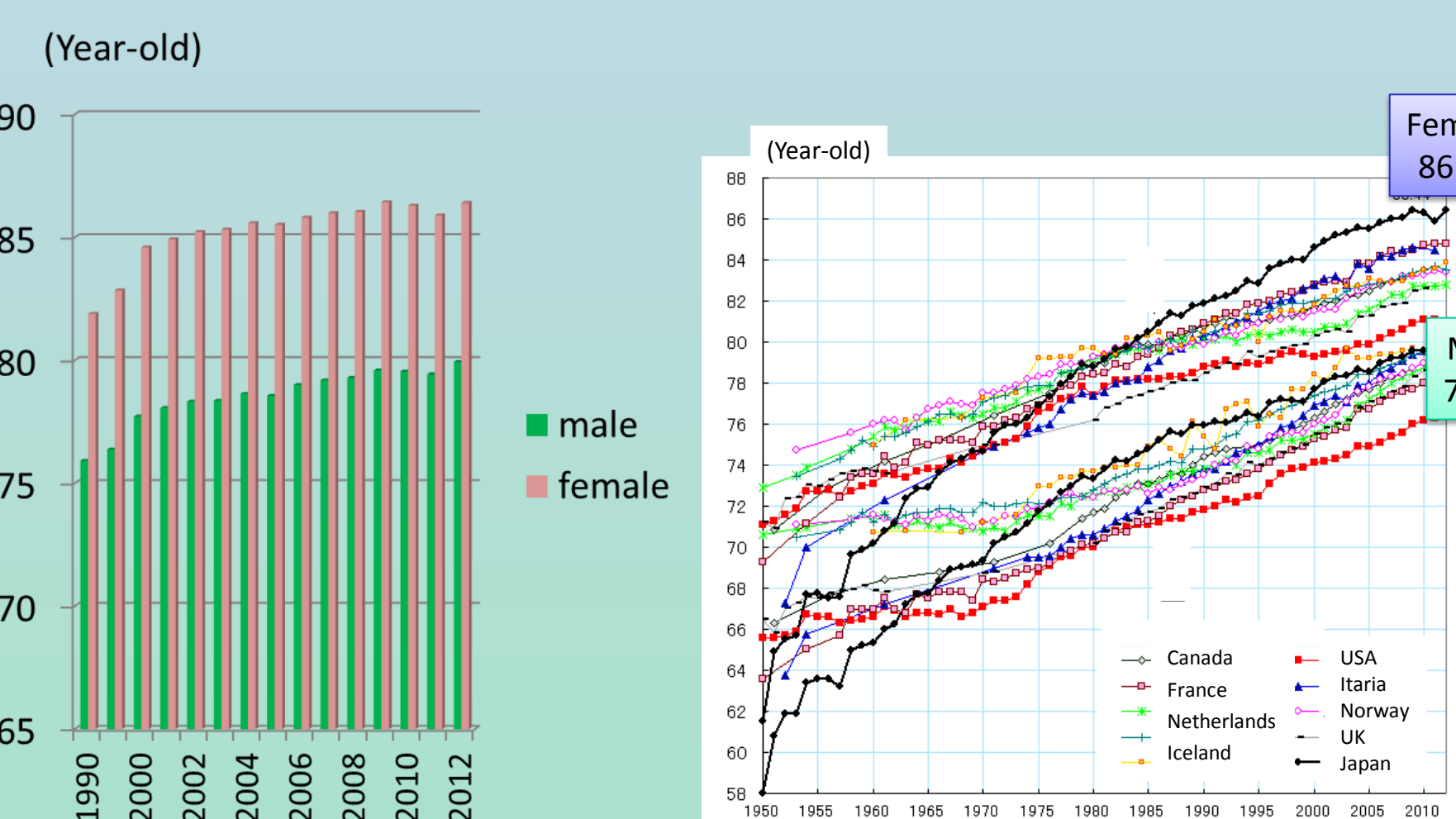
Background

- **We have shown that the rate of annual change in FEV1 was varied widely among patients with COPD over 5 years. (Nishimura M., AJRCCM 2012)**

Aim

- **In this follow-up study, we attempted to examine how baseline and/or annual changes of clinical parameters are related to mortality in patients with COPD.**

the Japanese average life span

(Year-old)

Hokkaido COPD Cohort Study

Study design: Multi-site, Observational cohort study

Subjects: The patients with COPD

Institutions: Hokkaido University Hospital, 10 affiliate hospitals

ENTRY: from 2003 - 2005

Collecting data for the first 5 years:
- Spirometry before and after inhalation of salbutamol (every 6 months)
- Diffusing capacity (every year)
- Blood test (every year)
- CT Scan, Health related QOL assessed by SGRQ (every year)
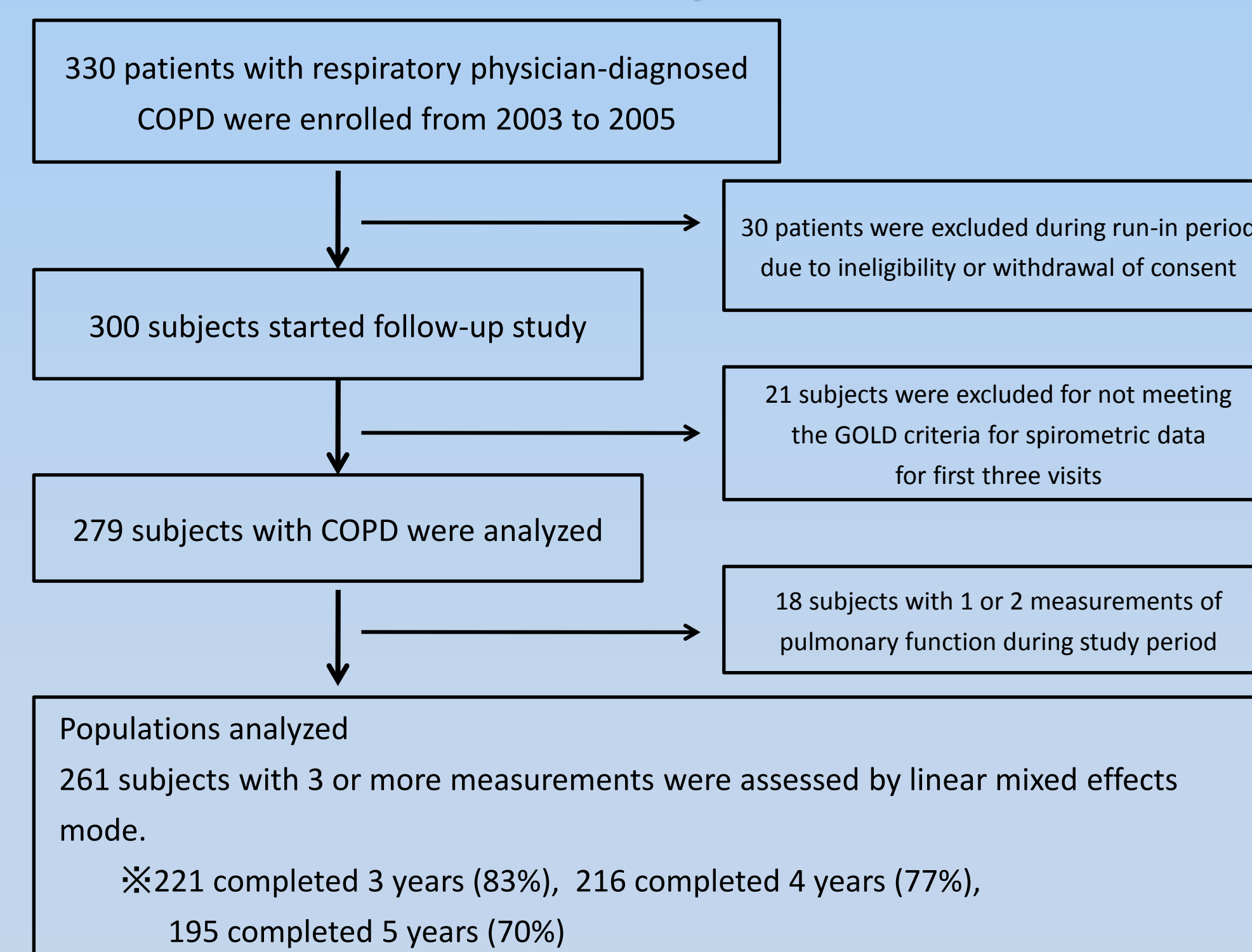- Exacerbation information (every month)

- **Entry criteria**
  - ✓ Clinically Diagnosed COPD
  - ✓ Current or former smokers
  - ✓ Age 40 years old or older

- **Exclusion criteria**
  - ✓ Patients with clinically diagnosed bronchial asthma
  - ✓ History of lung resection, cancer, tuberculosis, cystic fibrosis, bronchiectasis or interstitial pneumonia
  - ✓ Use of supplemental oxygen therapy for >12 hours/day

Flow chart for subject selection

330 patients with respiratory physician-diagnosed COPD were enrolled from 2003 to 2005

→ 30 patients were excluded during run-in period due to ineligibility or withdrawal of consent

300 subjects started follow-up study

→ 21 subjects were excluded for not meeting the GOLD criteria for spirometric data for first three visits

279 subjects with COPD were analyzed

→ 18 subjects with 1 or 2 measurements of pulmonary function during study period

Populations analyzed
261 subjects with 3 or more measurements were assessed by linear mixed effects mode.
※221 completed 3 years (83%), 216 completed 4 years (77%), 195 completed 5 years (70%)

## Method

The first 5 years
- Body mass index (BMI)
- Spirometric data (every 6 months)
- Diffusing capacity (DLco, every year)
- Blood test
- Health-related QOL assessed by SGRQ (every year)
- Exacerbation frequency
- Annual changes in post-bronchodilator FEV1 and DLco were determined using mixed effects models.

After ending the 5th year of follow-up, we continued data collection shown below
- Spirometric data, Diffusing capacity (every year)
- Information of exacerbation, smoking behavior and any medications have been carefully monitored throughout the study.
- Mortality of the subjects has been continuously recorded by physicians in regular visit, telephone interviews, and letters to their families.
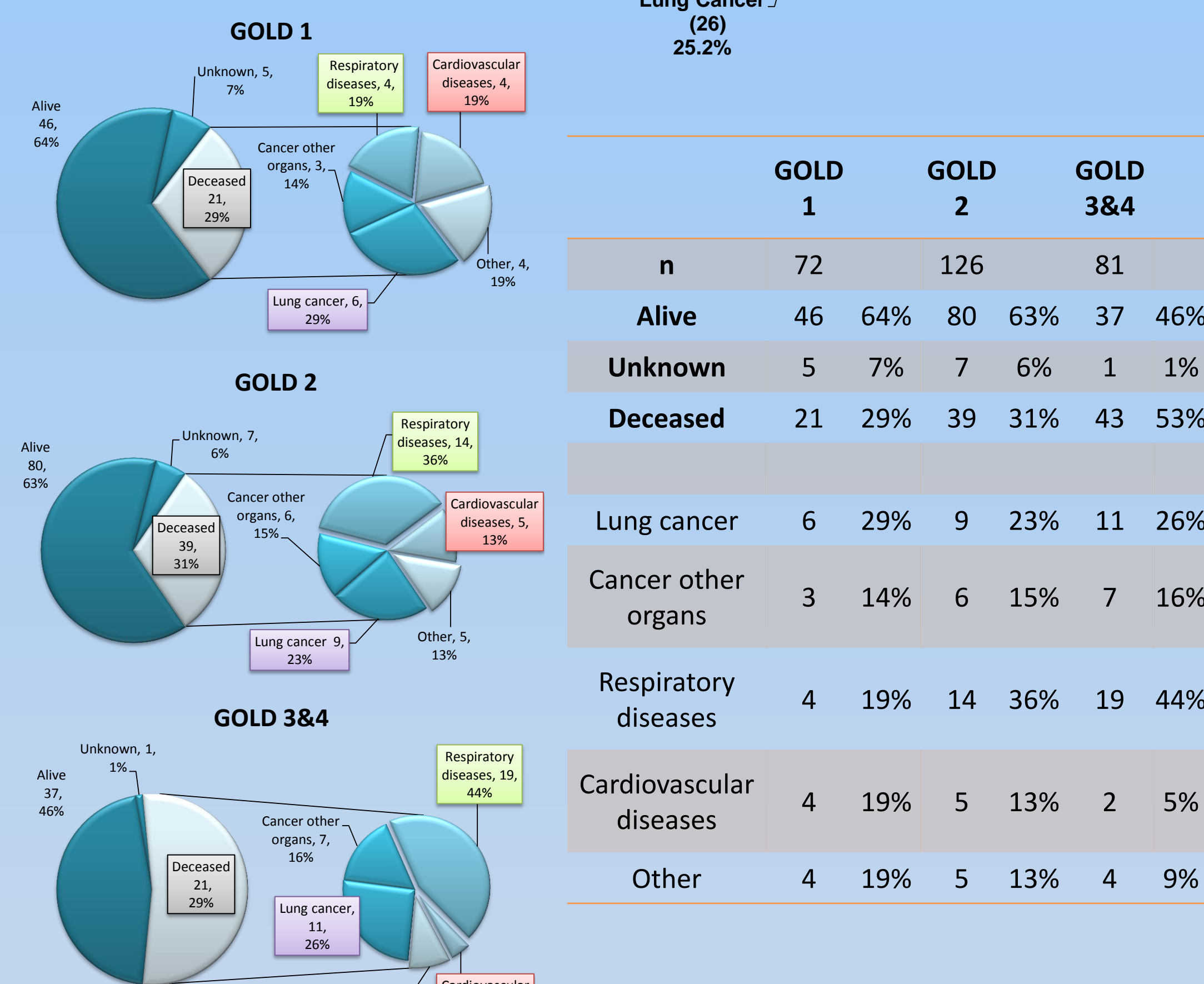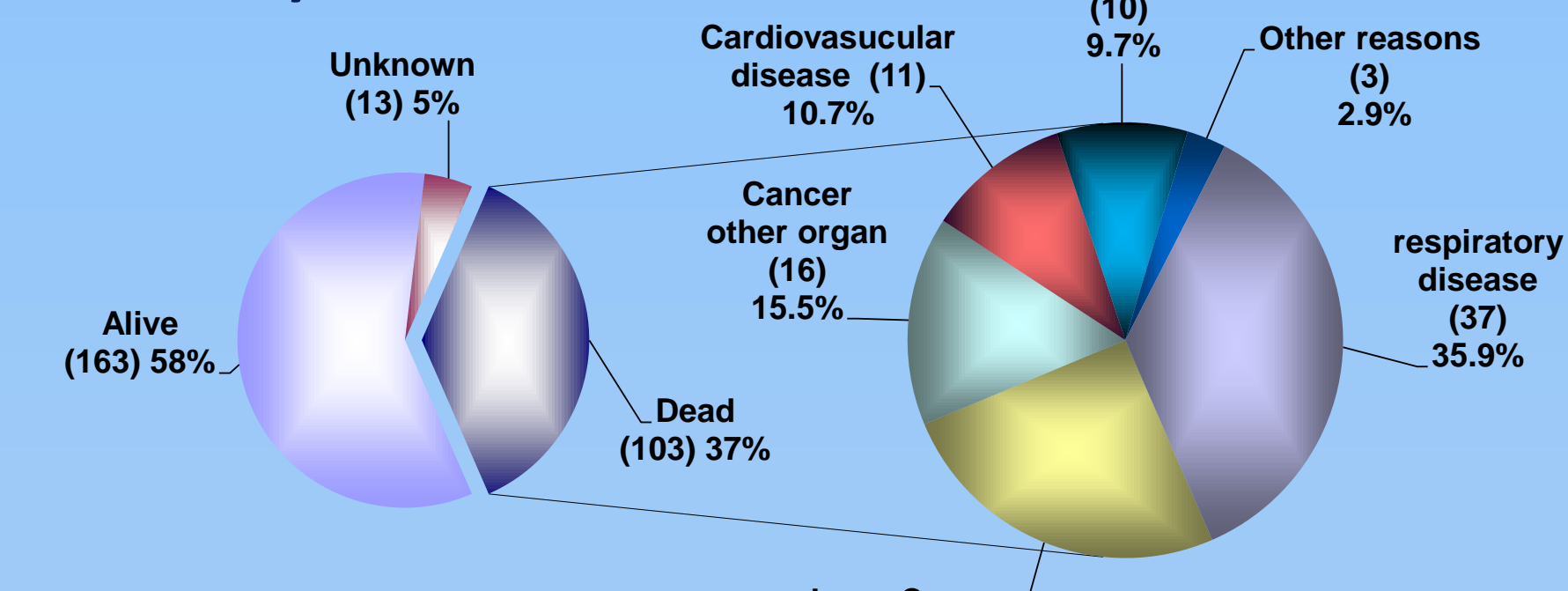
Results

Follow-up rate
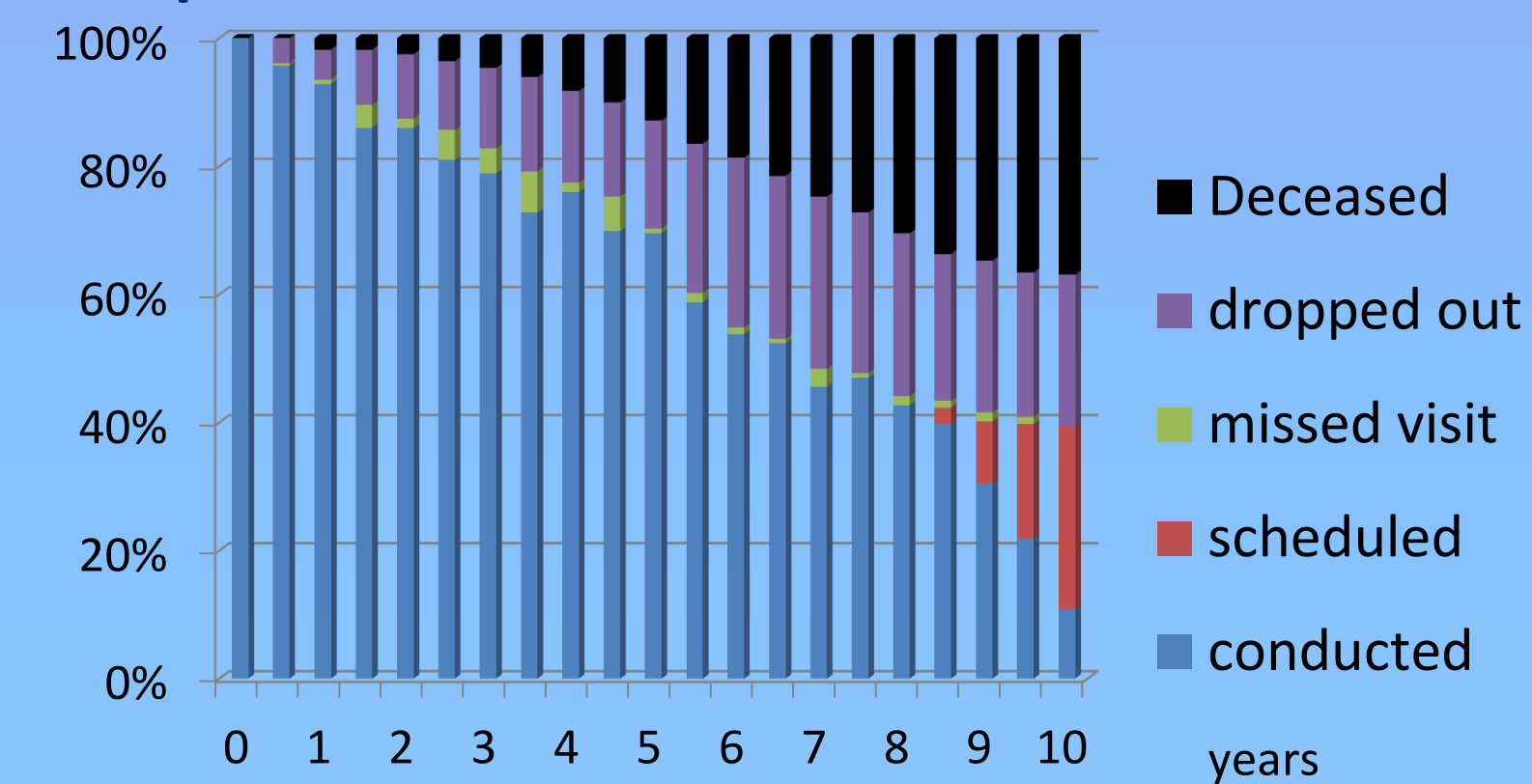
- The median follow-up time was 8.2 (7.0 – 9.1, IQR) years.
- Total of 103 subjects died. Still, 163 subjects are followed.

Mortality of all causes of death

Other diseases (10) 9.7%
Cardiovascular disease (11) 10.7%
Other reasons (3) 2.9%
Unknown (13) 5%
Cancer other organ (16) 15.5%
respiratory disease (37) 35.9%
Alive (163) 58%
Dead (103) 37%
Lung Cancer (26) 25.2%

GOLD 1
Unknown, 5, 7%
Respiratory diseases, 4, 19%
Cardiovascular diseases, 4, 19%
Alive 46, 64%
Cancer other organs 3, 14%
Deceased 21, 29%
Lung cancer, 6, 29%
Other, 4, 19%

GOLD 2
Unknown, 7, 6%
Respiratory diseases, 14, 36%
Alive 80, 63%
Cancer other organs, 6, 15%
Cardiovascular diseases, 5, 13%
Deceased 39, 31%
Lung cancer 9, 23%
Other, 5, 13%

GOLD 3&4
Unknown, 1, 1%
Respiratory diseases, 19, 44%
Alive 37, 46%
Cancer other organs, 7, 16%
Deceased 21, 29%
Lung cancer, 11, 26%
Other, 4, 9%
Cardiovascular diseases, 2, 5%

	GOLD 1		GOLD 2		GOLD 3&4	
n	72		126		81	
Alive	46	64%	80	63%	37	46%
Unknown	5	7%	7	6%	1	1%
Deceased	21	29%	39	31%	43	53%
Lung cancer	6	29%	9	23%	11	26%
Cancer other organs	3	14%	6	15%	7	16%
Respiratory diseases	4	19%	14	36%	19	44%
Cardiovascular diseases	4	19%	5	13%	2	5%
Other	4	19%	5	13%	4	9%

Clinical characteristics of patients

		Alive n=163	Deceased n=103	significance
Age,y	mean (SD)	67 (8)	74 (5)	<0.01
sex	male, (%)	153 (57)	100 (38)	0.22
	female, (%)	10 (4)	3 (1)	
BMI	mean (SD)	23 (3)	21 (3)	<0.01
Smoking status	current n, (%)	24 (9)	50 (19)	0.19
	former n, (%)	113 (42)	79 (30)	
Pack-years	mean (SD)	66 (32)	59 (25)	0.09
cough & sputum	n, (%)	18 (11)	11 (11)	0.93
FVC	%	102	99	0.24
FEV1	%	67	59	<0.01
DLco	%	80	72	<0.01
GOLD stage 1	n (%)	46 (17)	21 (8)	<0.01
GOLD stage 2	n (%)	80 (30)	39 (15)	
GOLD stage 3 &4	n (%)	37 (14)	43 (16)	
MRC scale	mean (SD)	1.3 (0.8)	1.6 (0.8)	<0.01
SGRQ	mean (SD)	30 (17)	35 (17)	0.03

Risk factors for mortality of all causes

Variables	Adjusted odds ratio	95% confidence interval Lower	Upper	p value
age	1.16	1.11	1.22	<0.001
BMI	0.86	0.78	0.94	0.001
%DLco : 10% increase in one unit	0.89	0.79	0.99	0.036

*multivariate analysis with a stepwise logistic regression model

Variables: sex, age, BMI, smoking status, pack-years, total SGRQ score, chronic cough & sputum, MRC scale, FVC (%), FEV1(%), reversibility(%), %DLco, blood eosinophils, blood neutrophils, CRP, IgE

Risk factors for mortality of any cancer

Variables	Adjusted odds ratio	95% confidence interval Lower	Upper	p value
age	1.11	1.05	1.17	<0.001
CRP	3.27	1.04	13.8	0.042

* crude odds ratio

Risk factors for mortality of respiratory diseases without lung cancer

Variables	Adjusted odds ratio	95% confidence interval Lower	Upper	p value
age	1.27	1.17	1.40	<0.001
BMI	0.78	0.65	0.92	0.002
%DLco †	0.76	0.61	0.92	0.005

† 10% increase in one unit

Risk factors for mortality when looking at annual changes of clinical parameters

Variables	Adjusted odds ratio	95% CI Lower	Upper	p value
annual change in DLco (per one unit increase)	0.32	0.12	0.84	0.020
annual change in FEV1	-	-	-	0.177
exacerbation (event/y) prescription change	-	-	-	0.127
continuous smoking*	-	-	-	0.159
annual change in BMI	-	-	-	0.604

* more than half of observation period

Variables	Adjusted odds ratio	95% confidence interval Lower	Upper	p value
annual change in DLco (per one unit increase)	0.25	0.06	0.97	0.045
exacerbation (event/y) prescription change	3.06	1.00	9.57	0.049

Conclusion

In conclusion, among the baseline data, older age, lower BMI, and lower %DLco, but not %FEV1, were significantly linked with higher mortality. When looking at annual changes in pulmonary function and BMI, only DLco, but again not FEV1, was related with all-cause mortality or respiratory deaths.