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ORIGINAL RESEARCH

Malnutrition, Airflow Limitation and Severe Emphysema are Risks for Exacerbation of Chronic Obstructive Pulmonary Disease in Japanese Subjects: A Retrospective Single-Center Study

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Background: Different characteristics of patients with chronic obstructive pulmonary disease (COPD) between Western and Japanese populations have been reported. Risk factors for COPD exacerbation have been reported in Western countries but have not been studied in Japan.

Patients and Methods: We retrospectively examined risk factors for COPD exacerbation. A total of 156 Japanese patients were enrolled, and the records of 136 patients were analyzed.

Results: In the exacerbation group (n=60), body mass index, forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), the FEV_1/FVC ratio (FEV_1/FVC), the percent predicted values of FEV_1 (%FEV_1), and serum total protein (TP) and albumin concentrations were lower, and age, mortality rate, frequency of common cold and pneumonia, COPD severity rankings, modified Medical Research Council (mMRC) dyspnea score, and proportions of patients with severe emphysema (>50% of low attenuation area) and receiving long-term oxygen therapy were higher than those in the nonexacerbation group (n=76). However, the proportion of patients with a greater number of eosinophils (≥200/μL and/or ≥2%) and the exhaled nitric oxide concentration did not differ between the two groups. In the univariate analysis, the risk factors for exacerbation were age; long-term oxygen therapy; low FVC, FEV_1, FEV_1/FVC and %FEV_1; high COPD severity ranking and mMRC score; severe emphysema; hypoproteinemia (<6.5 g/dL); hypoalbuminemia (<3.5 g/dL); leukocytosis; lymphocytopenia; and anemia. In the multivariate analysis, the risk factors were hypoalbuminemia, hypoproteinemia and low FEV_1. Additionally, in patients in the exacerbation-induced mortality subgroup, age, exacerbation frequency, mMRC score and the proportion of patients with lymphocytopenia were higher, and FVC, %FVC, FEV_1, serum TP concentration and the lymphocyte number were lower than those in the exacerbation survival subgroup.

Conclusion: Malnutrition, airflow limitation and severe emphysema were risks for exacerbation and mortality associated with infection in Japanese patients with COPD.

Keywords: malnutrition, chronic obstructive pulmonary disease, exacerbation, severe emphysema, airflow limitation

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Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with the aggravation of symptoms, such as dyspnea, cough and sputum, and respiratory failure-induced mortality.[1,2] Several risk factors for COPD exacerbation have been

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reported in Western countries, including severe airflow limitation, the presence of comorbidities such as bronchiectasis and heart failure, biomarkers including C-reactive protein (CRP), past history of exacerbation, poor health status, the presence of emphysema, long-term oxygen therapy and leukocytosis.[2,3] A recent report demonstrated the relationship between elevated levels of blood eosinophils and severe COPD exacerbations.[4]

Furthermore, several markers indicating malnutrition, such as low body mass index (BMI), weight loss, nutritional depletion and low serum vitamin D, are associated with increases in mortality or the recurrence of new exacerbations.[5–10] Additionally, the development of pulmonary infection, which causes COPD exacerbation,[11] is associated with hypoalbuminemia.[12] We demonstrated that low BMI values and hypoalbuminemia were risk factors for pneumonia in a Japanese population.[13] However, the roles of hypoalbuminemia, an important biomarker of malnutrition,[14] in the development of exacerbation have not been well studied.

It has been reported that Japanese and Korean patients with COPD have lower BMI values than Western patients with COPD.[15–17] In addition, Japanese patients with COPD tend to suffer from dominant emphysema in which the occurrence of malnutrition is more frequent.[18] These findings suggest the more important roles of the presence of malnutrition and severe emphysema in the development of exacerbations induced by pulmonary infection in Japanese and Asian patients with COPD. In fact, Lin et al reported the role of hypoproteinemia in early readmission following COPD exacerbation in Chinese subjects.[19] However, in Japanese patients with COPD, risk factors for COPD exacerbations associated with malnutrition, airflow limitation and severe emphysema have not been well studied.

The main purpose of this study was to identify exacerbation-related factors associated with infection in Japanese patients with COPD by focusing on the roles of hypoalbuminemia, airflow limitation and severe emphysema.

Patients and Methods

Design, Setting and Participants

We enrolled patients according to the order of the first visit date or discharge date and analyzed patient records. Patients meeting one of the following inclusion criteria were enrolled: patients who visited the Kurihara Central Hospital to receive treatment and/or examination for COPD or who were admitted to receive treatment for COPD between April 2008 and June 2019.

Ethics Statement

The Kurihara Central Hospital Ethics Committee approved this retrospective study. Informed consent was obtained from all patients, or an informed consent waiver was obtained from the Kurihara Central Hospital Ethics Committee in cases where patients were referred to other hospitals or clinics or were deceased at the review of the records. Patient data were reviewed with confidentiality and compliance with the Declaration of Helsinki.

Measurements

The following information regarding the characteristics and examination data was obtained at the first visit or upon admission to the hospital: age; sex; observation period from first visit or admission; frequency of exacerbation, common cold and pneumonia; smoking history; death during observation period and cause of death; comorbidities; drugs for treatment of COPD; treatment with long-term oxygen therapy; BMI; data of pulmonary function tests, including forced vital capacity (FVC), percent predicted values of FVC (%FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio (FEV_1%), percent predicted values of FEV_1 (%FEV_1) and severity rankings of COPD; severity of dyspnea [modified Medical Research Council (mMRC) score]; the concentration of nitric oxide in the exhaled air (FeNO); radiologic evidence; and the severity of emphysema. The severity rankings of COPD classification, such as GOLD I–IV, were defined based on %FEV_1 according to the GOLD guidelines.[20]

We also checked the following hospital data: the numbers of white blood cells (WBCs) and lymphocytes and the hemoglobin (Hb) level in the peripheral venous blood and serum levels of total protein (TP), albumin, total cholesterol, uric acid, blood urea nitrogen (BUN), creatinine and C-reactive protein (CRP).

We checked the examination data described above at the exacerbation time during the observation period, and the data at the first exacerbation time were used for analysis.

Qualitative Analysis of Emphysema

The patients underwent a chest computed tomography (CT) scan (Toshiba Medical Systems, Otawara, Japan) at full inspiration. The extent of emphysema was estimated using the low attenuation area (LAA) % (the percent of voxels with an apparent X-ray attenuation value below −950 HU). Emphysema was reported as absent, mild, moderate, or severe if the LAA% was <5%, 5–25%, 25–50%, or >50% of the lung, respectively.[2,21]

Definition of COPD Exacerbation, Common Cold and Pneumonia

An exacerbation event was defined as an emergency visit and/or admission to the hospital because of COPD.[9] Ten symptoms of upper respiratory tract infections were recorded, and common cold was defined as a total symptom score of greater than 5, as described previously.[22] Pneumonia was diagnosed based on the following standard criteria: fever (body temperature ≥37.8°C), high CRP level and infiltrate shadows on chest X-rays and/or CT scan.[23]

Statistical Analysis

The results are expressed as the means ± SDs. For the comparison of continuous variables between the two groups, Student's *t*-test, Pearson's chi-squared test or Fisher's exact test was used. The chi-squared test or Fisher's test was performed to assess differences in rates. Univariate and multivariate Cox proportional hazard regression analyses were also performed with the stepwise method to identify risk factors for COPD exacerbation. All analyses were performed using SPSS version 21 (IBM Japan, Tokyo, Japan).

Results

Characteristics of Subjects

In the present study, 156 patients were initially enrolled; 20 patients were excluded because the values of FVC/FEV_1 were 70% or greater in 5 patients and because the pulmonary function test was not performed in 15 patients due to severe condition (n=12), dementia (n=2) or pneumothorax (n=1) (Figure 1).

In the 136 analyzed patients, 60 patients presented exacerbation (exacerbation group), and 76 patients did not present exacerbation (nonexacerbation group). The characteristics of the analyzed patients are shown in Table 1.

The patients in the exacerbation group were older than those in the nonexacerbation group (Table 1). The sex distribution and observation period were matched in both groups.

The mean exacerbation frequency was 1.6 times during the observation period, with a mean of 50 months, in the exacerbation group. The frequency of the common cold and pneumonia and the proportion of patients who developed the common cold and pneumonia in the exacerbation group were higher than those in the nonexacerbation group (Table 1).

Among patients in the exacerbation group, 22 patients died, and the causes of death were respiratory failure (n=17), cancer (n=4) and uncertain (sudden death) (n=1) (Table 1). In patients in the nonexacerbation group, 4 patients died of causes other than respiratory failure.

In addition to treatment for COPD, the patients were treated with drugs for comorbid conditions (Table 1). The proportions of patients with comorbidities, including bronchial asthma, did not differ between the two groups. A total

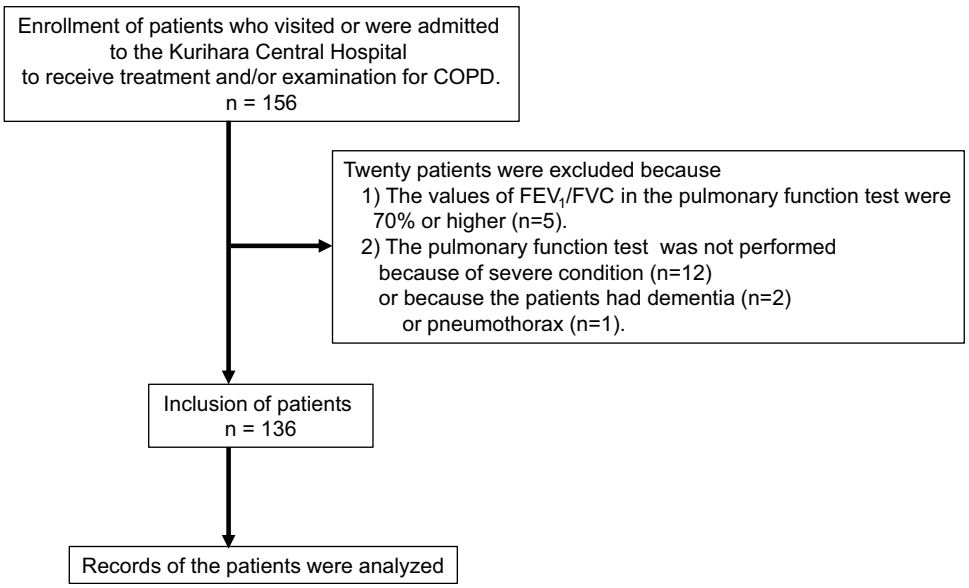

Figure 1 Schematic diagram outlining the patient selection process.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

Table 1 Characteristics of Patients

Characteristics, Interventions, and Effects	Exacerbation Group	Nonexacerbation Group	*P* value
Characteristics			
Number of patients, n	60	76	–
Age (years, mean ± SD)[a]	78.5 ± 9.1	73.3 ± 10.6	0.003
Males, n (%)[b]	56 (93.3)	66 (86.8)	0.216
Observation period (months, means ± SD)[a]	49.8 ± 45.4	41.8 ± 38.9	0.273
Frequency of exacerbation, common cold and pneumonia (mean times ± SD)		–	–
Frequency of exacerbation	1.6 ± 1.0	0.0 ± 0.0	<0.001
Frequency of common cold	2.3 ± 1.8	0.5 ± 1.0	<0.001
Frequency of pneumonia	1.0 ± 1.0	0.03 ± 0.23	<0.001
Proportion of patients with common cold and pneumonia, n (%)[a]			
Common cold, n (%)[a]	58 (96.7)	21 (27.6)	<0.001
Pneumonia, n (%)[a]	39 (65.0)	0 (0.0)	<0.001
Smoking history, n (%)			
Never-smokers or pack-years <10[b]	2 (3.3)	8 (10.5)	0.185
Ex-smokers[a]	45 (75.0)	42 (55.3)	0.017
Current smokers	13 (21.7)	26 (34.2)	0.122
Number of deaths, n (%)[a]	22 (36.7)	4 (5.3)	<0.001
Cause of death, n (%)			
Respiratory failure, n (%)[a]	17 (28.3)	0 (0.0)	<0.001
Cancer, n (%)[b]	4 (6.7)	0 (0.0)	0.036
Other, n (%)[b]	1 (1.7)	4 (5.3)	0.383
Comorbidities			
Bronchial asthma, n[a]	30 (50.0)	35 (46.1)	0.647
Pulmonary diseases, n[a,c]	10 (16.7)	11 (14.5)	0.725
Cardiovascular diseases, n[a]	23 (38.3)	27 (35.5)	0.736
Diabetes mellitus, n[a]	12 (21.6)	11 (14.1)	0.393
Hypertension, n[a]	24 (40.0)	19 (25.0)	0.062
Atrial fibrillation, n[b]	6 (10.0)	4 (5.3)	0.336
Cerebrovascular disease, n[a]	6 (10.0)	7 (9.2)	0.876
Cancer, n[a]	12 (20.0)	13 (17.1)	0.665
Other, n[a]	22 (36.7)	24 (31.6)	0.533
Medications, n (%)	55 (91.7)	64 (84.2)	0.192
LAMAs+LABAs[a]	21 (35.0)	23 (30.3)	0.558
LAMAs+LABAs+ICSs[a]	15 (25.0)	11 (14.5)	0.121
ICSs+LABAs[b]	3 (5.0)	7 (9.2)	0.512
LAMAs[a]	2 (3.3)	13 (17.1)	0.011
LABAs[a]	11 (18.3)	3 (3.9)	0.006
Mucolytics[a]	27 (45.0)	19 (25.0)	0.014
Theophylline[a]	15 (25.0)	8 (10.5)	0.025
Oral steroids[a]	13 (21.7)	1 (1.3)	<0.001
Others[b,d]	10 (16.7)	7 (9.2)	0.192
No treatment with any drug[a,e]	5 (8.3)	12 (15.8)	0.192
Long-term oxygen therapy, n (%)[a]	23 (38.3)	7 (9.2)	<0.001

Notes: [a]Pearson's chi-squared test. [b]Fisher's exact test. [c]Pulmonary diseases other than bronchial asthma. [d]In the exacerbation group, the "Others" category includes leukotriene receptor antagonists (n = 4) and macrolides (n = 4). In the nonexacerbation group, the "Others" category includes leukotriene receptor antagonists (n = 6), a macrolide (n=1) and a short-acting β_2-agonist (n = 2). [e]Patients did not receive any treatment with drugs during the observation period.
Abbreviations: SD, standard deviation; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting β_2-agonists; ICSs, inhaled corticosteroids.

of 119 patients received treatment with either long-acting muscarinic antagonists (LAMAs), long-acting β_2-agonists (LABAs), inhaled corticosteroids (ICSs), mucolytics, theophylline, oral corticosteroids, leukotriene receptor antagonists or macrolides alone or in combination (Table 1).

The proportion of patients who were treated with a combination of LAMAs and LABAs, a combination of LAMAs, LABAs and ICSs or a combination of ICSs and LABAs did not differ between the two groups (Table 1).

In addition, the proportions of patients who received treatment with mucolytics, theophylline or oral steroids in the exacerbation group were higher than the proportions of patients who received these treatments in the nonexacerbation group (Table 1).

The proportion of patients who received treatment with long-term oxygen therapy in the exacerbation group was more than four times higher than the proportion in the nonexacerbation group (Table 1).

BMI, Pulmonary Function Test, Dyspnea Score, FeNO and Chest CT

The mean BMI was 22.1 kg/m^2, and the total number of patients who were underweight (<20 kg/m^2)[5,9] was 37 (27.2%). The BMI values of patients in the exacerbation group were lower than those of patients in the nonexacerbation group (Table 2). The proportion of patients who were underweight did not differ between the two groups (Table 2).

The values of the pulmonary function test results, including FVC, %FVC, FEV_1, FEV_1/FVC and %FEV_1, of patients in the exacerbation group were lower than the values of the patients in the nonexacerbation group (Table 2), and the severity rankings of COPD (GOLD classification) were higher in the exacerbation group than those in the nonexacerbation group (Table 2). The mMRC score, which indicates the severity of dyspnea, was higher in the exacerbation group than that in the nonexacerbation group (Table 2).

The mean value of FeNO and the proportion of patients with high FeNO values (>35 ppb)[24] did not differ between the two groups (Table 2).

The proportion of patients who exhibited emphysema on chest CT was 98% in the exacerbation group and 88% in the nonexacerbation group; however, the proportion of patients with emphysema did not differ between the two groups (Table 2). In contrast, the proportion of patients with severe degrees of emphysema (>50% of LAA)[21] in the exacerbation group was more than three times higher than that in the nonexacerbation group (Table 2).

Peripheral Blood Biochemical Examination

The serum levels of TP and albumin in patients in the exacerbation group were lower than those in patients in the nonexacerbation group (Table 2). In particular, the serum albumin levels in the exacerbation group were more than 20% lower than those in the nonexacerbation group. Furthermore, serum CRP levels in the exacerbation group were higher than those in the nonexacerbation group (Table 2).

The proportions of patients with low values of serum TP (<6.5 g/dL) and albumin (<3.5 g/dL) and with high CRP values in the exacerbation group were higher than those in the nonexacerbation group (Table 2).

Peripheral Blood Examination

The number of WBCs and neutrophils in patients in the exacerbation group was higher than that in patients in the nonexacerbation group (Table 2). In contrast, the number of lymphocytes and the Hb value in the exacerbation group were lower than those in the nonexacerbation group (Table 2). The number of eosinophils did not differ between the two groups.

The proportions of patients with leukocytosis (>9000/μL WBC) and lymphocytopenia (<1000/μL lymphocytes) in the exacerbation group were higher than those in the nonexacerbation group (Table 2). In contrast, the proportion of patients with a greater number of eosinophils in the peripheral blood (≥200/μL or ≥2%) did not differ between the two groups.

Univariate and Multivariate Analyses of Risk Factors for Exacerbation

Univariate analysis showed that age and long-term oxygen therapy were associated with exacerbation (Table 3). In addition, FVC, %FVC, FEV_1, FEV_1/FVC, and %FEV_1 were negatively associated with exacerbation (Table 3). Furthermore, the severity rankings of COPD; mMRC score; presence of severe emphysema (>50%); low values of TP, albumin and Hb; high CRP values; leukocytosis; and lymphocytopenia were positively associated with the development of exacerbation (Table 3).

In the multivariate analysis, the following risk factors for exacerbation were identified: low FEV_1, hypoproteinemia

Table 2 Data on BMI, Pulmonary Function Test, Dyspnea Score, FeNO, Chest CT and Laboratory Examination

Risk Factors	Exacerbation Group (n = 60)	Nonexacerbation Group (n = 76)	*p* value
BMI			
BMI (kg/m^2, mean ± SD)	21.2 ± 3.6	22.7 ± 3.7	0.020
Underweight (<20 BMI), n (%)[a]	18 (30.0)	19 (25.0)	0.515
Pulmonary function			
FVC (L, mean ± SD)	2.16 ± 0.73	2.71 ± 0.96	<0.001
%FVC (%, mean ± SD)	71.5 ± 19.6	84.4 ± 19.6	<0.001
FEV_1 (L/s, mean ± SD)	1.10 ± 0.55	1.55 ± 0.75	<0.001
FEV_1/FVC (%, mean ± SD)	49.6 ± 14.5	55.2 ± 13.7	0.022
%FEV_1 (%, mean ± SD)	49.8 ± 20.7	60.7 ± 23.6	0.005
GOLD classification (mean ± SD)	2.6 ± 0.9	2.2 ± 1.0	0.013
Stage I, n, (%)[a]	5 (8.3)	21 (27.6)	0.004
Stage II, n, (%)[a]	25 (41.7)	25 (32.9)	0.292
Stage III, n, (%)[a]	18 (30.0)	22 (28.9)	0.894
Stage IV, n, (%)[a]	12 (20.0)	8 (10.5)	0.121
Dyspnea score			
mMRC (mean ± SD)	2.8 ± 1.2	1.4 ± 1.1	<0.001
FeNO			
FeNO (ppb, mean ± SD)	42.8 ± 60.1 (n=32)	34.4 ± 29.7 (n=45)	0.424
Proportion of patients with FeNO > 35 ppb (n, %)[a]	9 (26.9)	15 (33.3)	0.627
Chest CT			
Subjects No, n	55	60	
Absence of emphysema (< 5%), n (%)[b]	1 (1.8)	7 (11.7)	0.063
Presence of emphysema, n (%)[b]	54 (98.2)	53 (88.3)	0.063
5%–25%, n (%)[a]	9 (16.7)	26 (49.1)	0.002
25%–50%, n (%)[a]	20 (37.0)	18 (34.0)	0.469
>50%, n (%)[a]	24 (44.4)	7 (13.2)	<0.001
Laboratory data[c]			
Total protein (g/dL, mean ± SD)	6.32 ± 0.66	6.99 ± 0.43	<0.001
Albumin (g/dL), mean ± SD	3.20 ± 0.71	4.09 ± 0.39	<0.001
Total cholesterol (mg/dL mean ± SD)	162 ± 45	176 ± 36	0.060
Uric acid (mg/dL, mean ± SD)	5.2 ± 2.3	5.4 ± 1.7	0.621
BUN (mg/dL, mean ± SD)	21.9 ± 11.4	16.3 ± 7.5	0.001
Creatinine (mg/dL, mean ± SD)	1.05 ± 0.88	0.83 ± 0.30	0.050
CRP (mg/dL, mean ± SD)	4.34 ± 6.54	0.50 ± 1.22	<0.001
White blood cells (/μL, mean ± SD)	7648 ± 3248	6467 ± 1951	0.001
Neutrophils (/μL, mean ± SD)	5643 ± 2969	4107 ± 1534	<0.001
Lymphocytes (/μL, mean ± SD)	1291 ± 678	1727 ± 916	0.003
Hb (g/dL, mean ± SD)	12.6 ± 2.2	13.7 ± 1.7	0.002
Eosinophils			
(/μL, mean ± SD)	259 ± 316	228 ± 253	0.530
(% of WBC, mean ± SD)	3.6 ± 4.0	3.3 ± 3.5	0.721
Proportion of patients, n (%)			
With <6.5 g/dL TP[a]	33 (56.9)	7 (9.7)	<0.001
With <3.5 g/dL albumin[a]	38 (64.4)	4 (5.6)	<0.001
With >0.2 mg/dL CRP[a]	48 (80.0)	23 (31.9)	<0.001
With >9000/μL WBC[a]	18 (30.0)	6 (7.9)	0.001
With <1000/μL lymphocytes[a]	22 (36.7)	14 (18.9)	0.021

(*Continued*)

Table 2 (Continued).

Risk Factors	Exacerbation Group (n = 60)	Nonexacerbation Group (n = 76)	*p* value
With ≥200/μL eosinophils[a]	26 (43.3)	24 (33.8)	0.263
With ≥2% eosinophils[a]	31 (51.7)	46 (64.8)	0.128

Notes: For the comparison of continuous variables between the two groups, Student's *t*-test, Pearson's chi-squared test or Fisher's exact test was used. [a]Pearson's chi-squared test. [b]Fisher's test. [c]Numbers of subjects in the exacerbation group who received the laboratory examination: TP (n=58); albumin (n=59); total cholesterol (n=53); uric acid (n=56); and BUN, creatinine, CRP, WBCs, neutrophils, lymphocytes, eosinophils and Hb (n=60). Numbers of subjects in the non-exacerbation group who received the laboratory examination: TP and albumin (n=72): total cholesterol (n=62); uric acid (n=71); BUN (n=73); creatinine (n=74); CRP (n=72); WBC (n=76); neutrophil (n=74); lymphocytes (n=74); eosinophils (n=71) and Hb (n=75).

Abbreviations: SD, standard deviation; BMI, body mass index; FeNO, concentration of nitric oxide in the exhaled air; CT, computed tomography; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; FeNO, concentration of nitric oxide in the exhaled air; CT, computed tomography; BUN, blood urea nitrogen; CRP, C-reactive protein; TP, total protein; WBC, white blood cell; Hb, hemoglobin.

and hypoalbuminemia (Table 3). Hypoalbuminemia was the strongest indicator.

Characteristics of Patients in the Exacerbation-Induced Mortality Subgroup

We also examined the risks for mortality caused by exacerbation-induced respiratory failure. In patients in the subgroup of exacerbation-induced mortality caused by respiratory failure (n=17), age, frequency of exacerbation, proportion of patients receiving long-term oxygen therapy and mMRC score were higher than those in the exacerbation survival subgroup (n=38) (Table 4). In addition, the values of FVC, % FVC, FEV_1, serum concentrations of TP, the number of WBCs and lymphocytes in the exacerbation-induced mortality subgroup were lower than those in the exacerbation survival subgroup (Table 4).

In the exacerbation-induced mortality subgroup, the proportions of patients with lymphocytopenia were higher than those in the exacerbation survival subgroup (Table 4).

Discussion

We demonstrated that the values of FVC, %FVC, FEV_1, FEV_1/FVC, and % FEV_1 in the exacerbation group were lower than those in the nonexacerbation group and that the severity rankings of COPD, mMRC score and proportions of patients receiving long-term oxygen therapy in the exacerbation group were higher than those in the nonexacerbation group. In the univariate analysis, long-term oxygen therapy; low values of FVC, %FVC, FEV_1, FEV_1 /FVC and %FEV_1; and high COPD severity ranking and mMRC scores were associated with COPD exacerbation. Furthermore, in the multivariate analysis, low values of FEV_1 were associated with exacerbation. Thus, the factors that indicate airflow limitation were associated with COPD exacerbation in Japanese patients, as demonstrated in studies in Western patients with COPD.[2,3]

Furthermore, the patients in the exacerbation group were older than those in the nonexacerbation group, and age was associated with COPD exacerbation in the univariate analysis. Additionally, the proportion of patients with severe degrees of emphysema in the exacerbation group was higher than that in the nonexacerbation group. These findings were consistent with those of previous reports conducted in Western countries,[2,3,7] and these two factors, namely, older age and severe degree of emphysema, may be associated with increased mortality in older Japanese patients with COPD with severe emphysema.[25]

In addition, BMI and serum concentrations of TP and albumin were lower and the proportions of patients with hypoproteinemia and hypoalbuminemia were higher in the exacerbation group than in the nonexacerbation group. Univariate and multivariate analyses showed that hypoproteinemia and hypoalbuminemia were risks for exacerbation, and hypoalbuminemia was the strongest indicator. These findings suggest that hypoalbuminemia and hypoproteinemia are also risks for exacerbation in Japanese patients with COPD.

The role of hypoalbuminemia as a risk factor for COPD exacerbation has not been well studied, although hypoproteinemia has been reported as a risk factor for early readmission due to COPD exacerbation and for the worst prognosis in Chinese subjects.[12,19] Malnutrition causes decreased cell-mediated and humoral immunity, such as decreased lymphocyte proliferation, low function of polymorphonuclear leukocytes and monocytes, deficient release of cytokines including interleukin (IL)-6, and lower antibody response to vaccines.[26]

Cytokines, such as interferon and IL-6, have been suggested to act as host defense systems against viral infection in

Table 3 Univariate and Multivariate Analyses of Risk Factors for the Exacerbation of COPD (Stepwise Method)

	Univariate Analysis			Multivariate Analysis		
	PR	**95% CI**	***P*-value**	**PR**	**95% CI**	***P*-value**
Age	1.03	1.01–1.05	0.003			
Male sex	1.61	0.69–3.76	0.275			
Comorbidities						
All	0.64	0.39–1.06	0.080			
Bronchial asthma + pulmonary diseases	1.06	0.72–1.57	0.772			
Long-term oxygen therapy	2.20	1.59–3.04	<0.001			
BMI						
Underweight (BMI <20)	1.15	0.77–1.72	0.505			
Pulmonary function						
FVC	0.65	0.52–0.81	<0.001			
%FVC	0.98	0.97–0.99	<0.001			
FEV_1	0.54	0.40–0.74	<0.001	0.72	0.57–0.92	0.008
FEV_1/FVC	0.99	0.97–0.997	0.019			
%FEV_1	0.99	0.98–0.996	0.004			
GOLD classification						
Stage I	0.39	0.17–0.86	0.021			
Stage II	1.23	0.84–1.79	0.284			
Stage III	1.03	0.68–1.55	0.893			
Stage IV	1.45	0.95–2.20	0.082			
GOLD classification	1.28	1.07–1.54	0.009			
Dyspnea score						
mMRC	1.57	1.37–1.80	<0.001			
FeNO						
>35 ppb FeNO	0.86	0.47–1.58	0.634			
Chest CT						
<5%	0.69	0.14–3.47	0.654			
5%–25%	0.45	0.25–0.81	0.008			
25%–50%	1.16	0.79–0.171	0.459			
>50%	2.10	1.50–2.94	<0.001	1.31	0.98–1.75	0.065
Laboratory data						
With <6.5 g/dL TP	2.97	2.07–4.27	<0.001	1.65	1.16–2.33	0.005
With <3.5 g/dL albumin	3.83	2.61–5.64	<0.001	2.68	1.71–4.20	<0.001
With >0.2 mg/dL CRP	3.44	2.02–5.85	<0.001			
With >9000/μL WBC	2.00	1.43–2.79	<0.001			
With <1000/μL lymphocytes	1.58	1.10–2.26	0.013			
With ≥200/μL eosinophils	1.24	0.86–1.79	0.256			
With ≥2% eosinophils	0.75	0.52–1.08	0.125			
Hb	0.87	0.80–0.95	0.001			

Abbreviations: COPD, chronic obstructive pulmonary disease; PR, prevalence ratio; CI, confidence interval; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; FeNO, concentration of nitric oxide in the exhaled air; CT, computed tomography; TP, total protein; CRP, C-reactive protein; WBC, white blood cell; Hb, hemoglobin.

the lungs as well as to induce inflammation.[27] In the present study, the proportion of patients with the common cold and pneumonia and the frequency of the common cold and pneumonia in the exacerbation group were higher than those in the nonexacerbation group, although we could not collect sufficient information regarding the species of bacteria and viruses that caused pneumonia and the common cold. Therefore, the malnutrition observed in the present study

Table 4 Characteristics and Laboratory Examination Data in the Respiratory Failure-Induced Mortality Exacerbation Subgroup or Exacerbation Survival Subgroup

Risk Factors	Exacerbation Mortality Subroup[c] (n = 17)	Exacerbation Survival Subgroup (n = 38)	*p* value
Characteristics			
Age (years, mean ± SD)	83.6 ± 8.5	76.7 ± 8.9	0.010
Observation period (months, means ± SD)	62.8 ± 50.7	43.0 ± 43.8	0.146
Frequency of exacerbation, common cold and pneumonia (mean times ± SD)		–	–
Frequency of exacerbation	2.1 ± 1.4	1.3 ± 0.5	0.004
Frequency of common cold	2.4 ± 2.1	2.1 ± 1.6	0.548
Frequency of pneumonia	1.0 ± 1.3	0.9 ± 0.8	0.783
Long-term oxygen therapy, n (%)[c]	11 (64.7)	10 (33.3)	0.007
BMI			
BMI (kg/cm^2, mean ± SD)	20.5 ± 3.5	21.8 ± 3.6	0.201
Underweight (<20 BMI), n (%)[b]	6 (35.3)	9 (23.7)	0.514
Dyspnea score			
mMRC (mean ± SD)	3.4 ± 0.9	2.4 ± 1.2	0.008
Chest CT[d]			
Presence of emphysema, n (%)[b]	17 (100.0)	32 (97.0)	1.000
>50%, n (%)[a]	7 (41.2)	14 (42.4)	0.933
Pulmonary function			
FVC (L, mean ± SD)	1.70 ± 0.54	2.36 ± 0.69	0.001
%FVC (%, mean ± SD)	62.7 ± 20.0	75.4 ± 18.5	0.025
FEV_1 (L/s, mean ± SD)	0.86 ± 0.47	1.22 ± 0.52	0.020
FEV_1/FVC (%, mean ± SD)	48.8 ± 17.6	50.9 ± 13.0	0.624
%FEV_1 (%, mean ± SD)	43.5 ± 21.6	53.1 ± 19.5	0.109
GOLD classification (mean ± SD)	2.8 ± 1.0	2.6 ± 0.8	0.409
Laboratory data[d]			
Total protein (g/dL, mean ± SD)	6.06 ± 0.60	6.45 ± 0.66	0.045
Albumin (g/dL), mean ± SD	3.03 ± 0.56	3.33 ± 0.66	0.110
CRP (mg/dL, mean ± SD)	6.09 ± 8.69	3.95 ± 5.70	0.281
White blood cells (/μL, mean ± SD)	6057 ± 1877	8530 ± 3560	0.010
Neutrophils (/μL, mean ± SD)	4571 ± 2036	6256 ± 3296	0.057
Lymphocytes (/μL, mean ± SD)	968 ± 388	1456 ± 758	0.015
Proportion of patients, n (%)			
With <6.5 g/dL TP[a]	11 (64.7)	19 (51.4)	0.359
With <3.5 g/dL albumin[a]	14 (82.4)	22 (57.9)	0.078
With >0.2 mg/dL CRP[b]	15 (88.2)	29 (76.3)	0.471
With >9000/μL WBC[a]	1 (5.9)	16 (42.1)	0.007
With <1000/μL lymphocytes[a]	10 (58.8)	11 (28.9)	0.035

Notes: For the comparison of continuous variables between the two groups, Student's *t*-test, Pearson's chi-squared test or Fisher's exact test was used. [a]Pearson's chi-squared test. [b]Fisher's test. [c]Four patients in the exacerbation group who died of reasons other than respiratory failure were excluded from the analysis. [d]The number of subjects in the exacerbation group who received chest CT and laboratory examination was 17. The number of subjects in the nonexacerbation group who received chest CT was 33 and who received a laboratory examination was 38, except for TP (n=37).

Abbreviations: SD, standard deviation; BMI, body mass index; mMRC, modified Medical Research Council; CT, computed tomography; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CRP, C-reactive protein; TP, total protein; WBC, white blood cell.

might have caused immune-deficient conditions in combination with lymphocytopenia, which is associated with respiratory bacterial and viral infection and the subsequent development of COPD exacerbation.[11,28,29]

The mean BMI that we reported in the present study (22 kg/m^2) was lower than that reported in Western patients with COPD (27 kg/m^2)[15,16] and consistent with the values reported in Japan (22–23 kg/m^2).[17,18] Furthermore, the

proportion of patients with low BMI (<20 kg/m^2) in the present study (27.2%) was higher than that among Western patients with COPD (9.5%).[5] In contrast, several reports also demonstrated the association of low BMI with mortality and/or exacerbation in Western patients with COPD.[5,9] We demonstrated that the BMI in the exacerbation group was lower than that in the nonexacerbation group. Similar to a study conducted in Chinese patients,[30] these findings suggest a more important role of low BMI as a risk for exacerbation in Japanese patients with COPD than in Western patients.

Differences in the characteristics of patients with COPD between Japanese and Western patients have been reported, including emphysema-dominant COPD evidenced by chest CT in Japanese patients in addition to lower BMI and more frequent malnutrition.[18] In fact, in the present study, emphysema was observed on CT in 98% of patients in the exacerbation group and 88% of patients in the nonexacerbation group, and this proportion in the exacerbation group was higher than that in the report conducted in Western countries (75%).[2] Furthermore, the proportion of patients with severe emphysema in the exacerbation group was higher than that in the nonexacerbation group. These findings suggest that severe emphysema might also be a more important risk for exacerbation in Japanese patients with COPD than in Western patients with COPD.

The proportions of patients who received treatment with mucolytics, theophylline, oral steroids or long-term oxygen therapy in the exacerbation group were higher than the proportions of patients who received these treatments in the nonexacerbation group. Because the mMRC score and the severity rankings of COPD were higher in the exacerbation group than in the nonexacerbation group, the patients in the exacerbation group might be treated with these drugs and long-term oxygen therapy more frequently to improve severe dyspnea or to prevent exacerbation.[3,31,32]

In patients in the exacerbation-induced mortality subgroup, age, mMRC score, and the proportion of patients with lymphocytopenia was higher, and the values of FVC, %FVC, FEV_1, serum TP concentration and lymphocyte number were lower than those in the exacerbation survival subgroup. These findings may show the presence of more severe dyspnea due to air flow limitation and air flow limitation-induced severe air trapping in older patients in the exacerbation-induced mortality subgroup. Impaired mucociliary clearance due to severe airway obstruction may be associated with infection.[33] The combination of these risks might have caused more severe COPD exacerbation through impaired defense mechanisms in the exacerbation-induced mortality subgroup.

Couillard et al demonstrated the relationship between severe COPD exacerbations and higher eosinophil levels.[4] However, in the present study, the number of eosinophils and the proportions of patients with a greater number of eosinophils did not differ between the exacerbation group and the nonexacerbation group. The values were observed at the time of exacerbation, and it was uncertain whether the eosinophil values were persistent, as Singh et al suggested in Western patients with COPD,[34] because patients were treated with systemic steroids at the time of exacerbation and in the context of a stable condition in some patients. The reasons for the differences in eosinophil levels between the study by Couillard et al[4] and the present study are uncertain; however, increased neutrophils were reported in Western patients with COPD with exacerbation,[34,35] suggesting the role of neutrophilic inflammation rather than eosinophilic inflammation in COPD exacerbation in Japanese patients.

The patients were enrolled according to the order of the first visit date or the discharge date from the hospital after treating the exacerbation, and patient records were analyzed to prevent any selection bias.

This study had some limitations. The nature of the present study was exploratory, and the main purpose of this study was to identify factors that are associated with the development of exacerbation in patients with COPD. Therefore, we could not precisely estimate the necessary sample size at the beginning of this study. However, we presumed that we needed approximately 50 patients in each group based on the conventional estimation that a value of the number of events per variable = 10 is most prudent when a proportional hazard regression model is used.[36] Therefore, the sample sizes for the two groups (60 and 76) were thought to be sufficient to demonstrate the risks for exacerbation. As a result, we found that malnutrition, airflow limitation and severe emphysema were risks for exacerbation associated with infection in Japanese patients with COPD. These findings indicated that the effect sizes of these variables might be sufficient to detect statistical significance even in the small sample size in the present study.

Second, in the present study, patients visited the hospital by themselves or were referred from 8 clinics and 5 hospitals. The characteristics of patients with COPD that we demonstrated in the study, such as low BMI and high proportion of patients with emphysema, were similar to those of studies

that were conducted in different areas of Japan.[17,37,38] However, this study was performed as a retrospective and single-center study by analyzing records of patients who were treated in one hospital. Therefore, prospective and multicenter studies are needed to confirm that the evidence observed in the present study represents risk factors for COPD exacerbation in Japanese subjects.

In conclusion, malnutrition, airflow limitation and severe emphysema were risks for exacerbation and mortality associated with infection in Japanese patients with COPD.

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Disclosure

The authors report no conflicts of interest in this work.

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