ORIGINAL RESEARCH

Biomarker-based detection of asthma–COPD overlap syndrome in COPD populations

Tsutomu Tamada[1]
Hisatoshi Sugiura[1]
Tsuneyuki Takahashi[2]
Kazuto Matsunaga[3]
Keiji Kimura[4]
Uichiro Katsumata[5]
Daisuke Takekoshi[1]
Toshiaki Kikuchi[1]
Ken Ohta[6]
Masakazu Ichinose[1]

[1]Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, [2]Nippon Telegraph and Telephone East Corporation Tohoku Hospital, Sendai, [3]Division of Respiratory Medicine and Infectious Disease, Graduate School of Medicine, Yamaguchi University, Ube, [4]Hiraka General Hospital, Yokote, [5]Iwate Prefectural Isawa Hospital, Oshu, [6]National Hospital Organization, Tokyo National Hospital, Kiyose, Tokyo, Japan

Correspondence: Tsutomu Tamada
Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan
Tel +81 22 717 8539
Fax +81 22 717 8549
Email tamada@rm.med.tohoku.ac.jp

Abstract: Asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) was proposed by the science committees of both Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD). However, the definition of ACOS has remained unclear all over the world, and the prevalence rate of ACOS is basically dependent on the patient's symptoms or the physician's opinion, based on questionnaire testing. In the current case report, we investigated the prevalence rate of COPD patients with high levels of fractional exhaled nitric oxide (FENO) or immunoglobulin E (IgE) as candidate markers of ACOS in COPD, as a multicenter, cross-sectional study. Outpatients with COPD were enrolled from Tohoku University Hospital, Sendai, Japan, and five hospitals (Tohoku University Hospital, Sendai, Japan; NTT East Tohoku Hospital, Sendai, Japan; Wakayama Medical University Hospital, Kimiidera, Japan; Hiraka General Hospital, Yokote, Japan; Iwate Prefectural Isawa Hospital, Oshu, Japan) with pulmonary physicians from March 1, 2013 to February 28, 2014. When they were estimated using 35 ppb as the cutoff value of FENO, the prevalence rate of ACOS was 16.3% in COPD. When estimated by both FENO and IgE, the high-FENO/high-IgE group was 7.8% in COPD. To the best of our knowledge, this study is the first to detect the prevalence rate of ACOS in COPD populations by using objective biomarkers. The results from the current study should be useful to identify the subgroup requiring early intervention by inhaled corticosteroids/long-acting beta agonist combination in COPD in order to improve the long-term management for ACOS.

Keywords: FENO, IgE, ICS, LABA, airway inflammation, atopic factors

Introduction

In 2014, asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) was proposed by the science committees of both Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD).[1] This concept of ACOS was based on a detailed review of the available literature and consensus. ACOS patients without proper treatment are known to experience worse outcomes compared with COPD or asthma alone.[2–5] It is therefore very important to detect ACOS in COPD populations. To date, the definition of ACOS has remained unclear all over the world, and the prevalence rate of ACOS is basically dependent on the patient's symptoms or the physician's opinion based on questionnaire testing. It has been reported that 15 to 60% of asthma/COPD patients have ACOS when estimated by the patient's symptoms or the physician's opinion based on questionnaire testing, and those prevalence rates vary according to gender and age.[4,6–12] It is obvious that the criteria of ACOS should be based on more objective biomarkers, but there are few reports on the precise prevalence rate of ACOS based on reliable biomarkers. Concerning the definition of ACOS, a document jointly published by GINA and GOLD stipulates if

patients experience persistent symptoms and/or exacerbations despite treatment or if their comorbidities interfere with the assessment of their airway disease, referral for expert advice and further diagnostic evaluation is necessary.[1] Specialized investigations to distinguish between COPD and asthma are listed as follows: 1) lung function tests such as diffusing capacity of the lung for carbon monoxide (DLco); 2) imaging such as high-resolution CT; and 3) inflammatory biomarkers such as specific-immunoglobulin E (IgE) and fractional exhaled nitric oxide (FENO).[1]

In the current case report, we investigated the prevalence rate of COPD patients with asthma-like airway inflammation or atopic factors as candidates of ACOS in COPD. We revealed that the prevalence rate of subjects with FENO >35 ppb was 16.3% and that the prevalence rate of high-FENO/high-IgE was 7.8% in COPD. To the best of our knowledge, this study is the first to estimate ACOS in COPD using objective biomarkers recommended by international guidelines. These results should be useful in disseminating medications such as inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combinations for COPD in order to improve the long-term management for ACOS.

Materials and methods

Patient population

COPD patients were diagnosed according to the GOLD criterion, that is, a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) of <70% after bronchodilator use.[13] All data including FENO, pulmonary function test, and total IgE from participants were estimated under stable conditions. Medical information and patients' characteristics including age, pack-years of tobacco use, smoking status, severity of disease, and current medication information were obtained from patients' medical charts.

Study design

This was a multicenter, cross-sectional survey that targeted COPD outpatients. This study was approved by the ethics committee of Tohoku University Graduate School of Medicine (approval number, 2015-1-5). Informed consent was waived based on the ethical guidelines of Tohoku University Graduate School of Medicine. The protocol of our study has been disclosed in the URL: http://www.med.tohoku.ac.jp/public/doc/2015-1-5.pdf. In the current case report, we aimed to detect COPD patients with asthma-like airway inflammation or atopic factors. COPD outpatients were enrolled from Tohoku University Hospital and five hospitals with pulmonary physicians from March 1, 2013 to February 28, 2014.

Pulmonary function test

Pulmonary function tests were performed under stable conditions. If participants had performed pulmonary function tests no longer than 3 months before they entered the study, their data were collected from their patient chart. The procedures of the pulmonary function tests were according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.[14] Parameters collected were FVC, FEV_1, percent predicted values of these parameters (%FVC, %FEV_1), and FEV_1/FVC ratio. The severity rankings of COPD, such as GOLD I–IV, were based on %FEV_1 according to GOLD guidelines.[13]

FENO measurements

FENO was measured using the NIOX MINO® device (Aerocrine, Morrisville, NC, USA) according to the standard operating procedures recommended by the manufacturer. The FENO levels were acquired from all patients under a stable condition and expressed in parts per billion (ppb). FENO was measured in patients without viral infections and before spirometry. Because several cutoff values of FENO have been proposed in recent popular reports,[1,15–18] FENO was estimated by using three representative cutoff values (25, 35, and 50 ppb) in the present study. Some COPD patients used ICS, which is a potent drug that decreases FENO values.[19–21] However, they were also enrolled in our study, because this was a simple survey without any interventions in any patients.

IgE measurements

Data of total IgE were extracted from the patient chart if it had been measured no longer than 1 year before the patient entered the study. Total IgE values were acquired from 230 (69.8%) of the 331 COPD patients. The cutoff value was set at 173 IU/mL according to the reference range of the medical laboratory in our hospital.[22]

Statistical analyses

Data from age and pulmonary function were expressed as mean ± standard deviation (SD), and data from pack-years of tobacco use were expressed as median and interquartile range (IQR, Q1–Q3). The clinical characteristics between high- and low-FENO groups, and those between high- and low-IgE groups, were compared using the Mann–Whitney *U* statistic and Fisher's exact tests. All statistical analyses were performed using JMP Pro 11.2 software (SAS Institute, Inc, Cary, NC, USA).

Results

Prevalence rate of patients with high values of FENO in COPD

The characteristics of COPD patients are summarized in Tables 1 and 2. A subtotal of 307 (92.7%) of the 331 COPD patients were male. A subtotal of 41 (13.4%) of the male patients and five (20.8%) of the female patients were current smokers. Most COPD patients had normal levels of %FVC (94.8%±18.5%), but had low levels of %FEV$_1$ (61.5%±20.8%) and a low FEV$_1$/FVC (51.3%±12.9%). Concerning the GOLD classifications by pulmonary function of the male patients, 65 male patients (21.2%) corresponded to GOLD I, 145 male patients (47.2%) corresponded to GOLD II, 78 male patients

Table 1 Characteristics of the subjects

Characteristic	COPD
Total number of subjects	331
Age, years	72.2±8.0
Pack-years of tobacco use	52.5 (40–80)
Males, n (%)	307 (92.7)
Smoking status, n (%)	
Never-smokers or pack-years <10	10 (3.0)
Ex-smokers (>1 year)	257 (77.6)
Current smokers	46 (13.9)
Unknown	18 (5.4)
mMRC scale, n (%)	
Grade 0	57 (17.2)
Grade 1	116 (35.0)
Grade 2	83 (25.1)
Grade 3	59 (17.8)
Grade 4	16 (4.8)
History of exacerbation, n (%)	115 (34.7)
History of allergic rhinitis, n (%)	36 (10.9)
Pulmonary function, (%)	
%FVC	94.8±18.5
%FEV$_1$	61.5±20.8
FEV$_1$/FVC	51.3±12.9
GOLD classifications, n (%)	
I	68 (20.5)
II	159 (48.0)
III	85 (25.7)
IV	19 (5.7)
Medications, n (%)	
LAMA	260 (78.5)
LABA	212 (64.0)
ICS	126 (38.1)
Theophylline	79 (23.9)
Mucolytics	46 (13.9)
LTRA	15 (4.5)
OCS	7 (2.1)

Note: Data are expressed as mean ± SD or median (IQR, Q1–Q3).
Abbreviations: mMRC scale, modified Medical Research Council scale; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta agonist; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; IQR, interquartile range; FEV, forced expiratory volume; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SD, standard deviation.

(25.4%) corresponded to GOLD III, and 19 male patients (6.2%) corresponded to GOLD IV. Long-acting muscarinic antagonist was the most commonly used medication in 260 (78.5%) of the COPD patients. Subsequently, LABA was used in 212 (64.0%) patients, ICS in 126 (38.1%) patients, and theophylline in 79 (23.9%) patients (patients could take several medications). There were more current smokers in the low-FENO group, and there were more patients with a history of allergic rhinitis in the high-IgE group.

A histogram of the FENO values is shown in Figure 1. The median value of FENO was 20 ppb (IQR, 12–29 ppb). Because several cutoff values of FENO were proposed in recent popular reports,[1,15–18] FENO was estimated by three representative cut-off values in the current study. The number of cases with FENO >25 ppb were 112 (36.9%) >35 ppb were 54 (16.3%); and >50 ppb were 17 (5.1%). It is known that both smoking and ICS treatment decrease FENO levels.[21] In the present study, current smokers included 46 (13.9%) cases and ICS users included 126 (38.1%) cases (Table 1). It is thought that the effect of ICS on the FENO value is much more potent than the effect of smoking status.[19,20] The distributions of ICS users are indicated by gray bars in Figure 1. The FENO values of these patients are likely to be underestimated in the current study. The procedures of the pulmonary function tests were according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. In any case, our present study revealed that there were definitely patients with asthma-like airway inflammation as represented by the high FENO values among the COPD outpatients, and that its prevalence rate was 16.3% when these values were estimated using 35 ppb as the cutoff value of FENO.

Prevalence rate of patients with high levels of total IgE in COPD

A subtotal of 230 (69.8%) of the 331 COPD patients had been measured for total IgE before their enrollment in the current study. A histogram of their total IgE values is shown in Figure 2. The cutoff value of IgE was set at 173 IU/mL in the current survey. The median value of total IgE was 91 IU/mL (IQR, 27–287 IU/mL). Out of 230 COPD patients, 82 (35.7%) patients had high levels of total IgE. These findings indicated that 35.7% of patients had atopic factors in COPD.

Prevalence rate of patients with atopic factors in combination with high values of FENO in COPD

It is reported that both elevated FENO and elevated IgE may be useful markers for predicting good responders to

Table 2 Comparison of clinical characteristics between high and low groups in FENO and IgE

Characteristic	FENO, n=331			IgE, n=230		
	High (>35 ppb)	**Low (≤35 ppb)**	**P-value**	**High (≥173 IU/mL)**	**Low (<173 IU/mL)**	**P-value**
Age, years	71.4±7.1	72.4±8.1	0.35	71.6±7.4	73.5±8.1	<0.05
Pack-years of tobacco use	52.5 (40–80)	62.6 (40–80)	0.63	50.0 (42–72)	53.9 (38–80)	0.88
Smoking status, n (%)						
Never-smokers or pack-years <10	3 (5.6)	7 (2.5)	0.49	2 (2.4)	5 (3.4)	0.51
Ex-smokers (>1 year)	42 (77.8)	217 (78.3)	0.53	67 (81.7)	121 (81.8)	0.56
Current smokers	4 (7.4)	42 (15.2)	<0.01	11 (13.4)	17 (11.5)	0.40
Unknown	5 (9.3)	11 (4.0)	0.10	2 (2.4)	5 (3.4)	0.52
mMRC scale, n (%)						
Grade 0	12 (22.2)	45 (16.2)	0.19	13 (15.9)	20 (13.5)	0.38
Grade 1	16 (29.6)	99 (35.7)	0.24	30 (36.6)	53 (35.8)	0.51
Grade 2	12 (22.2)	71 (25.6)	0.37	21 (25.6)	40 (27.0)	0.47
Grade 3	12 (22.2)	47 (17.0)	0.23	14 (17.1)	28 (18.9)	0.39
Grade 4	2 (3.7)	14 (5.1)	0.45	3 (3.7)	6 (4.1)	0.59
History of exacerbation, n (%)	21 (38.9)	94 (33.9)	0.24	29 (35.4)	57 (38.5)	0.37
History of allergic rhinitis, n (%)	7 (13.0)	29 (10.5)	0.37	17 (20.7)	13 (8.8)	<0.01
Pulmonary function, (%)						
%FVC	93.3±21.2	95.1±18.1	0.36	96.0±15.8	92.0±20.0	0.12
%FEV$_1$	58.3±19.6	62.2±21.1	0.29	63.2±20.3	59.5±20.3	0.21
FEV$_1$/FVC	50.3±14.0	51.4±12.7	0.53	52.6±13.2	50.9±12.7	0.39
GOLD classifications, n (%)						
I	9 (16.7)	59 (21.3)	0.26	18 (22.0)	23 (15.5)	0.15
II	26 (48.1)	132 (47.7)	0.51	43 (52.4)	74 (50.0)	0.41
III	15 (27.8)	70 (25.3)	0.40	18 (22.0)	37 (25.0)	0.36
IV	4 (7.4)	15 (5.4)	0.38	3 (3.7)	13 (8.8)	0.11

Abbreviations: FENO, fractional exhaled nitric oxide; IgE, immunoglobulin E; mMRC scale, modified Medical Research Council scale; FEV, forced expiratory volume; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
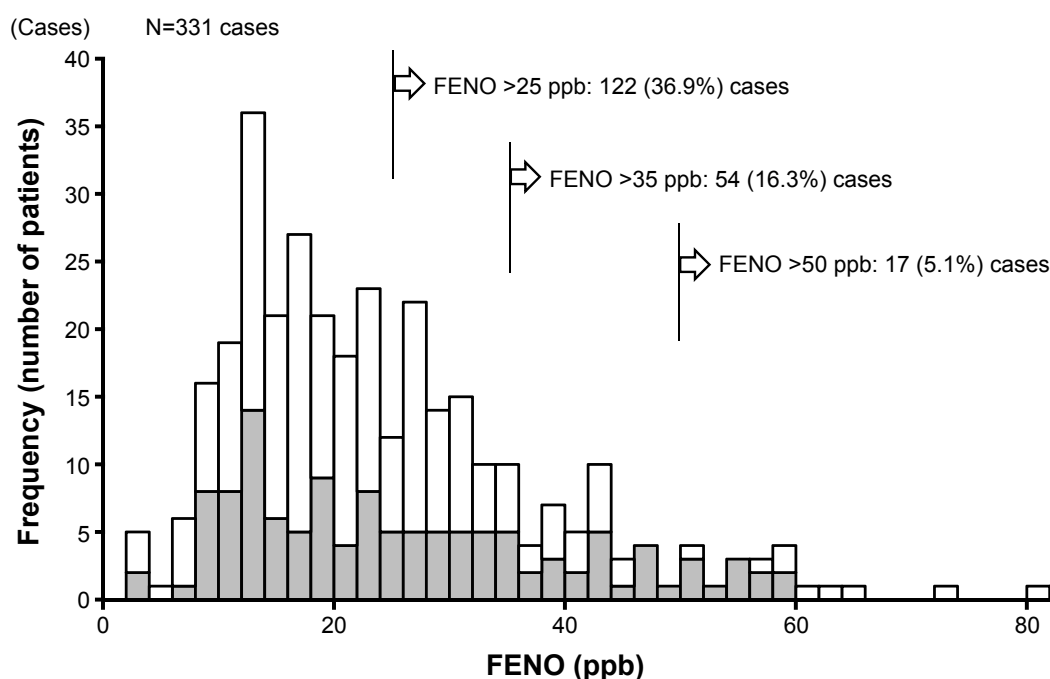
Figure 1 Histogram of FENO values in the subjects.
Notes: All 331 COPD patients were measured for FENO before their enrollment. The frequencies of patients without ICS are indicated by white bars, and ICS users are indicated by gray bars. The number of patients with FENO over 25 ppb were 112 (36.9%) cases; the number of patients with FENO over 35 ppb were 54 (16.3%) cases; and the number of patients with FENO over 50 ppb were 17 (5.1%) cases.
Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; FENO, fractional exhaled nitric oxide.
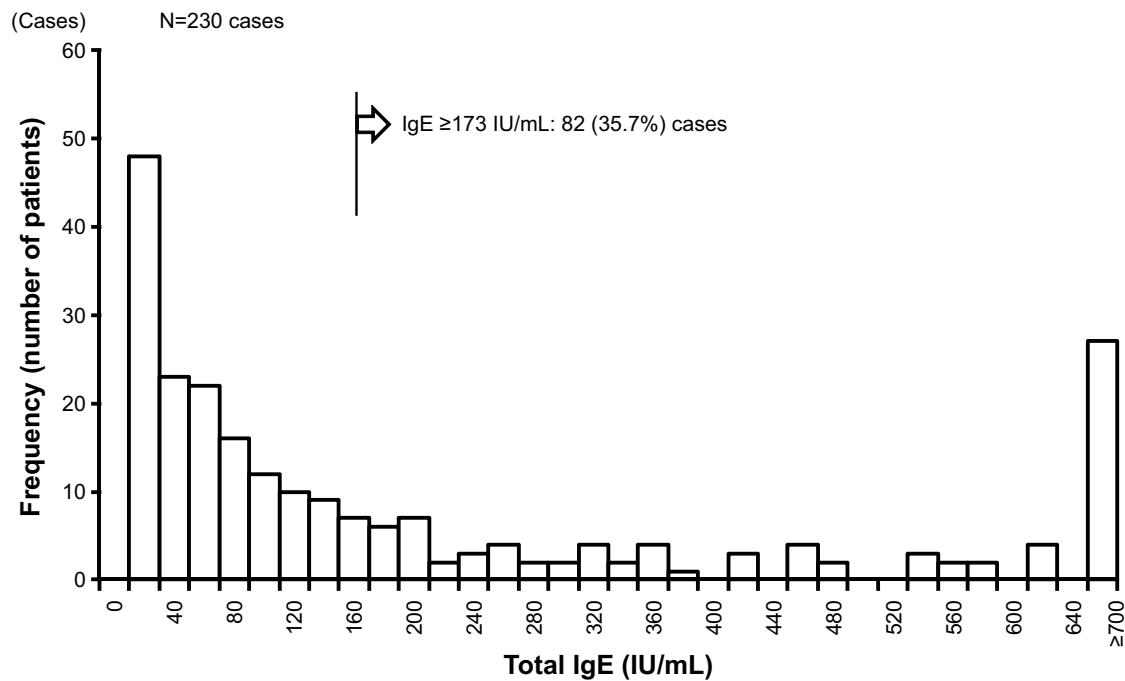
Figure 2 Histogram of total IgE values in the subjects.
Notes: A total of 230 (69.8%) of the 331 COPD patients were measured for total IgE before the enrollment. When the cutoff value of IgE was set at 173 IU/mL, there were 82 (35.7%) patients with a high level of total IgE out of 230 COPD patients.
Abbreviation: IgE, immunoglobulin E.

ICS/LABA combination in COPD.[23] As estimated by both FENO and IgE, the numbers of patients in each group are summarized in Figure 3. Out of 230 COPD patients, the high-FENO/high-IgE group comprised 18 cases (7.8% of patients), the high-FENO/low-IgE group comprised 22 cases (9.6% of patients), the low-FENO/high-IgE group comprised 64 cases (27.8% of patients), and the low-FENO/low-IgE group comprised 126 cases (54.8% of patients). These findings indicated that 7.8% of COPD patients have both asthma-like airway inflammation and atopic factors,
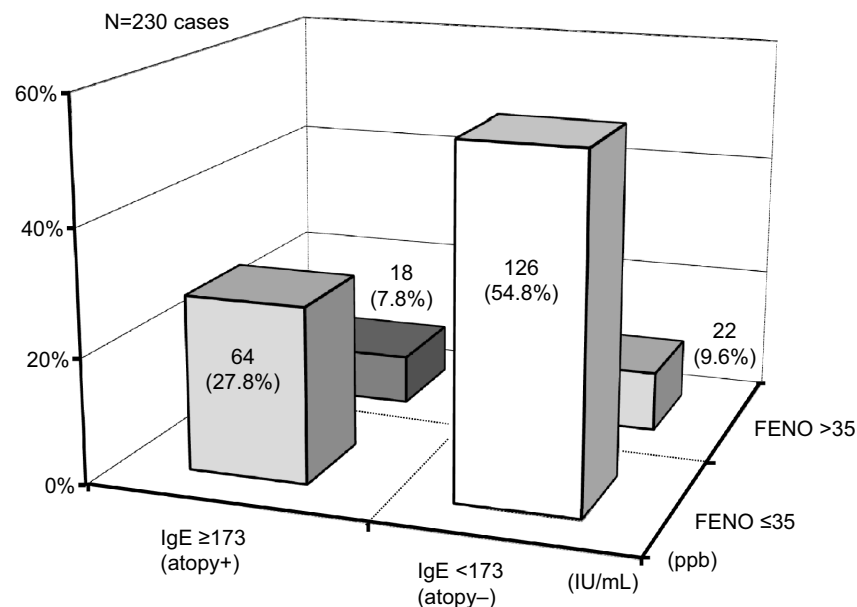
Figure 3 Number of patients when estimated by both FENO and IgE.
Notes: Patients were divided into subgroups by FENO and IgE as asthma-like inflammatory and atopic biomarkers, respectively. The dark gray bar represents the high-FENO/high-IgE group; the light gray bar represents either the high-FENO/low-IgE or low-FENO/high-IgE group; and the white bar represents the low-FENO/low-IgE group.
Abbreviations: FENO, fractional exhaled nitric oxide; IgE, immunoglobulin E.

and seem to be good responders to ICS/LABA combination treatment.

Discussion

As described in a document published by GINA and GOLD, patients with ACOS are known to experience frequent exacerbations.[10] ACOS patients are also known to have a poor quality of life, a more rapid decline in lung function, and higher mortality, in combination with using a disproportionate amount of health care resources compared to those with COPD or asthma alone.[4,10,24] It has therefore become very important to detect ACOS in COPD as early as possible. To date, the prevalence rate of ACOS is basically dependent on patient's symptoms or physician's opinions based on a questionnaire test. In 2003, Soriano et al mentioned that 30% of patients aged in their 50s, 40% of those aged in their 60s, and 70% of those aged in their 70s or older corresponded with the overlap syndrome when it was 1) diagnosed as asthma or emphysema by a doctor; 2) consisted of respiratory symptoms; and/or 3) was diagnosed using a pulmonary function test (including variable airflow obstruction or airway hyperresponsiveness).[11] In 2011, Zeki et al reported that 38% of elderly asthmatics corresponded with the overlap syndrome when it was defined as one of two clinical phenotypes: 1) allergic disease consistent with asthma (with or without emphysema or reduced DLco) or 2) COPD with emphysema accompanied by reversible or partially reversible airflow obstruction (with or without an allergic syndrome or reduced DLco).[12] These reports suggested that an overlap syndrome of asthma and COPD was the most common situation in older patients, as described in other reports.[25,26] We think that these prevalence rates are relatively high when compared to our results. In the present study, we used FENO and IgE as asthma-like inflammatory and atopic biomarkers, respectively. These biomarkers are recommended for a diagnosis of asthma in a document produced by GINA and GOLD.[1] In the current study, we revealed that when estimated by these objective biomarkers in addition to an original diagnosis by chest physicians, the prevalence rate of ACOS was 16.3% in COPD.

Concerning the subject selection, we enrolled COPD outpatients who had usually been treated by chest physicians in a general hospital without any particular intention. The original diagnosis for COPD had been carefully performed and strictly fit the criteria recommended by GOLD.[13] The distribution of the patient population of the present study did not show a remarkable deviation from the most popular clinical mega-trials, such as The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT)[27] or the Towards a Revolution in COPD Health (TORCH)[28] trials for COPD, although the ratio of mild and elderly patients was slightly high in our study. In the UPLIFT trial, the mean age of COPD patients was 64.5 years, and the percentages of GOLD stage II, III, and IV patients were 45%, 44%, and 8%, respectively.[27] In our current study, the mean age of the enrolled patients was 72.2 years, and the percentages of GOLD stage II, III, and IV patients were 48.0%, 25.7%, and 5.7%, respectively. The percentage of ICS users in the TORCH trial was approximately 45%,[28] which is similar to our present results (38.1% of ICS users). As a whole, the characteristics of COPD patients in our study did not differ from those in the most popular clinical mega-trials, although our current study only partly represented elderly patients.

Akamatsu et al reported that the baseline FENO levels and positive specific IgE were significantly associated with an improvement of the pulmonary function, such as FEV_1 or closing volume.[23] They also concluded that combining FENO and specific IgE may be a useful marker for predicting the response to ICS/LABA on airflow limitation in COPD.[23] When estimated by the cutoff values of FENO 35 ppb and IgE 173 IU/mL in the present study, the high-FENO/high-IgE group included 18 (7.8%) of the 230 COPD patients, and the low-FENO/low-IgE group included 126 (54.8%) patients (Figure 3). These findings indicate that patients with both asthma-like airway inflammation and atopic factors are 7.8% in COPD and that the expected nonresponders to ICS/LABA are 54.8% in COPD. In an ACOS document provided by GINA and GOLD, both FENO and IgE are recommended as inflammatory biomarkers to distinguish asthma from COPD.[1] All of these reports are in line with our strategies. We also believe that FENO and IgE are useful to reveal candidates of ACOS in COPD.

GINA refers to specific IgE, not total IgE, as a test for atopy.[1] However, one of our interests is showing the histogram of FENO or total IgE in COPD patients in order to reveal the prevalence of a high-FENO group or high-IgE group by some reliable cutoff values. In our current study, there were 148 patients with specific IgE in the high-IgE group, but only six cases with specific IgE in the low-IgE group. We therefore surmised that total IgE could be a substitute for specific IgE in the current study. As shown in a previous report,[15] the cutoff value of FENO to discriminate asthma from non-asthma was 28 ppb, even if the patients had allergic rhinitis. In the present study, we used the cutoff value of FENO 35 ppb as a predictive factor related to Th2-mediated airway inflammation. We think that patients with high FENO >35 ppb can be classified as ACOS, whether

they have allergic rhinitis or not. Concerning the effects of ICS or smoking status on FENO, the mean values of FENO were 23.7±14.2 ppb in ICS users and were 21.8±13.4 ppb in ICS nonusers. Because the FENO values before the ICS treatment were not included in the current study, we could not know the effects of ICS on FENO. The mean values of FENO were 18.9±12.5 ppb in current smokers and were 23.0±13.6 ppb in ex- and never-smokers.

Recently, Donohue et al used FENO in COPD patients to reveal Th2-mediated airway inflammation.[29] They showed that 8% of COPD patients had a FENO of 25–50 ppb, and 3% of COPD patients had a FENO >50 ppb. In our current study, 20.6% of COPD patients had a FENO of 25–50 ppb, and 5.1% had a FENO >50 ppb. We do not have a clear explanation for this discrepancy, but one factor is thought to be the difference in the age distribution. The mean age ± SD of the enrolled patients was 63.9±11.34 years in Donohue et al's study,[29] but it was 72.2±8.0 years in our current study. As described in other reports,[10–12,25,26] the prevalence rate of ACOS tends to increase with age. In any case, we think that FENO values are thought to be useful to detect ACOS in a COPD population.

There are several limitations in the present results, because our study design is a descriptive study, not an intervention study. First, there were 126 (38.1%) ICS users in a total of 331 COPD patients. It is known that ICS treatment decreases FENO levels.[19–21] These patients are likely to be underestimated in FENO values. Second, we did not confirm eosinophilic inflammation in the airway by immunohistochemical examinations or airway hyper-responsiveness. However, most COPD patients with high levels of FENO and IgE had a history of asthmatic symptoms or were diagnosed as asthmatics in the past. Another limitation is that FENO was measured in 331 patients, but IgE was measured in only 230 patients. This discrepancy for IgE was more than 30%. Further close examinations are needed to diagnose ACOS in future, but it is still necessary to establish routine estimation using objective biomarkers, as presented here.

Conclusion

In conclusion, we investigated COPD patients with asthma-like airway inflammation and atopic factors, who are candidates of ACOS in COPD. The prevalence rate of ACOS (FENO >35 ppb) was 16.3% in COPD. To the best of our knowledge, this study is the first of its kind to estimate ACOS in COPD using objective biomarkers recommended by international guidelines. The results of the current case report should be useful for detecting subgroups that need early intervention by ICS/LABA combination for COPD and for disseminating the proper treatment in order to improve the long-term management for ACOS in COPD.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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