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**Title: Histopathologic type of lung cancer and driver mutations in patients with chronic obstructive pulmonary disease(COPD) versus patients with Asthma and COPD Overlap : single-center retrospective study**

**Short Title: Type of lung cancer: COPD versus ACO**

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## Abstract

**Introduction:** Chronic obstructive pulmonary disease (COPD) increases the risk of lung cancer. The relationships between COPD and Asthma COPD Overlap (ACO) and histopathologic types of lung cancer and driver mutations remain unclear and need further study. The aim of this retrospective study was to examine the relationships between histopathologic type, frequency of the epidermal growth factor receptor (EGFR) driver mutations, and anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangements in lung cancers of patients with COPD and ACO.

**Materials and Methods:** Pure COPD (n = 198) or ACO (n = 318) who were admitted to our hospital were reviewed.

**Results:** Lung cancers were identified in 43 (21.7%) patients with pure COPD and 54 (17.0%) patients with ACO. The following lung cancers were seen: patients with pure COPD had 19 (44.2%) adenocarcinomas, 13 (30.2%) squamous cell lung carcinomas (SCC), 8 (18.6%) small cell lung carcinomas (SCLC); patients with ACO had 23 (42.6%) adenocarcinomas, 23 (42.6%) SCC, 2 (3.70%) SCLC. Significantly more SCLC occurred in the patients with pure COPD ( $p < 0.05$ ). Differences between the numbers of other histological types of lung cancer and numbers of driver mutations in the 2 groups of patients were not significant.

**Conclusion:** The differences between patients with pure COPD and those with ACO in the rate of lung cancer and prevalence of EGFR mutations were not significant.

**Key words:** Asthma, COPD: chronic obstructive pulmonary disease, ACO: Asthma COPD Overlap, histopathologic types, driver mutations

## Introduction

COPD and smoking are risk factors for the development of lung cancer, especially the SCC

histological subtype in Japan (1, 2) Asthma increases the risk of SCC and SCLC (3). Asthma had

an inverse association with lung cancer (4). Atopic disease is associated with a reduced risk for

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cancer (5). Eosinophils appear to have beneficial effects on colorectal carcinoma, oral squamous carcinoma, pulmonary adenocarcinoma, and prostate carcinoma. For example, high blood levels of eosinophils correlate with better outcomes, and nonmetastatic carcinomas are correlated with high levels eosinophilic infiltration of tumors (6).

Compared with patients with pure COPD or asthma, ACO is known to accelerate the decline in lung function (7), and increase the risk of disease exacerbations in both asthma and COPD and hospitalization (8). Few studies have investigated patients with this condition concomitant with lung cancer. The aim of this retrospective study was to examine the relationships between histopathologic type, frequency of the epidermal growth factor receptor (EGFR) driver mutation, and anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangements in lung cancers of patients with COPD and ACO.

## **Materials and methods**

Patients were diagnosed COPD by fulfilling the inclusion criteria. And the patients with exclusion criteria were excluded.

## **Inclusion criteria**

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- ① Outpatients,  $\geq 40$  years of age, with smoking history of  $> 10$  pack years
- ② The study period was April 1, 2011 to July 16, 2015. Patients who examined for bronchodilator reversibility test at our hospital were reviewed retrospectively.
- ③ FEV<sub>1</sub>% (forced expiratory volume in one second)  $< 70\%$  post-bronchodilator.

#### **Exclusion criteria**

Patients with any of the following conditions were excluded from the study: sinobronchial syndrome, interstitial lung disease, bronchiectasis, tuberculosis, pneumoconiosis, radiation pneumonitis, and bronchiolitis obliterans

The patients were diagnosed ACO by fulfilling the selection criteria below in reference to the “guideline of diagnosis and treatment of COPD 4<sup>th</sup> edition” published by The Japanese Respiratory Society (9). Briefly, asthma coexisting with COPD was diagnosed in patients with any of the following: reversible airflow obstruction, elevated FeNO level, elevated IgE level, and clinical findings.

#### **Selection criteria**

- ① FEV<sub>1</sub> after short-acting bronchodilator  $\geq 12\%$  and  $\geq 200$  mL
- ② Fractional exhaled nitric oxide (FeNO)  $\geq 37$  ppb (10). FeNO was measured by a portable

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analyzer (NIOX MINO; Aerocrine, Solna, Sweden) or a stationary analyzer (CHEST Inc., Tokyo, Japan). FeNO values determined by the portable analyzer were converted as follows

$$(11) : \text{FeNO (NIOX MINO)} = (\text{FeNO (CHEST)} - 3.065) / 1.278$$

- ③ IgE  $\geq$  100 IU/L (12)
- ④ Clinically diagnosed bronchial asthma (paroxysmal apnea, wheezing, recurrent coughs)

### **Ethical consideration**

The study was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was approved by the Standards of Official Conduct Committee of our hospital. (clinical trial number : 2016-008). Informed consent was exempted because the data were examined retrospectively from medical records.

### **Statistical analysis**

Values for age, smoking history, IgE, FeNO, FEV<sub>1</sub>%, %FEV<sub>1</sub> were expressed as the mean  $\pm$  standard deviation (SD). The Wilcoxon test was used to compare age, smoking history, IgE, FeNO, FEV<sub>1</sub>%, %FEV between COPD and ACO patients. The chi-squared test was use to evaluate the histopathologic type of lung cancer and driver mutations.

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## Results

Figure 1 shows the CONSORT diagram of the study. Among all the patients with COPD, 61.6% had ACO [Table 1]. The differences between the age and gender ratio of the patients with pure COPD and ACO were not significant. The number of pack years of smoking was higher in the patients with pure COPD than in the patients with ACO ( $54.6 \pm 29.0$  pack-years vs.  $49.9 \pm 31.9$  pack-years, respectively;  $p < 0.05$ ). The IgE level was higher in ACO than in pure COPD patients ( $470.9 \pm 912.4$  IU/L vs.  $29.9 \pm 20.2$  IU/L, respectively;  $p < 0.01$ ). The FeNO value was higher in ACO patients than in pure COPD patients ( $39.7 \pm 27.4$  ppb vs.  $18.0 \pm 8.6$  ppb, respectively;  $p < 0.01$ ). FEV<sub>1</sub>% was higher in pure COPD than in ACO patients ( $60.9 \pm 8.5$  vs.  $57.2 \pm 10.8$ , respectively;  $p < 0.01$ ). %FEV<sub>1</sub> was higher in pure COPD than in ACO patients ( $93.9\% \pm 40.3\%$  vs.  $78.8\% \pm 42.7\%$ , respectively;  $p < 0.01$ ). Details on the GOLD classification of airflow limitation in COPD were shown in Table 1. The risk of lung cancer among pure COPD and ACO patients was 21.7% (43/198) and 17.0% (54/318), respectively, which was not significant [Table 2]. The following types of lung cancers were seen: in 43 patients with pure COPD, 19 (44.2%) adenocarcinomas, 13 (30.2%) squamous cell lung carcinomas (SCC), 8 (18.6%) small cell lung carcinomas (SCLC) and 1 (2.3%) not otherwise specified (NOS); in 54 patients with ACOS, 23

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(42.6%) adenocarcinomas, 23 (42.6%) SCC, 2 (3.70%) SCLC, 1 (3.70%) NOS, 1 (1.9%) large cell neuroendocrine carcinoma, 1 (1.9%) large cell carcinoma, 1 (1.9%) anaplastic carcinoma. Both patient groups also had 2 cases with unknown types. Significantly more SCLC occurred in the patients with pure COPD ( $p < 0.05$ ).

EGFR mutations were identified in 25% (3/12, analyzed in 12 cases of adenocarcinoma and found positive in 3 cases; 2 with L858R, 1 with 19del mutation) of pure COPD patients and 22.2% (4/18; 1 with L858R, 3 with 19del mutation) of ACO patients [Table 2]. ALK rearrangements were identified in 0% (0/6), 0% (0/11), respectively. Differences between the numbers of other histological types of lung cancer and numbers of driver mutations in the 2 groups of lung adenocarcinoma patients were not significant. The difference between the mortality rates up to April 1, 2016, of the 2 groups of patients was not significant [Table 2].

## Discussion

COPD and smoking are risk factors for the development of lung cancer, especially the SCC histological subtype in Japan (1, 2). Asthma increases the risk of SCC and SCLC (3). Few studies have investigated the risk of lung cancer in patients with ACO. A cohort study performed in the

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Republic of China found that respective men and women with COPD, asthma, and ACO had HRs of lung cancer of 1.68 and 1.38, 1.57 and 1.35, and 2.21 and 1.64, respectively; HRs of adenocarcinoma of 1.59 and 1.40, 1.31 and 1.40, 1.76 and 2.36, respectively; HRs of SCC of 1.82 and 1.51, 1.81 and 1.61, 2.21 and 1.64, respectively; HRs of SCLC of 1.57 and 1.61, 1.84 and 1.56, 2.14 and 3.33, respectively (13). Patients with coexisting pulmonary diseases were more likely to develop any type of lung cancer. However, in this study, the risk of developing SCLC was higher in pure COPD patients. In the same Republic of China study, the respective HRs of SCLC for men and women aged 60 to 79 years were 7.16 (95% CI 6.52-7.86) and 5.71 (95% CI 4.27-7.63). Age had a greater effect than the coexistence of asthma or COPD. We selected study patients with a history of smoking, but the smoking history of the study patients in the study from the Republic of China was not reported. The study populations of our study and that study are different, and therefore comparing the results is difficult. In a retrospective Japanese study (14), 23/474 (4.8%) patients with asthma and 15/176 (8.5%) patients with ACO developed lung cancer. The following histopathological types of lung cancer were identified:

adenocarcinoma in 78.3%, SCC in 13.0%, and SCLC in 8.7% of asthma patients; SCC in 46.7%, adenocarcinoma in 40.0%, SCLC in 6.7%, and unknown in 6.7% of ACO patients. In Japanese

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patients with COPD or ACO, we need a large cohort study containing a group of patients with pure asthma to evaluate the risk of lung cancer and histological type. Lim et al reported that lung cancers in patients with COPD were associated with prevalence of EGFR mutations and ALK rearrangements. The proportions of EGFR mutations and ALK rearrangements decreased as the severity of airflow obstruction increased (15). Interestingly, in never smokers, the prevalence of EGFR mutations was significantly lower in the patients with COPD than in patients without COPD (15). In our study we mainly selected patients with a smoking history longer than a specific duration. We didn't examine patients who were never smokers.

The Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) developed the below a joint statement. ACO was defined as a syndrome characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. A review of the literature on ACO (16) did not find established diagnostic criteria for ACO. For example, reversibility of airflow obstruction, eosinophilia of sputum were used as a reference (17). In this study, prevalence of asthma in patients with COPD was 61.6%. The prevalence was higher than previous

announcement. There were three possible explanations for the high prevalence of asthma. The

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first was the older mean age of our study population ( $69.2 \pm 8.3$  years). The frequency of ACO increases with age (7, 18). The prevalence of ACO is higher than 50% in elderly COPD patients. The second was that differences between the ACO diagnostic criteria used on our study and others may have resulted in our finding of an increased prevalence of ACO. With 35 ppb as the cutoff value of FeNO, the prevalence rate of ACO was 16.3% in our COPD population (19). With both FeNO and IgE  $\geq 173$  IU/mL, the prevalence rate of ACO was 7.8% (19). And the last explanation was that, in enrolling our study patients, we initially evaluated 2390 patients who had been examined for bronchodilator reversibility test [Figure 1], and the increased prevalence of ACO in our study cohort might be accounted for by selection bias of patients. This study has several shortcomings. The first limitation was that we didn't examine patients who were never smokers. The second limitation was the selection bias because we selected patients who had been identified with reversible airflow obstruction.

## **Conclusion**

The difference between patients with pure COPD and those with ACOS in the risk of lung cancer was not significant. SCLC more commonly occurred in patients with pure COPD ( $p <$

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0.05). Differences between the numbers of other histopathological types of lung cancer and numbers of driver mutations in the 2 groups of patients were not significant. This was a small retrospective study. An additional prospective study containing patients with pure bronchial asthma is needed to assess the risk of lung cancer and histopathological type. The concept of ACO should be further evaluated and diagnostic criteria for ACO should be established.

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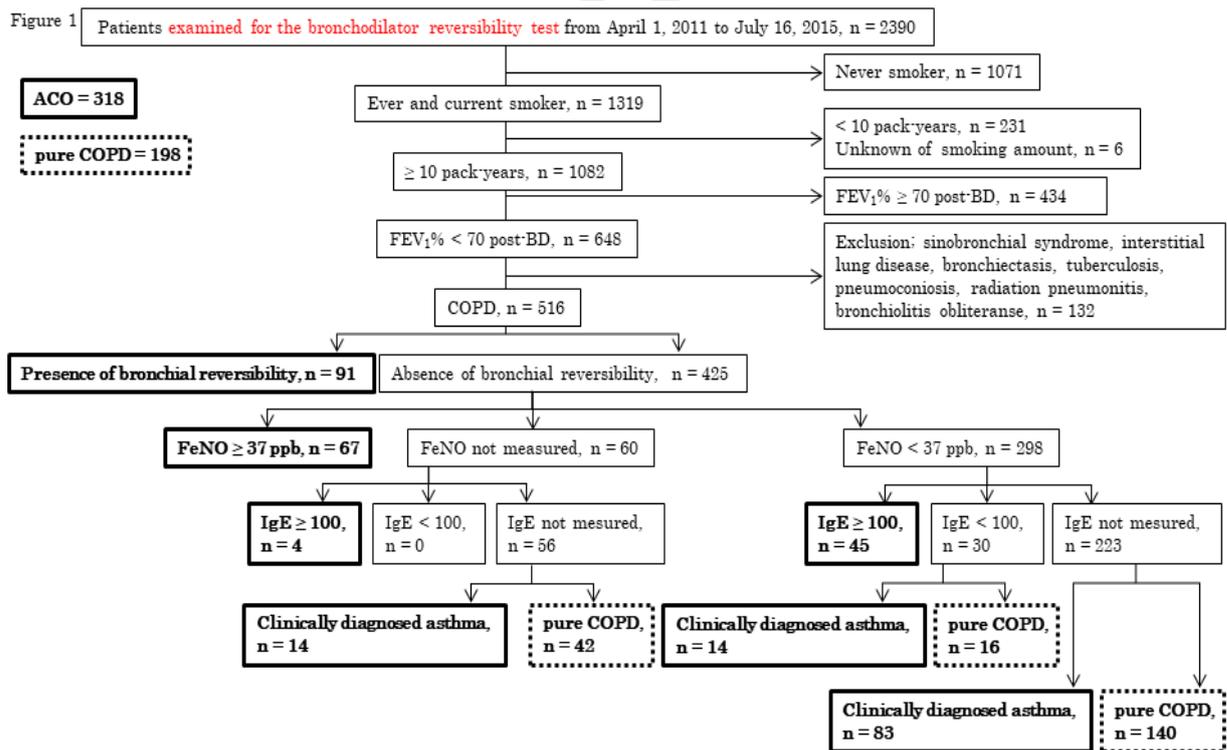
## Figure legends

**Figure 1. Study design and inclusion and exclusion criteria of ACO and pure COPD**

post-BD; post-bronchodilator

line box; ACO

dotted box; pure COPD



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**Table 1. Differential characteristic of patients of pure COPD and ACO**

Characteristics		COPD n = 516	pure COPD n = 198 (38.4%)	ACO n = 318 (61.6%)	P Value
Age, y		69.2 ± 8.3	69.7 ± 8.0	68.9 ± 8.5	N.S
Gender	Male	466	184	282	N.S
	Female	50	14	36	N.S
Smoking history (pack-years)		51.7 ± 30.9	54.6 ± 29.0	49.9 ± 31.9	p < 0.05
IgE (IU/L)		422.3 ± 871.4	29.9 ± 20.2	470.9 ± 912.4	p < 0.01
FeNO (ppb)		25.7 ± 23.3	18.0 ± 8.6	39.7 ± 27.4	p < 0.01
FEV <sub>1</sub> % (%)		58.6 ± 10.1	60.9 ± 8.5	57.2 ± 10.8	p < 0.01
%FEV <sub>1</sub> (%)		86.4 ± 42.4	93.9 ± 40.3	78.8 ± 42.7	p < 0.01
			I n = 126	I n = 142	
			II n = 54	II n = 95	
			III n = 8	III n = 51	

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		IV	n = 10	IV	n = 30	
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N.S.; not significant Mean  $\pm$  SD

**Table 2. Prevalence of lung cancer and histopathology and genetic assessments in pure COPD and ACO**

		pure COPD n=198	ACO n=318	P Value	
Prevalence of malignancy		43 (21.7%)	54 (17.0%)	N.S.	
histopathology	SCLC	8 (18.6%)	2 (3.7%)	p < 0.05	
		19 (44.2%)	23 (42.6%)	p < 0.05	
	Ad	EGFR	3/12	4/18	N.S.
		L858R; 2	L858R; 1		
		19del1; 1	19del1; 3		
	ALK	0/6	0/11		
Sq	13 (30.2%)	23 (42.6%)	N.S.		

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	Others	NOS 1 (2.3%)	NOS 1 (1.9%) LCNEC 1 (1.9%) large cell carcinoma 1 (1.9%) anaplastic carcinoma 1 (1.9%)	N.S.
	Unknown	2 (4.7%)	2 (3.7%)	N.S.
Dead		12 (27.9%)	13 (24.1%)	N.S.

adenocarcinoma; Ad

ALK; ALK rearrangement

EGFR; EGFR mutations

LCNEC: large cell neuroendocrine carcinoma

NOS; not otherwise specified

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N.S.; not significant Mean  $\pm$  SD

small cell carcinoma; SCLC

squamous cell carcinoma; Sq

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