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Original Article

Thymus and activation-regulated chemokine (TARC/CCL17) predicts decline of pulmonary function in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background: The deterioration of pulmonary function, such as FEV₁-decline, is strongly associated with poor prognosis in patients with chronic obstructive pulmonary disease (COPD). However, few investigations shed light on useful biomarkers for predicting the decline of pulmonary function. We evaluated whether thymus and activation-regulated chemokine (TARC), a Th2 inflammation marker, could predict rapid FEV₁-decline in COPD patients.

Methods: We recruited 161 patients with stable COPD and performed pulmonary function test once every six months. At the time of registration, blood tests, including serum levels of TARC were performed. We assessed the correlation between changes in parameters of pulmonary function tests and serum levels of TARC. The rapid-decline in pulmonary function was determined using 25th percentile of change in FEV₁ or FEV₁ percent predicted (%FEV₁) per year.

Results: In the FEV₁-rapid-decline group, the frequency of exacerbations, the degree of emphysema, and serum levels of TARC was higher than in the non-rapid-decline group. When using %FEV₁ as a classifier instead of FEV₁, age, the frequency of exacerbations, the degree of emphysema and serum levels of TARC in the rapid-decline group was significantly greater than those in the non-rapid-decline group. In univariate logistic regression analysis, TARC was the significant predictive factor for rapid-decline group. In multivariate analysis adjusted for emphysema, serum levels of TARC are independently significant predicting factors for the rapid-decline group.

Conclusions: TARC is an independent predictive biomarker for the rapid-decline in FEV₁. Measuring serum TARC levels may help the management of COPD patients by predicting the risk of FEV₁ decline.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a lung disorder defined by irreversible and progressive airflow obstruction. Additionally, COPD is a major cause of chronic morbidity and mortality in the world.¹ Deterioration of pulmonary function such as a decline in forced expiratory volume in one second (FEV₁) is

strongly associated with poor prognosis in patients with COPD.² However the rate of change in FEV₁ among patients with COPD varies considerably.^{3,4} Epidemiological study of the general Japanese population revealed that serum iron levels are biomarkers for pulmonary function susceptibility to individuals that smoke cigarettes and that hyperhomocysteinemia predicts a decrease in pulmonary function.^{5,6} There are several valuable blood biomarkers for predicting the progression of COPD. Previous studies have reported an association between systemic inflammation markers, namely increasing CRP and neutrophil counts, with a decrease in pulmonary function.^{7–9} Furthermore, other investigators demonstrated that higher age and serum levels of CRP were associated with poor prognosis in patients with COPD.^{10–12}

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In addition, fibrinogen and CRP tend to correlate with COPD severity and risk of exacerbations.¹³ However, some data is inconsistent with these results.

Thymus and activation-regulated chemokine/C–C motif chemokine 17 (TARC/CCL17) is a chemokine (CC) that is constitutively expressed in the thymus.¹⁴ TARC is produced by macrophages, epithelial cells, dendritic cells, vascular endothelial cells, fibroblasts, and lymphocytes such as CD4 positive T cells.^{15–17} TARC is induced by cellular activation of peripheral blood mononuclear cells, macrophages, endothelial cells, dendritic cells, and keratinocytes.^{18–20} TARC binds to chemokine receptor CCR4, highly expressed in Th2 cells.²¹

TARC has been suggested to be an important mediator for accumulating Th2 cells in allergic diseases such as atopic dermatitis, asthma, and allergic rhinitis.^{17,22–24} Elevated levels of TARC have been detected in patients with atherosclerotic lesions and chronic lesion mucosa of Crohn's disease.^{25,26} Also, CCR4 plays an important role in a model of sepsis,²⁷ and these diseases are mainly associated with Th1 inflammation. Although smoking is mainly associated with Th1 inflammation, elevation of TARC in lungs and bronchial alveolar lavage has been reported in a rat model smoking-induced pulmonary inflammation.¹⁴

Based on these findings, we hypothesized that TARC is related to airway inflammation and may also play a role in the onset and progression of COPD. Therefore, the purpose of this investigation was to determine if serum levels of TARC are associated with pulmonary function in patients with COPD.

Methods

Study population

The Institutional Ethics Committee of the Yamagata University Faculty of Medicine approved all procedures (approval number; H23-134, approval date January 5, 2012). Written informed consent was obtained from all the subjects.

In this prospective cohort study, we recruited 253 patients with stable COPD in Yamagata University Hospital from January 2014 to March 2016, and follow-up until January 2020. All subjects were over 40 years old and had a former or current smoking history of at least ten pack-years or more. The subject's COPD diagnosis was based on the spirometric criteria of Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline standards (a ratio of post-bronchodilator FEV₁ to FVC <0.70). Subjects with asthma and a history of asthma were also included in this study. The subject's Asthma-COPD overlap (ACO) diagnosis was based on The JRS Guidelines for the Management of ACO 2018 (Japanese Respiratory Society). That is, we defined ACO when the COPD patients meet two of 1–3 or meet at least one of 1–3 and at least two of 4; 1: Variable or paroxysmal clinical symptoms, 2: Previous diagnosis of asthma before 40 years-old, 3: Increase of fractional exhaled nitric oxide (FeNO) > 35 ppb, 4: 1) a history of allergic rhinitis, 2) bronchodilator reversibility (>12% and >200 ml), 3) elevated peripheral eosinophils (>5% or > 300/μl), 4) elevated total or allergen-specific immunoglobulin (Ig) E level.²⁸

Ninety-two patients were excluded for reasons; pulmonary function tests for less than two years (n = 69), lack of laboratory data (n = 14), lack of TARC data (n = 9). Ninety-two patients were excluded for reasons; pulmonary function tests for less than two years (n = 69), lack of laboratory data (n = 14), lack of TARC data (n = 9). Therefore, the actual number of participants analyzed was 161.

Table 1

Clinical characteristics of the subjects.

	Mean, number or median (interquartile range)
Age (yr)	69.7 ± 8.7
Male/Female	156/5
Follow-up period (yr)	4.8 ± 1.3
BMI (kg/m ²)	23.0 ± 3.4
Pack-years	52.3 ± 32.1
Current smoker (%)	20 (12.4)
GOLD I/II/III/IV	52/79/21/9
CAT (score)	8 (4–14)
Exacerbations (/yr)	0 (0–0.16)
LAA (score)	5 (2–8)
Changes of FEV ₁ (ml/yr)	–9.0 (–47.0–28.0)
Changes of %FEV ₁ (%/yr)	0.332 (–0.936–1.804)
Non-ACO/ACO	134/27
Use of ICS at registration (%)	21 (13.0)
AST (IU/l)	21.0 (18.5–27.0)
ALT (IU/l)	19.0 (14.0–25.5)
BUN (mg/dl)	16.7 ± 5.0
Creatinine (mg/dl)	0.81 ± 0.21
hsCRP (mg/dl)	0.09 (0.04–0.20)
IgE (IU/ml)	69.3 (23.1–230.5)
TARC (pg/ml)	380.4 ± 206.3
WBC (/μl)	6440.7 ± 2018.4
Neut (/μl)	3812.3 ± 1472.5
Lymph (/μl)	1861.7 ± 702.5
Eos (/μl)	188.8 ± 125.4
RBC (10 ⁶ /μl)	4.60 ± 0.53
Hb (g/dl)	14.1 ± 1.6
Ht (%)	43.1 ± 4.2
Plt (10 ⁴ /μl)	22.1 ± 6.2

Data are presented as mean ± SD, median (with ranges in parentheses, 25th–75th percentile) or n. BMI, body mass index; LAA, low attenuation area on CT scan; ACO, asthma-COPD overlap; ICS, inhaled corticosteroid; hsCRP, high sensitive C-reactive protein; TARC, Thymus and activation-regulated chemokine.

Study protocol

At the time of registration sex, age, height, weight, smoking status, past treatment history, internal history, and symptoms, including COPD assessment test (CAT) score were recorded. Additionally, spirometry measurements before and after bronchodilator inhalation, blood test including serum levels of TARC, and chest CT were performed and registered. Evaluation of emphysema by CT was scored using Lung Vison® (SYBERNET). In chest CT, Lung Vison® visualizes the low attenuation area (LAA) in yellow and can be evaluated by score (0–4; 0: less than 5% of lung field, 1: 5% or more and less than 25% of the lung field, 2: 25% or more and less than 50% of the lung field, 3: 50% or more and less than 75% of the lung field, 4: over 75% of the lung field). The low attenuation area of the upper, middle and lower parts of the left and right lung fields were measured and scored (0–24; 0–7 as mild, 8–15 as Moderate, 16– as severe).²⁹ The treatment for patients was decided by the attending physicians and was not particularly limited. The interval of outpatient visits was once a month, every two months, or every three months. In every visit, smoking status, medication status, and presence of exacerbations during the interval were confirmed by oral communication. Additionally, exacerbations due to unscheduled visits and hospitalization were recorded. In this study, exacerbation was defined as the need to change or add treatment during the stable period due to increased shortness of breath, increased cough and sputum, and appearance or enhancement of chest discomfort and discomfort.

Laboratory data

Peripheral blood counts, renal and liver function, IgE, inflammatory response [indicated by high sensitivity-CRP (hsCRP)], and

TARC were measured at the time of registration with routine laboratory techniques. TARC was quantified by the enzyme-linked immunosorbent assay (SRL, Tokyo, Japan).

Pulmonary function tests

Spirometry before and after inhalation of bronchodilator (Salbutamol) was performed once every six months. Changes in individual annual FEV₁ after bronchodilator inhalation and percent predicted FEV₁ (%FEV₁) after bronchodilator inhalation were calculated for subjects who underwent spirometry for more than two years (at least three times). A regression analysis was performed, and the slope was expressed as an annual change in respiratory function of an individual. We classified subjects into two groups according to the magnitude of the annual change in FEV₁ and %FEV₁. We defined those whose pulmonary function declined more than the 25th percentile per year as a rapid-decline group, and the other subjects were placed in the non-rapid-decline group.

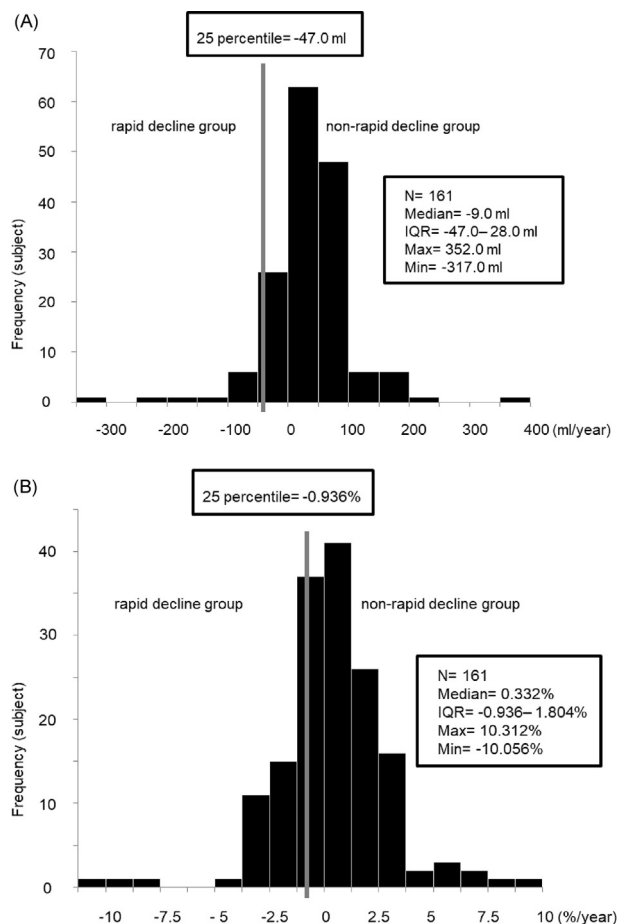


Fig. 1. Histogram of annual change in FEV₁ (A) and %FEV₁ (B) of subjects after inhalation of a bronchodilator. We defined those whose pulmonary function declined more than the 25th percentile per year as a rapid-decline group, and the other subjects were placed in the non-rapid-decline group. (A) The average of the annual change in FEV₁ of subjects after inhalation of bronchodilator was -9.0 ml (-47.0–28.0 ml). The annual change in FEV₁ in the rapid-decline group was -73.5 ml (-103.0 to -55.3 ml), and in the non-rapid-decline group was 0.182% (-18.0–35.0 ml). (B) The average annual change in %FEV₁ was 0.332% (-0.936–1.804%). The annual change in %FEV₁ in the rapid-decline group was -2.018% (-3.193–1.372%), and in the non-rapid-decline group was 0.850% (0.114–2.198%). IQR, interquartile range.

Statistical analyses

Data are presented as mean $\pm$ standard deviation (SD), median (with ranges in parentheses, 25th–75th percentile) or n. JMP® (ver13) was used to perform all statistical analyses. The univariate analysis was performed as necessary using the chi-square test, Student's *t*-test, and Wilcoxon rank sum test. Multivariate analysis was performed on the relevant factors in the univariate analysis. The TARC value at which “sensitivity- (1- specificity)” became the maximum was adopted as the cutoff value of the receiver operating characteristic (ROC) curve. A *p* value less than 0.05 was considered statistically significant.

Results

Table 1 shows the clinical characteristics of the subjects. The mean age was 69.7 $\pm$ 8.7 years old, and body mass index was 23.0 $\pm$ 3.4 kg/m². The mean follow-up period was 4.8 $\pm$ 1.3 years. The average of the annual change in FEV₁ of subjects after inhalation of bronchodilator was -9.0 ml (-47.0–28.0 ml) (Fig. 1A). The annual change in FEV₁ of the subjects was normally distributed.

Table 2
Clinical characteristics of patients relative to the decline of FEV₁.

	Rapid decliner (n = 38)	Non-rapid decliner (n = 123)	P
Age (yr)	71.7 $\pm$ 6.1	69.0 $\pm$ 9.3	0.0967
Male/Female	38/0	118/5	0.5925
Follow-up period (yr)	4.6 $\pm$ 1.2	4.9 $\pm$ 1.3	0.2632
BMI (kg/m ²)	23.0 $\pm$ 3.3	23.0 $\pm$ 3.5	0.9983
Pack-years	52.7 $\pm$ 27.6	51.5 $\pm$ 32.5	0.8304
Current smoker (%)	4 (10.5)	16 (13.0)	0.7859
GOLD I/II/III/IV	16/14/4/4	36/65/17/5	0.1444
CAT (score)	9.0 (4.8–16.5)	7.0 (3.0–13.0)	0.1760
Exacerbations (/yr)	0 (0–0.30)	0 (0–0)	0.0110
LAA (score)	6 (4–9)	4 (1–6)	0.0018
Changes of FEV ₁ (ml/yr)	-73.5 (-103.0 to -55.3)	1.0 (-18.0–35.0)	<0.0001
Changes of %FEV ₁ (%/yr)	-2.018 (-5.025 to -1.350)	0.822 (0.080–2.147)	<0.0001
Non-ACO/ACO	34/4	99/23	0.3225
Use of ICS at registration (%)	4 (10.5)	17 (13.8)	0.7847
Use of ICS during the follow-up period (%)	15 (39.5)	30 (24.4)	0.0970
Use of LAMA at registration (%)	10 (26.3)	29 (23.6)	0.8288
Use of LAMA during the follow-up period (%)	31 (81.6)	103 (83.7)	0.8048
Use of LABA at registration (%)	8 (21.1)	25 (20.3)	1.000
Use of LABA during the follow-up period (%)	27 (71.1)	82 (66.7)	0.6940
hsCRP (mg/dl)	0.09 (0.04–0.30)	0.09 (0.04–0.19)	0.4846
IgE (IU/ml)	60.2 (19.9–153.5)	69.6 (24.3–250.5)	0.7332
TARC (pg/ml)	445.0 $\pm$ 239.2	360.4 $\pm$ 191.8	0.0237
WBC (/μl)	6255.0 $\pm$ 1772.3	6498.1 $\pm$ 2091.9	0.5180
Neut (/μl)	3867.4 $\pm$ 1264.5	3795.3 $\pm$ 1535.4	0.7929
Lymp (/μl)	1817.6 $\pm$ 806.8	1875.3 $\pm$ 670.1	0.6598
Eos (/μl)	160.3 $\pm$ 84.0	197.6 $\pm$ 134.7	0.1091
RBC (10 ⁶ /μl)	4.72 $\pm$ 0.56	4.57 $\pm$ 0.51	0.1473
Hb (g/dl)	14.3 $\pm$ 1.5	14.1 $\pm$ 1.6	0.3704
Ht (%)	43.9 $\pm$ 3.8	42.9 $\pm$ 4.3	0.2324
Plt (10 ⁴ /μl)	22.5 $\pm$ 5.9	21.9 $\pm$ 6.2	0.6027

Analyzed by Student *t*-test or Wilcoxon rank sum test or chi-square test. Data are presented as mean $\pm$ SD, median (with ranges in parentheses, 25th–75th percentile) or n. BMI, body mass index; LAA, low attenuation area on CT scan; ACO, asthma-COPD overlap; ICS, inhaled corticosteroid; LAMA, Long-acting muscarinic antagonist; LABA, Long-acting beta2-agonist; hsCRP, high sensitive C-reactive protein; TARC, Thymus and activation-regulated chemokine.

Table 3
Clinical characteristics of patients relative to the decline of %FEV₁.

	Rapid decliner (n = 40)	Non-rapid decliner (n = 121)	P
Age (yr)	72.5 ± 6.3	68.8 ± 9.2	0.0201
Male/Female	40/0	116/5	0.3333
Follow-up period (yr)	4.7 ± 1.3	4.8 ± 1.3	0.7019
BMI (kg/m ²)	22.5 ± 3.3	23.1 ± 3.5	0.3308
Pack-years	53.0 ± 28.1	51.4 ± 32.5	0.7832
Current smoker (%)	5 (12.5)	15 (13.0)	1.0000
GOLD I/II/III/IV	13/15/7/5	39/64/14/4	0.1048
CAT (score)	10.0 (4.3–16.8)	7.0 (3.0–13.0)	0.1219
Exacerbations (/yr)	0.16 (0–0.32)	0 (0–0)	<0.0001
LAA (score)	7 (5–11)	4 (1–6)	<0.0001
Changes of FEV ₁ (ml/yr)	–72.5 (–99.75 to –52.0)	2.0 (–17.0–35.0)	<0.0001
Changes of %FEV ₁ (%/yr)	–2.018 (–3.193 to –1.372)	0.850 (0.114–2.198)	<0.0001
Non-ACO/ACO	36/4	97/23	0.2275
Use of ICS at registration (%)	7 (17.5)	14 (11.6)	0.4159
Use of ICS during the follow-up period (%)	15 (37.5)	30 (24.8)	0.1545
Use of LAMA at registration (%)	14 (35.0)	25 (20.7)	0.0879
Use of LAMA during the follow-up period (%)	33 (82.5)	101 (83.5)	1.0000
Use of LABA at registration (%)	12 (30.0)	21 (17.4)	0.1128
Use of LABA during the follow-up period (%)	28 (70.0)	81 (66.9)	0.8459
hsCRP (mg/dl)	0.09 (0.04–0.29)	0.09 (0.04–0.19)	0.8688
IgE (IU/ml)	54.6 (18.0–144.5)	77.3 (24.8–281.0)	0.3591
TARC (pg/ml)	454.5 ± 243.5	335.9 ± 187.2	0.0084
WBC (/μl)	6206.5 ± 1924.7	6518.2 ± 2050.3	0.3989
Neut (/μl)	3761.0 ± 1079.1	3829.3 ± 1584.8	0.8003
Lymph (/μl)	1830.1 ± 894.4	1872.0 ± 630.6	0.7427
Eos (/μl)	157.8 ± 87.1	199.0 ± 134.4	0.0710
RBC (10 ⁶ /μl)	4.61 ± 0.60	4.61 ± 0.50	0.9445
Hb (g/dl)	14.2 ± 1.6	14.1 ± 1.6	0.7677
Ht (%)	43.4 ± 4.5	43.1 ± 4.1	0.7173
Plt (10 ⁴ /μl)	22.1 ± 5.8	22.1 ± 6.3	0.9884

Analyzed by Student t-test or Wilcoxon rank sum test or chi-square test. Data are presented as mean ± SD, median (with ranges in parentheses, 25th–75th percentile) or n. BMI, body mass index; LAA, low attenuation area on CT scan; ACO, asthma-COPD overlap; ICS, inhaled corticosteroid; LAMA, Long-acting muscarinic antagonist; LABA, Long-acting beta2-agonist; hsCRP, high sensitive C-reactive protein; TARC, Thymus and activation-regulated chemokine.

Many subjects maintained pulmonary function during the follow-up period.

According to the above definition, the annual change in FEV₁ in the rapid-decline group was –73.5 ml (–103.0 to –55.3 ml), and in the non-rapid-decline group was 1.0 ml (–18.0–35.0 ml). Table 2 shows the clinical characteristics of subjects in the two groups. There were no significant differences in sex, pack-years, GOLD stage, and CAT score between the two groups. Conversely, in the rapid-decline group, emphysematous score evaluated by CT scan (LAA) was significantly higher, and the frequency of exacerbations was more than in the non-rapid group. Furthermore, in the rapid-decline group, serum levels of TARC were higher than in the non-rapid-decline group. Although not significantly, in rapid-decline group tended to be older than non-rapid decline group.

Next, we performed a similar analysis using %FEV₁. The average annual change in %FEV₁ was 0.332% (–0.936–1.804%, Fig. 1B). According to the cutoff mentioned above, the annual change in %FEV₁ in the rapid-decline group was –2.018% (–3.193 to –1.372%), and in the non-rapid-decline group was 0.850% (0.114–2.198%). Table 3 shows the clinical characteristics of subjects in the two groups. There were no significant differences in sex, pack-years, GOLD

Table 4
Univariate and multivariate logistic regression analysis for discriminating the subjects who rapidly decline in FEV₁ and %FEV₁.

FEV ₁	Odds ratio	95% confidence interval	p value
Univariate analysis			
LAA (increasing 1-score)	1.15	1.05–1.25	0.0029
TARC (increasing 1-SD)	1.46	1.04–2.07	0.0316
Multivariate analysis			
LAA (increasing 1-score)	1.15	1.04–1.26	0.0033
TARC (increasing 1-SD)	1.44	1.01–2.06	0.0478
%FEV ₁			
Univariate analysis			
LAA (increasing 1-score)	1.22	1.10–1.34	<0.0001
TARC (increasing 1-SD)	1.56	1.11–2.20	0.0108
Multivariate analysis			
LAA (increasing 1-score)	1.22	1.11–1.35	<0.0001
TARC (increasing 1-SD)	1.56	1.07–2.26	0.0190

TARC, Thymus and activation-regulated chemokine.

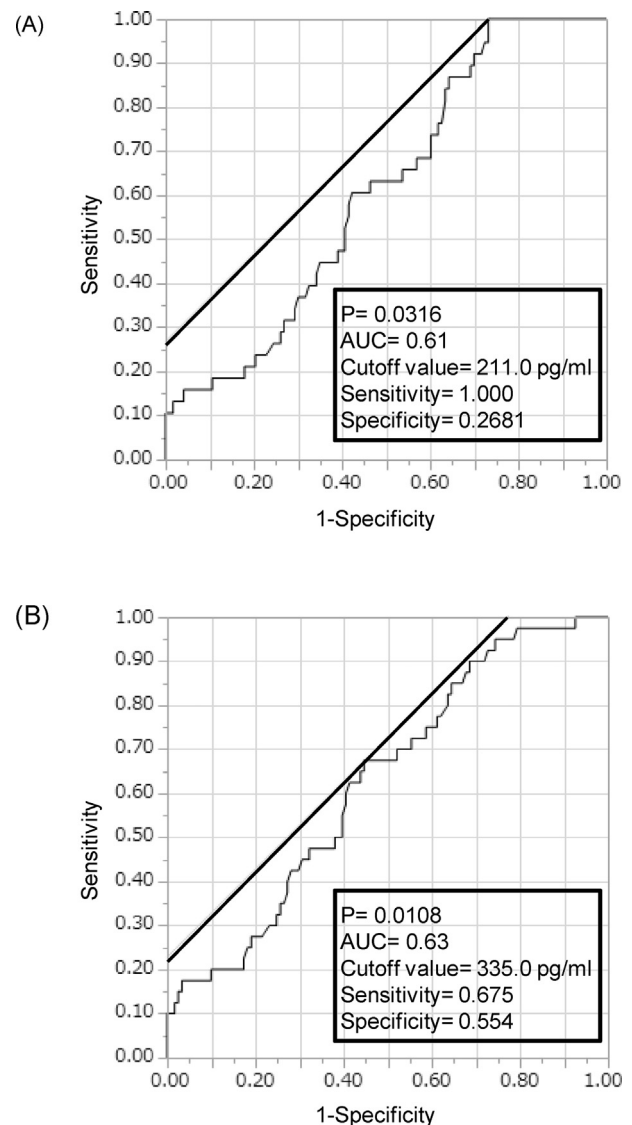


Fig. 2. ROC curve analysis of TARC for discriminating the subjects who rapidly decline in FEV₁ (A) and %FEV₁ (B). AUC, area under the curve.

stage, and CAT score between the two groups. Conversely, in the rapid-decline group, age was significantly older, and emphysematous score evaluated by CT scan was significantly higher, and the frequency of exacerbations was significantly more than in the non-rapid group. Furthermore, in the rapid-decline group, serum levels of TARC were higher than those in the non-rapid-decline group.

Table 4 shows the univariate and multivariate logistic regression analysis for discriminating the subjects who had a rapid-decline in FEV₁. Covariates that were significantly different between the two groups were applied to this analysis. In the univariate logistic regression analysis, higher serum levels of TARC was the significant predicting factor for the rapid-decline group (OR: 1.46, 95% CI: 1.04–2.07, *p* value = 0.0316). Furthermore, in multivariate analysis, serum levels of TARC are significant predicting factor for the rapid-decline group, independent from severity of emphysema (OR: 1.44, 95%CI: 1.01–2.06, *p* value = 0.0478).

Similarly, we performed univariate and multivariate logistic regression analysis for discriminating the subjects who rapidly decline in %FEV₁ (Table 4). Since %FEV₁ was already adjusted for age, which was not included in the analysis. High serum levels of TARC were the significant predicting factor for rapid the decline group (OR: 1.56, 95%CI: 1.07–2.26, *p* value = 0.0190).

A ROC curve was used to determine the cutoff value for serum levels of TARC that detect the rapid-decline of FEV₁ and %FEV₁ (Fig. 2A, B). When using FEV₁-rapid-decline group, the area under the curve was 0.61, and the cutoff value was 211.0 pg/ml, the

sensitivity was 1.000, and the specificity was 0.268 (*p* value = 0.0316) (Fig. 2A). Further, when using %FEV₁-rapid-decline group, the area under the curve was 0.630, and the cutoff value was 335.0 pg/ml, the sensitivity was 0.675, and the specificity was 0.554 (*p* value = 0.0108) (Fig. 2B). Differences in subject characteristics who had high serum TARC levels over cutoff value and subjects who had them within cutoff range are indicated in Table 5. Serum levels of IgE, numbers of platelet in peripheral blood and percentage of the patients with decliner were higher in the subjects who had high serum levels of TARC than in subjects who had them within cutoff range when using FEV₁. Similarly, age was significantly older, serum levels of IgE, numbers of eosinophil, lymphocytes and platelet, and percentage of the patients with decliner were higher in the subjects who had high serum levels of TARC than in subjects who had them within cutoff range when using %FEV₁.

Figure 3 shows the relationship between changes of FEV₁ (A) and %FEV₁ (B), and serum levels of TARC. There were statistically significant inverse relationships between changes of FEV₁ and %FEV₁, and serum levels of TARC (*r* = −0.1871, *p* = 0.0175 and *r* = −0.2158, *p* = 0.0060 respectively).

Discussion

In this prospective cohort study, 161 COPD patients were followed for an average of 4.8 years. As reported in the Hokkaido COPD Cohort Study, the present investigation confirms that many

Table 5

Differences of the characteristics between subjects who had high serum TARC levels over cutoff value and subjects who have them within cutoff range, using FEV₁ and %FEV₁.

FEV ₁	High serum TARC level group (≥211 pg/ml) (n = 127)	Low serum TARC level group (<221 pg/ml) (n = 34)	P
Rapid decliner (%)	37 (29.1)	1 (2.9)	0.0006
Age (yr)	70.1 ± 8.0	68.0 ± 10.8	0.2139
Pack-years	52.7 ± 32.5	47.5 ± 26.9	0.4907
Current smoker (%)	17 (13.4)	3 (8.8)	0.5720
GOLD I/II/III/IV	43/59/19/6	9/20/2/3	0.2851
Exacerbations (/yr)	0 (0–0.16)	0 (0–0.16)	0.9056
LAA (score)	5 (2–8)	4 (0–7)	0.2242
Non-ACO/ACO	105/21	28/6	1.0000
Use of ICS at registration (%)	16 (12.6)	5 (14.7)	0.7759
Use of LAMA at registration (%)	33 (26.0)	6 (17.6)	0.3737
Use of LABA at registration (%)	22 (17.3)	11 (32.4)	0.0914
IgE (IU/ml)	87.6 (31.6–300.8)	24.8 (8.6–75.3)	0.0003
WBC (/μl)	6475.0 ± 1890.7	6312.9 ± 2466.1	0.6790
Neut (/μl)	3805.6 ± 1366.2	3837.4 ± 1840.1	0.9115
Lymph (/μl)	1927.5 ± 694.9	1615.9 ± 685.8	0.0211
Eos (/μl)	191.3 ± 127.9	179.4 ± 116.5	0.6260
Plt (10 ⁴ /μl)	23.1 ± 6.1	18.4 ± 5.1	<0.0001
%FEV ₁	High serum TARC level group (≥335 pg/ml) (n = 80)	Low serum TARC level group (<335 pg/ml) (n = 81)	P
Rapid decliner (%)	26 (32.5)	14 (17.3)	0.0294
Age (yr)	71.1 ± 7.5	68.3 ± 9.6	0.0418
Pack-years	52.5 ± 28.5	51.0 ± 34.1	0.7642
Current smoker (%)	12 (15.0)	8 (9.9)	0.3498
GOLD I/II/III/IV	23/40/14/3	29/39/7/6	0.2580
Exacerbations (/yr)	0 (0–0.18)	0 (0–0.16)	0.7047
LAA (score)	5 (2–8)	4 (1.3–7.8)	0.3575
Non-ACO/ACO	66/13	67/14	1.0000
Use of ICS at registration (%)	11 (13.8)	10 (12.4)	0.8191
Use of LAMA at registration (%)	22 (27.5)	17 (21.0)	0.3624
Use of LABA at registration (%)	16 (20.0)	17 (21.0)	1.0000
IgE (IU/ml)	95.1 (31.6–323.0)	51.3 (15.2–138.0)	0.0070
WBC (/μl)	6433.4 ± 1789.7	6448.0 ± 2232.6	0.9634
Neut (/μl)	3816.4 ± 1418.7	3808.3 ± 153,274	0.9723
Lymph (/μl)	1927.5 ± 694.9	1615.9 ± 685.8	0.0211
dEos (/μl)	210.9 ± 148.6	166.9 ± 93.1	0.0256
Plt (10 ⁴ /μl)	23.4 ± 6.1	20.7 ± 5.9	0.0046

Analyzed by Student t-test or Wilcoxon rank sum test or chi-square test. Data are presented as mean ± SD, median (with ranges in parentheses, 25th–75th percentile) or n. TARC, Thymus and activation-regulated chemokine.

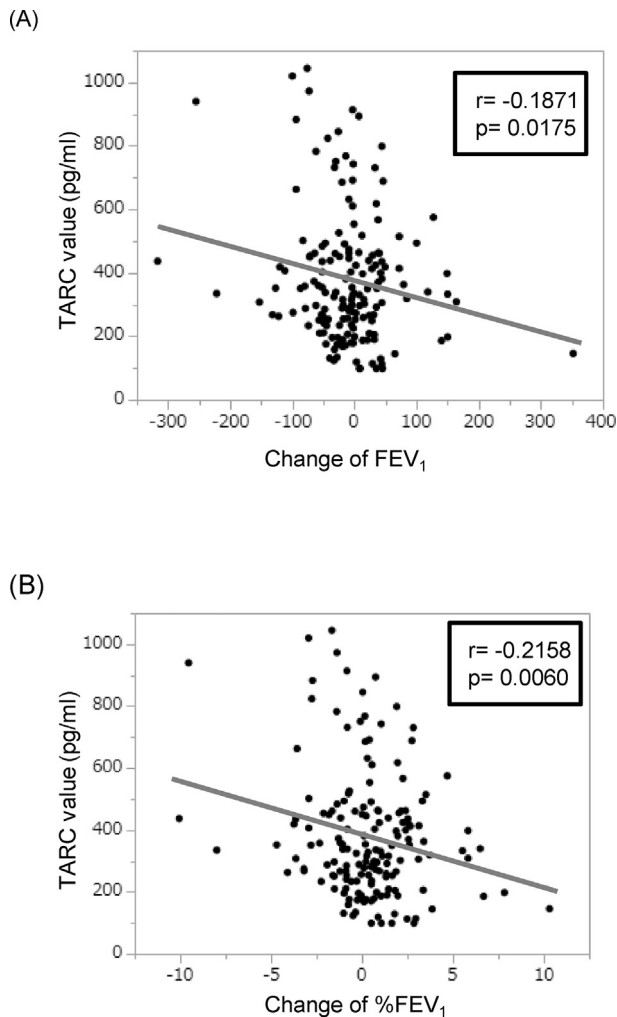


Fig. 3. The relationship between change of FEV₁ (A) and %FEV₁ (B), and TARC values. There were inverse relationships between change of FEV₁ and %FEV₁, and TARC values. TARC, Thymus and activation-regulated chemokine.

COPD patients maintain pulmonary function during the follow-up period.⁴ In this study, COPD patients were classified into a rapid-decline and non-decline group, according to the level of decline in pulmonary function, FEV₁ and %FEV₁. Patients in the rapid-decline group had significantly higher serum levels of TARC than those in the non-rapid-decline group. In the current study, serum levels of TARC were predictive for the rapid-decline in FEV₁ and %FEV₁. These results show a clear relationship between serum TARC levels and decline in pulmonary function in patients with COPD.

Nishimura and colleagues reported that the severity of emphysema was independently related to the rapid-decline in FEV₁ in patients with COPD.⁴ Haruna *et al.* also reported that the degree of pulmonary emphysema was a predictive factor of patient prognosis.³⁰ In our study, the rapid-decline group was significantly higher emphysematous score evaluated by CT scan (LAA) than in the non-rapid decline group. This finding is consistent with previous studies.

In the rapid-decline group, exacerbation rate was significantly more frequent than in the non-rapid-decline group (Table 2, 3). Exacerbation frequency affects FEV₁ decline, and COPD patients who frequently have exacerbations have a poorer prognosis.^{4,31} In the present study, the observation period was relatively short to evaluate patient prognosis easily. However, it is suggested that the

prognosis of the rapid-decline group may be poorer than that of non-rapid-decline since exacerbation deteriorates the health status of the patients. In this regard, further investigations are warranted.

COPD is a pulmonary disease closely associated with cigarette smoking. Cigarette smoke-induced chronic accumulation of Th1 cells, such as alveolar macrophages, neutrophils, and CD8+ lymphocyte, thought to be dominant in the lungs of COPD patients.^{14,32} However, some clinical studies suggest that accumulation of eosinophils into airways, like Th2 type cells, has a significant influence on the outcome of patients with COPD.³³ Higher blood eosinophilic concentration has also been associated with frequent exacerbation of patients with COPD, and the use of inhaled corticosteroid has been shown to reduce the rate of exacerbation.³⁴ Additionally, recent epidemiological studies indicated the importance of bronchial asthma and allergic sensitization for the development of COPD.^{35,36} In the Tasmanian Longitudinal Health Study, 8583 residents in Tasmania were followed from 7 to 53 years of age and spirometry was performed at 7, 13, 18, 45, 50, and 53 years of age.³⁵ They showed that not only personal smoking but also maternal smoking, childhood asthma, bronchitis, pneumonia, allergic rhinitis, and eczema were important risk factors for the reduced pulmonary function. Additionally, when the FEV₁ was below average early in life, it became accelerated in the decline group and was associated with a high rate of child food asthma (37%), and 46% subjects in the group developed COPD by 53 years of age.³⁵ Since bronchial asthma is a disease associated with Th2 cell inflammation, these studies strongly suggest that involvement of Th2 inflammation in the pathogenesis of COPD.

TARC is a chemokine associated with Th2 inflammation and is a biomarker of allergic dermatitis.¹⁷ As Table 5 shows, the higher serum TARC was associated with higher blood eosinophil and IgE. While TARC is slightly expressed in the bronchial epithelium of healthy subjects, its expression has been reported to be enhanced in subjects with an allergic disease such as bronchial asthma.³⁷ In the present investigation, it is considered that the increase of serum TARC levels may reflect the co-existence of bronchial asthma. However, the frequency of ACO in the rapid-decline group was equivalent to the frequency of non-rapid-decline group (Table 2, 3). In addition, there is controversy about changes in pulmonary function and prognosis in ACO and non-ACO patients. Park HY *et al.* reported that patients with ACO showed favorable longitudinal changes in lung function compared to COPD patients.³⁸ Similarly, in the Hokkaido Cohort Study, the presence of features such as asthma was associated with improved clinical course in COPD patients receiving appropriate treatment.³⁹ In contrast, subjects with ACO are reported to have worse lung function and more symptoms than subjects with asthma or COPD alone.⁴⁰ Studies using data from the European Community Respiratory Health Survey have shown that the ACO group has lower FEV₁ changes than the COPD group.⁴¹ In this study, there was no difference in annual changes in pulmonary function between the ACO group and the non-ACO group (data not shown). Therefore, it is likely that the increases in serum TARC levels were not affected by the co-existence of bronchial asthma.

TARC is produced from alveolar macrophages, airway smooth muscle, and bronchial epithelial cells, and cytokines upregulate their production.^{14,37,42–44} TARC binds to CCR4 on T-lymphocyte, mast cell, natural killer cell, and platelet.⁴⁵ It has also been reported that the bronchial epithelium expresses CCR4.^{14,37,44} However, the precise role of TARC-CCR4 in bronchial epithelial cells has not been fully determined yet. In this study, the higher serum TARC was associated with higher platelet concentration (Table 5). Platelets may be another major source of increasing serum TARC.^{46,47} TARC induces platelet activation via CCR4. The release of TARC from activated platelets may further enhance their aggregation and the

release of CCL17 in an autocrine manner.⁴⁸ Sin and Man reported that platelet counts increased in patients with moderate to severe COPD.⁴⁹ Therefore, both TARC and platelet concentration may be associated with COPD severity. TARC induce the chemotaxis of lymphocytes of the Th2 phenotype.¹⁶ Th2 phenotype T cells play a key role in immune and inflammatory processes that cause IgE production, allergic inflammation (such as eosinophil infiltration), and concomitant tissue damage.⁴² In fact, our study showed that the high TARC group had higher IgE and a tendency to increase eosinophils.

In contrast to the classical role of TARC-CCR4 in Th2 inflammation, recent papers demonstrated that TARC-CCR4 has roles in Th1 inflammation in various diseases. TARC has been reported to play an important role in animal models of smoking-induced pulmonary inflammation.¹⁴ Greaves *et al.* showed that high levels of TARC were detected in atherosclerotic lesions, thought to be related to a Th1 type of inflammation.²⁵ Also, TARC was reported to be elevated in chronic lesion mucosa of Crohn's disease caused by excessive Th1 response.²⁶ Furthermore, several reports have also suggested that CCR4 plays an important role in sepsis.²⁷ Taken together, TARC may play complicated roles like a double-edged sword through enhancing both Th1 and Th2 inflammations in the pathogenesis of COPD.

This study has several limitations. We prospectively performed this study at a single institute, and the study size was not so large. Second, we could not observe large decline in pulmonary function in this study, since the average observation period was 4.8 years. However, we can routinely measure TARC in blood examination in daily practice, it is considered that TARC is useful biomarker.

In conclusion, TARC is a predictive biomarker for identifying COPD patients at risk for a rapid decline in FEV₁. Measuring serum TARC levels may help the management of COPD patients by predicting the longitudinal risk of decline in FEV₁.

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Conflict of Interest

SI received lecture fee from AstraZeneca. YS received lecture fee from AstraZeneca, GlaxoSmithKline, Novartis Pharma, and Boehringer Ingelheim. SI and MW received research funding from Chugai Pharmaceutical. KS received research funding from GlaxoSmithKline. The rest of the authors has no conflict.

Authors' contributions

Conception: YS, Study design: HMa, SI, YS, TK, Making data base: TK, Data collection: KS, KA, HMu, SY, HN, TN, CS, MN, KY, YT, Data analysis: HMa, SI, YS, KS, MW, Data interpretation, all authors, Writing and reviewing the manuscript: all authors. Final approval of the manuscript: all authors.

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