

# Prognostic Nutritional Index (PNI) as a Potential Prognostic Tool for Exacerbation of COPD in Elderly Patients

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**Purpose:** In COPD, exacerbation of the disorder causes a deterioration in the quality-of-life and worsens respiratory dysfunction, leading to a poor prognosis. In recent years, nutritional indices have been reported as significant prognostic factors in various chronic diseases. However, the relationship between nutritional indicators and prognosis in elderly subjects with COPD has not been investigated.

**Patients and methods:** We enrolled 91 subjects who received COPD assessment tests (CAT), spirometry, blood tests, and multidetector computed tomography (MDCT). We divided the subjects into two groups according to age (<75 years (n=57) and ≥ 75 years (n=34)). The prognostic nutritional index (PNI) was used to assess immune-nutritional status and was calculated as  $10 \times \text{serum albumin} + 0.005 \times \text{total lymphocyte count}$ . We then examined the relationship between PNI and clinical parameters, including exacerbation events.

**Results:** There was no significant correlation between the PNI and CAT, the FEV<sub>1</sub>%pred, or low attenuation volume percentage (LAV%). In the elderly group, there were significant differences between the groups with or without exacerbation in the CAT and PNI ( $p=0.008$ ,  $p=0.004$ , respectively). FEV<sub>1</sub>%pred, neutrophil-to-lymphocyte ratio (NLR) and LAV% did not differ between the two groups. The analytical model combining CAT and PNI improved the prediction of exacerbations in the elderly subjects ( $p=0.0068$ ).

**Conclusion:** In elderly subjects with COPD, CAT were associated significantly with the risk of COPD exacerbation, with PNI also a potential predictor. The combined assessment of CAT and PNI may be a useful prognostic tool in subjects with COPD.

**Keywords:** chronic obstructive pulmonary disease, exacerbation, prognostic nutritional index

## Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world and is associated with increasing economic costs and social burdens.<sup>1,2</sup> Although spirometry is the gold standard for the clinical measurement of COPD, it does not provide sufficient essential information on exacerbation, leading to worsening respiratory impairment and prognosis.<sup>3</sup>

Exacerbation of COPD decreases the quality-of-life, causes respiratory dysfunction, and adversely affects prognosis. Numerous studies have discussed exacerbation and risk factors. The prognostic factors of COPD vary between smoking status, degree of dyspnea, severity of airflow limitation, degree of emphysema, exercise tolerability, and physical inactivity.<sup>4-6</sup> Recent reports have also described the impact of the neutrophil-lymphocyte ratio (NLR)<sup>7</sup> and the existence of asthmatic components.<sup>8</sup>

The nutritional status of a patient has also been established as a prognostic factor for various chronic diseases.<sup>9</sup> Since Japan and Western countries have entered the era of an unprecedented ultra-aging society,<sup>10</sup> there has been a focus on nutritional status as a risk factor for chronic diseases, especially in elderly patients.<sup>11</sup> For example, malnutrition is common in elderly patients with heart failure, with evidence showing that nutritional status is strongly linked to their prognosis.<sup>12</sup>

In 1980, Buzby et al suggested the concept of the prognostic nutritional index (PNI).<sup>13</sup> Subsequently, Onodera et al proposed that PNI could be calculated easily using serum albumin level and total lymphocyte count and showed that the index was a risk indicator for postoperative complications and prognosis for patients undergoing gastrointestinal cancer surgery.<sup>14</sup> Subsequent studies reported a relationship between PNI and clinical outcomes in various other malignant diseases.<sup>15–17</sup>

Nutritional status has also been reported to be a significant prognostic indicator in patients with COPD.<sup>18</sup> Previously, the body mass index (BMI) was the health indicator mainly used to assess prognosis in COPD.<sup>19</sup> It remains unclear, however, whether the PNI is related to COPD exacerbations and prognosis of elderly patients.

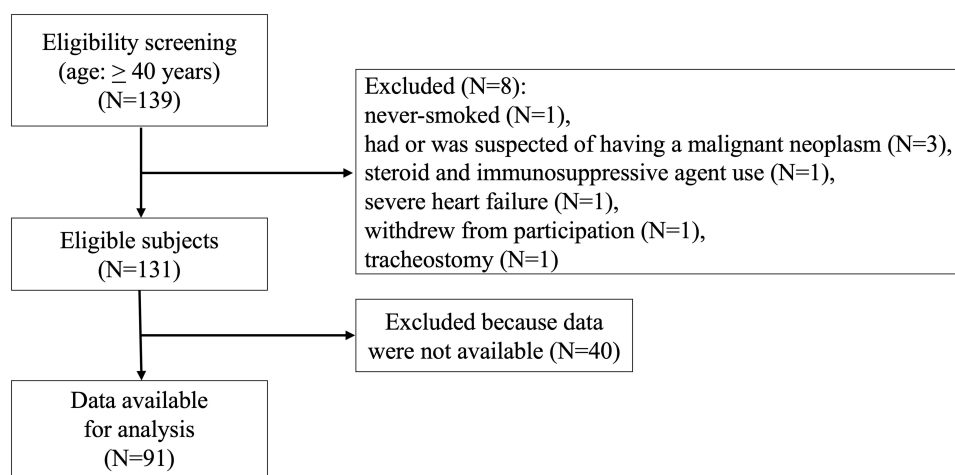
Therefore, the aim of the present study was to elucidate whether PNI was associated with exacerbation and to clarify the clinical value of assessing the immune-nutritional status in elderly patients with COPD.

## Methods

### Subjects

This prospective, observational study enrolled 139 subjects who presented to Chiba University Hospital from March 2014 to June 2019 for management of COPD. The subjects were required to meet all of the following inclusion criteria: (a)  $\geq 40$  years; (b) smoking history  $\geq 10$  pack-years; (c) COPD diagnosed or suspected to have COPD based on subjective symptoms/other findings/pulmonary function tests/imaging findings; (d) no history of acute exacerbation or hospitalization within 2 months. Exclusion criteria were any of the following: (a) obvious respiratory diseases other than COPD; (b) any malignancy within the past 3 years; (c) severe heart failure; (d) currently receiving oral systemic corticosteroids; (e) deemed unsuitable for inclusion by investigators for any other reason.

At enrollment, eight subjects were excluded for the following reasons: one never-smoked without a history of smoking; three with malignant neoplasms; one prescribed a steroid and an immunosuppressive agent; one with severe heart failure; and one with a tracheostomy. During the follow-up period, one subject was excluded as they decided to withdraw from participating in the study. 40 subjects were excluded by the end of follow-up due to discrepancies in each data set, such as a discontinuation of hospital visits, confirmation of worsening symptoms, COPD assessment test (CAT), pulmonary function tests, and chest CT scans. Finally, 91 subjects with COPD were enrolled in the study (Figure 1).



**Figure 1** Flow chart of the study subjects.

The diagnosis of COPD was made comprehensively by respiratory specialists according to the recommendations of the American Thoracic Society (ATS) and European Respiratory Society (ERS),<sup>20</sup> that included the subject's smoking history, respiratory symptoms including dyspnea, cough and sputum, physical examination, spirometry results. Pulmonary function tests (PFTs) were performed using a Fudac-60 (Fukuda Denshi, Tokyo, Japan) and included forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV<sub>1</sub>), which were expressed as their predicted values based on the Japanese Respiratory Society (JRS) guidelines.<sup>21</sup> The subjects underwent a CAT, PFTs, laboratory tests, and multidetector computed tomography (MDCT) at the time of enrollment. The CAT is a simple tool for comprehensively evaluating the clinical symptoms of subjects with COPD,<sup>22,23</sup> and consists of eight items rated on a scale of 0 to 5, and is an excellent indicator for assessing respiratory and extrapulmonary symptoms.

This study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of the Chiba University School of Medicine approved the study protocol (approval number, 857). Written, informed consent was obtained from all the study subjects.

## Calculation of the Prognostic Nutritional Index

As an immune-nutritional index, the PNI was calculated as follows, in accordance with the original description of Onodera et al<sup>14</sup>  $10 \times$  serum albumin level (g/dL) + 0.005  $\times$  total lymphocyte count ( $\times 10^3/\mu\text{L}$ ). Originally, the PNI was used to assess surgical risk for gastrointestinal malignancies, with a resection anastomosis contraindicated in subjects with PNI values  $\leq 40$ .

## MDCT Scanning and CT Measurements of Low Attenuation Volume

All CT studies were performed on a 64-MDCT Aquilion ONE and Aquilion PRIME (Canon Medical Systems, Otawara, Tochigi, Japan) at full inspiration, with no contrast medium being used. The CT parameters used were as follows: collimation 120kV; CT-AEC; gantry rotation time, 0.5s; and beam pitch, 0.70–0.83. All the images were reconstructed using standard reconstruction algorithms, with a slice thickness of 0.5 mm and a reconstruction interval of 0.5 mm. The reconstructed CT images were transferred to a commercial workstation (Ziostation2, Ziosoft Ltd., Tokyo, Japan). Total lung volume (LV) and low attenuation volume (LAV) were measured based on a threshold of  $-950$  Hounsfield units (HU). LAV% was calculated as  $100\% \times \text{LAV}/\text{LV}$ .<sup>24</sup>

## Clinical Events

We investigated the clinical events during a two-year observation period. The clinical events were identified as COPD exacerbations. An exacerbation was defined as a worsening of COPD requiring a change in therapy, the use of antibiotics or steroids, and/or hospital admission.<sup>25</sup>

## Statistical Analysis

The results were expressed as means  $\pm$  standard deviation ( $\pm$  SD) or as medians (interquartile range [IQR]) as appropriate. Categorical data were expressed as the number (%). After confirming the normality of the study parameter data, the correlations between PNI and CAT, and LAV%, and FEV<sub>1</sub>%pred were assessed by Spearman rank correlation analysis, as appropriate. For clinical outcome, comparisons between the subject groups with or without an exacerbation requiring treatment changes were performed using the Mann–Whitney *U*-test for continuous variables and the chi-square test or Fisher exact test for categorical variables.

For the selection of variables in the multivariate analysis, we used those that showed a causal relationship with COPD exacerbations based on previous reports<sup>7,25–27</sup> and those that were significant in our univariate analysis. The association of selected variables with clinical outcome was assessed by univariate logistic regression analysis, and significant variables in this analysis then entered into a multivariate logistic regression analysis.

The variables selected were age, CAT as a comprehensive indicator of subjective symptoms, NLR as an indicator of the level of inflammation, PNI as an indicator of nutrition and immunity, FEV<sub>1</sub>% pred as an indicator of airflow limitation to measure disease severity, and LAV% as an imaging indicator to determine the degree of emphysema. In accordance with previous reports, CAT was treated as a continuous variable in the analysis.<sup>28,29</sup>

In the group with subjects aged > 75 years, we also calculated the areas under the receiver operating curve (ROC) analysis for using PNI and CAT to predict COPD exacerbation, with the optimal cut-off of the PNI and CAT determined by the Youden index. In addition, based on Akaike's information criterion,<sup>30</sup> we examined whether PNI improved the predictive accuracy of the analytical model for exacerbations in the elderly group. The original model was constructed with items that were significant in the univariate analysis. A statistically significant increase in the global chi-square of the model was interpreted as indicating an increase in prognostic value.<sup>31,32</sup> All the statistical analyses were performed by JMP Pro version 14.0 software (SAS Institute, Cary, NC, USA). For all the statistical analyses, the level of significance was set at  $p < 0.05$ .

## Results

### Subject Characteristics

The clinical characteristics of all the subjects are presented in Table 1.

**Table 1** Characteristics of the Total Subjects (Comparison of the Group Aged <75 Years vs the Group Aged  $\geq 75$  Years)

	All Subjects (n=91) Mean ( $\pm$ SD)	Age <75 yr (n=57) Mean ( $\pm$ SD)	Age $\geq 75$ yr (n=34) Mean ( $\pm$ SD)	P-value
Age (yr)	71.3 $\pm$ 7.6	67.2 $\pm$ 6.2	78.3 $\pm$ 3.2	<0.0001
Female gender, n (%)	4 (4.4%)	3 (5.3%)	1 (2.9%)	0.601
Pack-years	59.6 $\pm$ 33.8	57.2 $\pm$ 30.7	63.6 $\pm$ 38.5	0.447
Body weight (kg)	63.3 $\pm$ 11.7	63.9 $\pm$ 11.9	62.3 $\pm$ 11.5	0.682
Height (m)	1.65 $\pm$ 0.07	1.66 $\pm$ 0.07	1.641 $\pm$ 0.062	0.296
BMI (kg/m <sup>2</sup> )	23.1 $\pm$ 3.8	23.2 $\pm$ 3.8	23.1 $\pm$ 3.8	1.000
CAT score	12.0 $\pm$ 8.6	12.3 $\pm$ 8.5	11.5 $\pm$ 8.8	0.665
VC (L)	3.4 $\pm$ 0.8	3.6 $\pm$ 0.8	3.0 $\pm$ 0.7	0.002
%VC	95.1 $\pm$ 17.6	97.6 $\pm$ 16.5	91.0 $\pm$ 18.9	0.141
FVC (L)	3.3 $\pm$ 0.9	3.5 $\pm$ 0.8	2.9 $\pm$ 0.7	0.001
FEV <sub>1</sub> (L)	1.8 $\pm$ 0.8	1.8 $\pm$ 0.8	1.7 $\pm$ 0.7	0.446
FEV <sub>1</sub> / FVC (%)	53.3 $\pm$ 15.6	51.3 $\pm$ 16.2	56.7 $\pm$ 14.1	0.111
FEV <sub>1</sub> % pred	64.6 $\pm$ 24.8	63.2 $\pm$ 23.7	67.1 $\pm$ 26.7	0.697
LAV%	16.3 $\pm$ 15.0	19.8 $\pm$ 16.2	10.5 $\pm$ 10.7	0.01
WBC count ( $\times 10^3/\mu\text{L}$ )	6724 $\pm$ 1592	6647 $\pm$ 1515	6853 $\pm$ 1728	0.631
Neutrophil count ( $\times 10^3/\mu\text{L}$ )	4116 $\pm$ 1327	4008 $\pm$ 1230	4297 $\pm$ 1476	0.412
Lymphocyte count ( $\times 10^3/\mu\text{L}$ )	1853 $\pm$ 689	1885 $\pm$ 687	1799 $\pm$ 700	0.514
Eosinophil count ( $\times 10^3/\mu\text{L}$ )	266 $\pm$ 292	263 $\pm$ 295	271 $\pm$ 290	0.838
Serum albumin (g/dL)	4.1 $\pm$ 0.4	4.2 $\pm$ 0.3	4.0 $\pm$ 0.5	0.02
NLR	2.5 $\pm$ 1.3	2.4 $\pm$ 1.1	2.8 $\pm$ 1.5	0.365
PNI	50.8 $\pm$ 5.9	51.7 $\pm$ 5.7	49.2 $\pm$ 6.0	0.09
Treatment	70 (76.9%)	45 (78.9%)	25 (73.5%)	0.553

(Continued)

**Table 1** (Continued).

	<b>All Subjects (n=91) Mean (±SD)</b>	<b>Age&lt;75 yr (n=57) Mean (±SD)</b>	<b>Age ≥75 yr (n=34) Mean (±SD)</b>	<b>P-value</b>
LAMA	14	9	5	
LABA	5	2	3	
ICS	0	0	0	
LAMA/LABA	13	9	4	
ICS/LABA	9	5	4	
ICS/LAMA	1	0	1	
ICS/LAMA/LABA	28	20	8	
Exacerbations, n (%)	31 (33.7%)	21 (36.8%)	10 (29.4%)	0.469
Exacerbations per 1 year	0.4 ± 0.7	0.5 ± 0.7	0.3 ± 0.5	0.345

**Notes:** Data are presented as n or mean ± SD. P-values were determined using the Mann–Whitney U-test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Values in bold indicate statistical significance at the  $P < 0.05$  level.

**Abbreviations:** yr, year; BMI, body mass index; CAT, COPD assessment test; VC, vital capacity; %VC, vital capacity percentage; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in one second; FEV<sub>1</sub>/FVC (%), forced expiratory volume % in one second; FEV<sub>1</sub>% pred, forced expiratory volume in one second in % predicted; LAV%, low attenuation volume percentage; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; LAMA, long-acting muscarinic antagonist; LABA, long-acting β<sub>2</sub>-agonist; ICS, Inhaled corticosteroids.

In the total subjects (n=91), 34 subjects were aged ≥75 years (33 males and 1 female; mean age, 78.3 ± 3.2 years) and 57 subjects were aged < 75 years (54 males and 3 females; mean age, 67.2 ± 6.2 years). There were no differences between the two groups for sex, body weight, height, BMI, and CAT score. For the pulmonary function tests, VC and FVC were lower in subjects ≥75 years than in those aged <75 years. LAV% in the group aged ≥75 years was also lower than that measured in subjects <75 years. For nutritional status, there was no significant difference in PNI between the two groups, although albumin was slightly lower in the group aged ≥75 years. An exacerbation occurred in 21 of 57 of the younger subjects (36.8%) compared to 10 of the 34 older subjects (29.4%). The median duration of follow-up was 735 days.

Comparisons of the clinical indices in subjects aged ≥75 years with or without an exacerbation are shown in Table 2. In the exacerbation group, the CAT score was significantly higher and PNI was significantly lower compared to those

**Table 2** Characteristics of COPD Subjects in the Group Aged ≥75 Years (Comparison of the Exacerbation and Non-Exacerbation Groups)

	<b>All Subjects (n=34) Mean (±SD)</b>	<b>Exacerbation + (n=10) Mean (±SD)</b>	<b>Exacerbation - (n=24) Mean (±SD)</b>	<b>P-value</b>
Age (yr)	78.3 ± 3.2	78.9 ± 4.7	78.0 ± 2.5	0.909
Female gender, n (%)	1 (2.9%)	1 (10.0%)	0 (0%)	0.116
Pack-years	63.6 ± 38.5	66.8 ± 39.2	62.3 ± 39.0	0.733
Body weight (kg)	62.3 ± 11.5	58.2 ± 12.2	64.0 ± 11.0	0.168
Height (m)	1.64 ± 0.06	1.65 ± 0.08	1.64 ± 0.05	0.461
BMI (kg/m <sup>2</sup> )	23.1 ± 3.8	21.5 ± 4.3	23.7 ± 3.4	0.219
CAT score	11.5 ± 8.8	18.0 ± 8.7	8.8 ± 7.4	<b>0.009</b>
VC (L)	3.0 ± 0.7	2.8 ± 0.8	3.1 ± 0.6	0.374
%VC	91.0 ± 18.9	84.7 ± 20.6	93.6 ± 17.9	0.265
FVC (L)	2.9 ± 0.7	2.7 ± 0.9	3.0 ± 0.7	0.307

(Continued)

**Table 2** (Continued).

	<b>All Subjects (n=34) Mean (±SD)</b>	<b>Exacerbation + (n=10) Mean (±SD)</b>	<b>Exacerbation - (n=24) Mean (±SD)</b>	<b>P-value</b>
FEV <sub>1</sub> (L)	1.7 ± 0.7	1.5 ± 0.7	1.8 ± 0.7	0.299
FEV <sub>1</sub> / FVC (%)	56.7 ± 14.1	53.7 ± 13.5	58.0 ± 14.4	0.461
FEV <sub>1</sub> % pred	67.1 ± 26.7	59.1 ± 27.5	70.4 ± 26.2	0.219
LAV%	10.5 ± 10.7	11.0 ± 14.5	10.3 ± 9.0	0.484
WBC count (×10 <sup>3</sup> /μL)	6853 ± 1728	7040 ± 1487	6775 ± 1843	0.664
Neutrophil count (×10 <sup>3</sup> /μL)	4297 ± 1476	4702 ± 1599	4128 ± 1422	0.317
Lymphocyte count (×10 <sup>3</sup> /μL)	1799 ± 700	1536 ± 606	1909 ± 719	0.146
Eosinophil count (×10 <sup>3</sup> /μL)	271 ± 290	317 ± 472	252 ± 178	0.484
Serum albumin (g/dL)	4.0 ± 0.5	3.7 ± 0.6	4.2 ± 0.4	<b>0.016</b>
NLR	2.8 ± 1.5	3.6 ± 2.1	2.4 ± 1.1	0.086
PNI	49.2 ± 6.0	44.4 ± 6.6	51.2 ± 4.5	<b>0.004</b>
Treatment	25 (73.5%)	7 (70.0%)	18 (75.0%)	0.763
LAMA	5	1	4	
LABA	3	0	3	
ICS	0	0	0	
LAMA/LABA	4	0	4	
ICS/LABA	4	2	2	
ICS/LAMA	1	0	1	
ICS/LAMA/LABA	8	4	4	
Exacerbations per 1 year	0.3 ± 0.5	1.1 ± 0.3	0	<b>&lt;0.0001</b>

**Notes:** Data are presented as n or mean ± SD. P-values were determined by the Mann–Whitney U-test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Values in bold indicate statistical significance at the p < 0.05 level.

**Abbreviations:** yr, year; BMI, body mass index; CAT, COPD assessment test; VC, vital capacity; %VC, vital capacity percentage; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in one second; FEV<sub>1</sub> /FVC (%), forced expiratory volume % in one second; FEV<sub>1</sub>% pred, forced expiratory volume in one second in % predicted; LAV%, low attenuation volume percentage; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; LAMA, long-acting muscarinic antagonist; LABA, long-acting β<sub>2</sub>-agonist; ICS, Inhaled corticosteroids.

measured in the non-exacerbation group. The serum albumin levels were also significantly different between the two groups.

Comparisons of the clinical indices in subjects aged <75 years with or without an exacerbation are shown in Table 3. In the exacerbation group, the CAT score, LAV%, WBC count, and neutrophil count were significantly higher than those measured in the non-exacerbation group. The BMI was significantly lower in the exacerbation group than in the non-exacerbation group. Obstructive impairment was also significantly more severe in the exacerbation group compared to that observed in the non-exacerbation group.

## Associations Between the Prognostic Nutritional Index and Airflow Limitation and Pulmonary Emphysema

The associations between the PNI and other clinical indices in the entire cohort of subjects are shown in Figure 2. The PNI showed no significant association with CAT ( $r = -0.20$ ,  $p = 0.06$ ). Similarly, there was no significant correlation between PNI and either FEV<sub>1</sub>%pred ( $r = 0.03$ ,  $p = 0.78$ ) or LAV% ( $r = 0.03$ ,  $p = 0.75$ ).

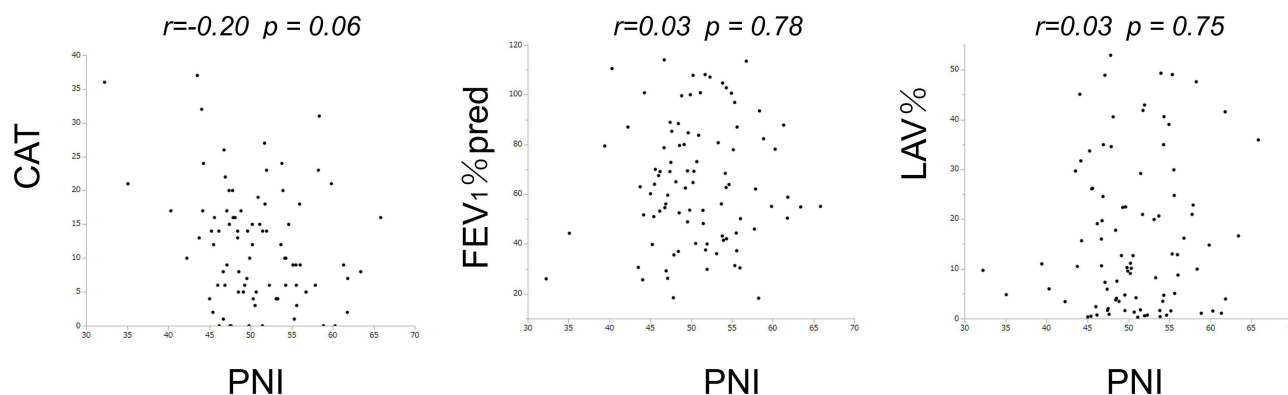
**Table 3** Characteristics of COPD Subjects in the Group Aged <75 Years (Comparison of the Exacerbation and Non-Exacerbation Groups)

	All Subjects (n=57) Mean (±SD)	Exacerbation + (n=21) Mean (±SD)	Exacerbation - (n=36) Mean (±SD)	P-value
Age (yr)	67.2 ± 6.2	66.8 ± 7.5	67.4 ± 5.5	0.752
Female gender, n (%)	3 (5.3%)	1 (4.8%)	2 (5.4%)	0.897
Pack-years	57.2 ± 30.7	62.0 ± 34.2	54.4 ± 28.6	0.267
Body weight (kg)	63.9 ± 11.9	60.2 ± 10.3	66.0 ± 12.3	0.06
Height (m)	1.66 ± 0.07	1.66 ± 0.08	1.65 ± 0.07	0.728
BMI (kg/m <sup>2</sup> )	23.2 ± 3.8	21.6 ± 2.5	24.1 ± 4.1	<b>0.009</b>
CAT score	12.3 ± 8.5	15.7 ± 9.3	10.4 ± 7.4	<b>0.044</b>
VC (L)	3.6 ± 0.8	3.4 ± 0.8	3.6 ± 0.8	0.234
%VC	97.6 ± 16.5	92.3 ± 17.4	100.7 ± 15.4	0.178
FVC (L)	3.5 ± 0.8	3.3 ± 0.8	3.6 ± 0.8	0.165
FEV <sub>1</sub> (L)	1.8 ± 0.8	1.5 ± 0.7	2.0 ± 0.8	<b>0.005</b>
FEV <sub>1</sub> / FVC (%)	51.3 ± 16.2	43.3 ± 18.0	55.9 ± 13.2	<b>0.002</b>
FEV <sub>1</sub> % pred	63.2 ± 23.7	50.3 ± 24.8	70.7 ± 19.8	<b>0.002</b>
LAV%	19.8 ± 16.2	30.3 ± 16.6	13.7 ± 12.6	<b>0.0006</b>
WBC count (×10 <sup>3</sup> /μL)	6647 ± 1515	7129 ± 1058	6367 ± 1677	<b>0.027</b>
Neutrophil count (×10 <sup>3</sup> /μL)	4008 ± 1230	4342 ± 988	3814 ± 1327	0.055
Lymphocyte count (×10 <sup>3</sup> /μL)	1885 ± 687	1918 ± 682	1866 ± 698	0.836
Eosinophil count (×10 <sup>3</sup> /μL)	263 ± 295	361 ± 442	206 ± 136	0.15
Serum albumin (g/dL)	4.2 ± 0.3	4.2 ± 0.4	4.2 ± 0.3	0.803
NLR	2.4 ± 1.1	2.5 ± 1.0	2.3 ± 1.2	0.237
PNI	51.7 ± 5.7	51.6 ± 6.2	51.8 ± 5.4	0.980
Treatment	45 (78.9%)	19 (90.5%)	26 (72.2%)	0.103
LAMA	9	3	6	
LABA	2	0	2	
ICS	0	0	0	
LAMA/LABA	9	4	5	
ICS/LABA	5	2	3	
ICS/LAMA	0	0	0	
ICS/LAMA/LABA	20	10	10	
Exacerbations per 1 year	0.5 ± 0.7	1.3 ± 0.5	0	<b>&lt;0.0001</b>

**Notes:** Data are presented as n or mean ± SD. P-values were determined by the Mann–Whitney U-test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Values in bold indicate statistical significance at the  $P < 0.05$  level.

**Abbreviations:** yr, year; BMI, body mass index; CAT, COPD assessment test; VC, vital capacity; %VC, vital capacity percentage; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in one second; FEV<sub>1</sub> /FVC (%), forced expiratory volume % in one second; FEV<sub>1</sub>% pred, forced expiratory volume in one second in % predicted; LAV%, low attenuation volume percentage; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; LAMA, long-acting muscarinic antagonist; LABA, long-acting β<sub>2</sub>-agonist; ICS, Inhaled corticosteroids.





**Figure 2** The relationship between PNI and CAT and FEV<sub>1</sub>%pred and LAV% in all the subjects.

**Notes:** The associations between the PNI and other clinical indices are shown for the entire cohort of subjects (n=91).

**Abbreviations:** PNI, prognostic nutritional index; CAT, COPD assessment test; FEV<sub>1</sub>, forced expiratory volume in one second; LAV%, low attenuation volume percentage.

## Clinical Factors Associated with Exacerbation Events

The results of the univariate and multivariate analyses for exacerbation in the two groups grouped according to age are shown in [Table 4](#) and [Table 5](#).

In the group aged  $\geq 75$  years, univariate analysis showed that CAT (OR = 1.15, 95% CI = 1.03–1.29,  $p = 0.013$ ), NLR (OR=1.70, 95% CI=1.01–2.86,  $p = 0.046$ ), and PNI (OR = 0.74, 95% CI =0.58–0.96,  $p = 0.023$ ) were associated significantly with exacerbation. Multivariate analysis identified CAT as an independent factor for exacerbation (OR = 1.15, 95% CI = 1.00–1.33,  $p = 0.047$ ), while PNI showed a trend of being associated with exacerbation (OR = 0.73, 95% CI =0.52–1.02,  $p = 0.063$ ).

ROC curve analysis was performed for the group  $\geq 75$  years of age to evaluate the accuracy of CAT and PNI and to identify the value of the cut-off points. ROC curve analysis in the group  $\geq 75$  years of age demonstrated that the optimal cut-off values for CAT and PNI to predict events were 14.0 (sensitivity, 0.80; 1-specificity, 0.21; area under the curve [AUC], 0.79; [Figure 3a](#)) and 48.85 (sensitivity, 0.90; 1-specificity, 0.33; AUC, 0.82; [Figure 3b](#)), respectively.

In the group aged  $< 75$  years, univariate analysis showed that CAT (OR = 1.083, 95% CI = 1.00–1.17,  $p = 0.038$ ), FEV<sub>1</sub>% pred (OR = 0.957, 95% CI = 0.931–0.986,  $p = 0.003$ ) and LAV% (OR = 1.077, 95% CI = 1.032–1.123,  $p = 0.0007$ ) were associated significantly with exacerbation. Multivariate analysis identified LAV% as an independent factor for exacerbation (OR = 1.074, 95% CI = 1.003–1.149,  $p = 0.031$ ).

**Table 4** Results of the Logistic Analysis of COPD Exacerbation in the  $\geq 75$  Year Age Group

Subjects Age $\geq 75$	Univariate			Multivariate		
	Odds Ratio	95% CI	P value	Odds Ratio	95% CI	P value
Age	1.08	0.86–1.15	0.48			
CAT	1.15	1.03–1.29	0.013	1.15	1.00–1.33	0.047
NLR	1.70	1.01–2.86	0.046	0.99	0.45–2.17	0.974
PNI	0.74	0.58–0.96	0.023	0.73	0.52–1.02	0.063
FEV <sub>1</sub> % pred	0.98	0.95–1.01	0.26			
LAV%	1.00	0.94–1.08	0.87			

**Abbreviations:** CAT, COPD assessment test; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; FEV<sub>1</sub>, forced expiratory volume in one second; LAV%, low attenuation volume percentage;



**Table 5** Results of the Logistic Analysis of COPD Exacerbation in the <75 Year Age Group

Subjects Age<75	Univariate			Multivariate		
	Odds Ratio	95% CI	P value	Odds Ratio	95% CI	P value
Age	0.99	0.90–1.07	0.73			
CAT	<b>1.08</b>	<b>1.00–1.7</b>	<b>0.038</b>	1.03	0.95–1.12	0.43
NLR	1.22	0.76–1.98	0.41			
PNI	1.00	0.90–1.09	0.91			
FEV <sub>1</sub> % pred	<b>0.98</b>	<b>0.93–0.99</b>	<b>0.003</b>	1.00	0.96–1.95	0.91
LAV%	<b>1.08</b>	<b>1.03–1.12</b>	<b>0.0007</b>	<b>1.07</b>	<b>1.00–1.14</b>	<b>0.039</b>

**Abbreviations:** CAT, COPD assessment test; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; FEV<sub>1</sub>, forced expiratory volume in one second; LAV%, low attenuation volume percentage.

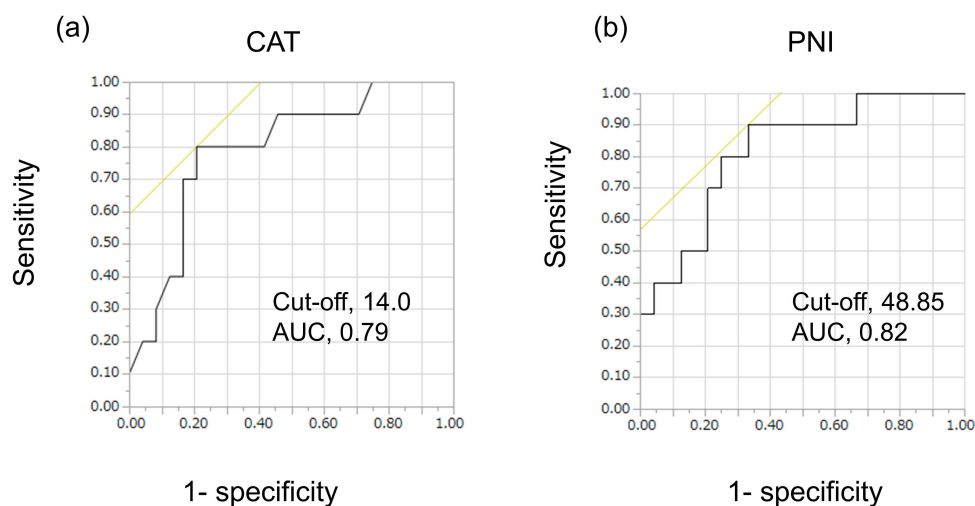
## Incremental Value of the PNI in Elderly Subjects with COPD

The incremental value of the PNI in the group  $\geq 75$  years of age is shown in Figure 4. CAT was selected as the conventional variable for the prognostic model from Table 4 (Model 1). The addition of PNI to the conventional variable significantly improved the prognostic utility of the model (Model 2,  $p = 0.0084$ ).

## Discussion

The key findings of this study were as follows. There were differences in factors related to COPD exacerbations between subjects aged  $\geq 75$  years and those aged  $< 75$  years. High CAT values were associated with exacerbation in elderly subjects with COPD, while a combined model of CAT and PNI more accurately predicted COPD exacerbations. In other words, a low PNI in combination with a high CAT increased the risk of an exacerbation in elderly subjects with COPD.

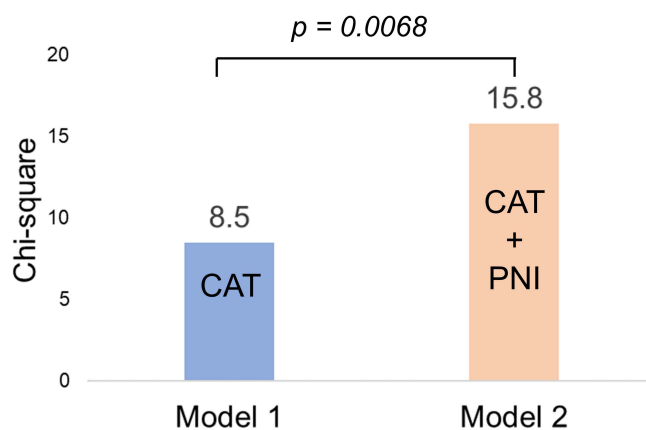
The PNI was calculated using serum albumin levels and the total circulating lymphocyte count. The PNI score has been validated and reported to correlate significantly with subjective global assessment (SGA), a well-established nutritional index and also other nutritional screening tools.<sup>33–35</sup> While the SGA is a simple, inexpensive, and quick assessment, it is a subjective assessment that requires skill and experience. In contrast, the PNI is based on the results of



**Figure 3** Receiver operating characteristic curve (ROC) analysis of CAT and PNI in the group  $\geq 75$  years of age.

**Notes:** ROC curve analysis was used to evaluate the sensitivity and specificity of CAT (a) and PNI (b) for COPD exacerbation in the group  $\geq 75$  years of age. (n=34).

**Abbreviations:** PNI, prognostic nutritional index; CAT, COPD assessment test.



**Figure 4** The incremental benefit of adding PNI to the CAT, to predict exacerbation events in the group  $\geq 75$  years of age.

**Notes:** Model 1, based on CAT, was improved significantly by the addition of the PNI (model 2) in the group  $\geq 75$  years of age ( $n=34$ ).

**Abbreviations:** CAT, COPD assessment test; PNI, prognostic nutritional index.

peripheral blood tests, thereby allowing a physician to easily and objectively assess the immune-nutritional status of their patients.

Many earlier studies have described that nutrition and immune status are associated closely with tumor progression and prognosis. The PNI reflects both the nutritional and immunological status of patients with a variety of malignancies.<sup>36,37</sup> In the respiratory field, the PNI of pretreatment in patients with non-small cell lung cancer has been shown to have prognostic value.<sup>38</sup> Recently, it was reported that a lower PNI at the time of admission was related to the risk of mortality in subjects with severe COVID-19.<sup>39,40</sup> Regarding chronic respiratory diseases, the present study has shown that the PNI score raised the risk of exacerbation in elderly with COPD.

The CAT is a simple tool for comprehensive evaluation of the clinical symptoms in COPD patients.<sup>22</sup> The CAT consists of eight items and is an excellent indicator for assessing respiratory symptoms, such as cough, phlegm, and dyspnea associated with exercise, and extra-pulmonary symptoms, such as activity, insomnia, and energy level. The CAT scores were increased by greater than five points during exacerbations.<sup>26</sup> In the present study, the PNI was not associated with CAT in all the subjects. Yoshikawa et al reported that nutritional status using the Mini-nutritional Assessment Short-form predicted COPD exacerbations independently of CAT.<sup>41</sup> The present study also showed no significant relationship between PNI and either FEV<sub>1</sub>%pred and low attenuation volume percentage (LAV%). These findings might indicate that PNI may be an independent predictor from CAT, the degree of obstructive impairment, and emphysema, which have conventionally been reported as predictive factors.<sup>42</sup>

A cut-off value of 40 for the PNI has been proposed for perioperative evaluation of gastrointestinal cancers.<sup>14</sup> In the current study, the cut-off value for PNI for the presence of exacerbations in subjects aged  $\geq 75$  years was set at 48.85, a value higher than that used for other diseases. A prognostic pretreatment cut-off of 45.5 was used for lung cancer patients receiving immune checkpoint inhibitors.<sup>43</sup> Recently, a lower cut-off value of 33 was used for survival in patients with severe COVID-related pneumonia.<sup>39</sup> Since COPD is a gradually progressive disease, the serum albumin levels and lymphocyte counts were obtained at the time of consultation, and we speculate that this may be one of the reasons for the higher cut-off values compared to those used for other diseases. Therefore, patients with COPD should be cautioned against exacerbations even if the initial PNI value is higher than previously reported for other diseases.

In the group aged  $< 75$  years, the conventional variables, such as emphysema and the degree of airflow limitation, contributed to exacerbations.<sup>25</sup> Most previous studies have focused on relatively young to middle-aged patients, with only a minority carried out in older subjects.<sup>44</sup>

In the present study we identified prognostic factors for elderly subjects and showed that the complex of subjective symptom scores and immune-nutritional status contributed more to exacerbations than the severity of COPD. The prognosis of elderly patients with chronic diseases is not necessarily determined by the severity of the underlying disease.<sup>45</sup> Poor nutritional status is associated with a poor prognosis and exercise intolerance in elderly patients with

COPD.<sup>41,46</sup> More severe subjective symptoms are associated with a worse prognosis.<sup>22</sup> We propose that the combination of CAT and PNI would allow assessment of the risk of exacerbation more accurately in elderly patients with COPD.

Serum albumin level is a conventional marker of nutrition and has been reported to be associated with a poor outcome in many different diseases. On the other hand, the NLR is a reliable indicator of systematic inflammation and has also been investigated as a diagnostic and prognostic marker in COPD.<sup>47</sup> Chronic inflammation causes recruitment of the main white blood cell populations, neutrophils and lymphocytes. These factors participate actively in the pathophysiological mechanisms of COPD. A higher NLR has been reported widely to be associated with poor survival in patients with various diseases.<sup>48,49</sup> However, the NLR only reflects the inflammation status. In recent studies, the PNI was shown to be superior to the NLR as a prognostic marker in many cancer patients.<sup>36,50</sup> PNI as a nutrition plus immunity indicator may therefore be more useful in the evaluation of COPD than either nutrition or immunity alone.

There has been a focus on the role of the asthma-COPD overlap (ACO), including eosinophilia in COPD, and the impact of asthmatic components on the clinical course of COPD.<sup>51</sup> Recent studies have reported that eosinophilia in COPD does not affect the clinical course, however, this view is controversial.<sup>52</sup> The present study also showed no relationship between eosinophilia and clinical outcome. In recent years, the clinical significance of personalized treatment in COPD has been proposed, with some studies showing that appropriate treatment, such as triple therapy in patients with asthmatic components, decreases symptoms and the risk of exacerbations, thereby contributing to an improved clinical course.<sup>53</sup>

## Limitations

Our study had some limitations. First, the study only enrolled a relatively small number of subjects and was a preliminary and exploratory investigation conducted at a single institute. Second, the observational period was relatively short. Third, because of the small number of subjects we could not fully evaluate the differences in gender, each treatment, or the rate of smoking cessation. Fourth, we could not perform nutritional intervention. Nutritional intervention may be important for preventing COPD exacerbations, especially in elderly patients.<sup>54</sup> And finally, previous papers reporting an association between PNI and prognosis used unadjusted multivariate analyses.<sup>43,45</sup> The present study also performed unadjusted multivariate analysis of each item. However, this was a single-center, small-group, exploratory study and therefore a larger cohort is needed to confirm the results of the current study that would also require more rigorous examination and exclusion of confounding factors. Further prospective studies on larger study populations and a longer observational period are therefore required to confirm our results.

## Conclusions

In elderly subjects with COPD, CAT was associated significantly with the risk of COPD exacerbation, with PNI also a potential predictor. The combined assessment of CAT and PNI may be a useful prognostic tool in patients with COPD.

## Abbreviations

BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; FEV<sub>1</sub>/FVC, forced expiratory volume in 1 second per forced vital capacity; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Pulmonary Obstructive Lung Disease; ICS, inhaled corticosteroid; LAA, low attenuation area; LABA, long-acting  $\beta$ -2 agonist; LAMA, long-acting muscarinic antagonists; LAV, low attenuation volume; LAV%, low attenuation volume percentage; LV, lung volume; MDCT, multi-detector row computed tomography; MRI, magnetic resonance imaging; NLR, neutrophil-to-lymphocyte ratio; PFT, pulmonary function testing; PNI, prognostic nutritional index; TLA, total lung area; VC, vital capacity; %VC, vital capacity percentage; WBC, white blood cell.

## Data Sharing Statement

The data sets analyzed during the current study are available from the corresponding author upon reasonable request.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The author reports no conflicts of interest in this work.

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