The association of delta neutrophil index with the prognosis of acute exacerbation of chronic obstructive pulmonary disease

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Abstract

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is associated with infective triggers including bacterial or viral in many cases, and pneumonia is a major contributor to hospitalization for AECOPD and has a close relationship with poor outcomes. Increased delta neutrophil index (DNI) can be useful in the detection of COPD patients with pneumonia.

Methods: A retrospective cohort study was performed to investigate the mortality rate of the patients who were re-admitted within 6 months after discharge from the hospital due to AECOPD with or without CAP. We analyzed the difference of cumulative survival rate according to serum DNI level and readmission duration.

Results: Finally, 140 AECOPD patients with community-acquired pneumonia (CAP) and 174 AECOPD patients without CAP were enrolled during 6 months, respectively. The mean age was 72.2 ± 9.4 year-old, and 240 patients (76.4%) were male. When comparing the cumulative survival rate according to readmission duration (≤ 30 vs > 30 days) and DNI level (< 3.5 vs ≥ 3.5%), AECOPD patients with readmission ≤30 days and DNI ≥ 3.5% showed the lowest cumulative survival rate compared to other groups (P < 0.001). Multivariate analysis revealed readmission duration ≤30 days (HR 7.879, 95% CI 4.554–13.632, P < 0.001); and serum DNI level (HR 1.086, 95% CI 1.043–1.131, P < 0.001) were significantly associated with the mortality of AECOPD patients during 6 months. The area under the curve for readmission (≤30 days) + DNI level (≥ 3.5%) was 0.753 (95% CI 0.676–0.830, P < 0.001) with a sensitivity of 73.7% and a specificity of 67.3%.

Conclusion: AECOPD patients who were readmitted ≤30 days and DNI ≥ 3.5% showed higher mortality. DNI level can be used as a predictor of prognosis in AECOPD patients who were readmitted after discharge.

Keywords: Acute exacerbation, Chronic obstructive pulmonary disease, Community-acquired pneumonia, Delta neutrophil index, Mortality, Readmission

Background

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are major health issues in COPD patients, and are important causes of hospital admission and mortality [1–3]. AECOPD is diagnosed on clinical grounds, when specific symptoms (including dyspnea, increased sputum volume, and purulence) deteriorate beyond day-to-day variability, whereas severity is rated according to healthcare resource utilization [4].

The observational study showed that the readmission for AECOPD within 30 days is associated with a progressive increased long-term risk of death [5]. Nationwide study also demonstrated that 30-day readmissions after an AECOPD remain a major healthcare burden, associated with both patient and clinical factors (longer length of stay and discharge to a skilled nursing facility) [6]. Most exacerbations appear to be associated with infective triggers including bacterial or viral causatives [3]. Increased frequency of exacerbations is also significantly associated with...
forced expiratory volume in 1 s (FEV<sub>1</sub>) decline [7], and can thereby increase disease severity and mortality [8]. Community-acquired pneumonia (CAP) is a frequently accompanied disease [9] and is a valuable predictive factor of poor prognosis in AECOPD patients who require hospitalization [10]. AECOPD patients with pneumonia were found to use non-invasive ventilation more frequently and remain hospitalized longer than those without pneumonia [11]. Several studies have identified that old age, disease severity, and use of inhaled corticosteroids are predisposing factors better inducing CAP in COPD patients [10, 12]. There is also another problem that readmission of AECOPD patients discharged after inpatient treatment. In fact, some studies explained that about 20% were readmitted due to AECOPD within 30 days after discharge [13, 14].

The delta neutrophil index (DNI) is the immature granulocyte fraction determined by subtracting the fraction of mature polymorphonuclear leukocytes and reflects the number of immature neutrophils as a blood biomarker [15]. DNI can easily be calculated and reported without an additional cost. Recently, systematic review and meta-analysis showed that the DNI has prognostic value in adults with sepsis and high DNI values tended to be associated with mortality in septic patients [16]. Increased DNI can be useful to evaluate the prognosis of COPD patients, especially with pneumonia. However, many studies about on AECOPD patients who were readmitted after receiving inpatient treatment and discharge have not yet been published and there is no study of the relationship between DNI and AECOPD prognosis.

Therefore, we performed a retrospective cohort study to investigate the mortality rate of AECOPD patients with or without CAP who were readmitted within 6 months after discharge from the hospital. Then, we analyzed the cumulative survival rate according to serum DNI level and readmission duration of AECOPD patients.

**Methods**

**Subjects**

We conducted a retrospective study of the patients who admitted with AECOPD at Yonsei University Wonju Severance Tertiary Hospital from January 2012 to December 2016 (Fig. 1). Patients were 45 years old or older and had a smoking history of ≥10 pack-years. The diagnostic criteria for COPD were as follows according to the GOLD guideline; a post-bronchodilator FEV<sub>1</sub>/forced vital capacity (FVC) < 70% confirms airflow limitation that is not fully reversible [1, 3]. We reviewed demographic data and comorbidities including diabetes mellitus, cardiac, liver and renal diseases and also investigated the treatments for COPD including long-acting muscarinic antagonists, beta<sub>2</sub> agonist, and inhaled corticosteroids. We evaluated lung function via using the Korean language version of the COPD assessment test (CAT) questionnaire [17], the modified Medical Research Council (mMRC) dyspnea scale, and most recent spirometry performed before admission, respectively. The following patients were excluded; valvular heart disease, myocardial infarction, cerebral infarction or hemorrhage, asthma, untreated malignancy, and renal disease on hemodialysis.

**Admission criteria**

AECOPD can be diagnosed when a patient with COPD experiences a sustained (24–48 h) increase in cough, sputum production, and/or dyspnea [18]. The admission criteria of AECOPD were as follows: 1) failed response to initial medical management, 2) severe symptoms (resting dyspnea, respiratory rates ≥ 30 breaths/min, oxygen saturation ≤ 90%, confusion, or drowsiness), 3) new onset of cyanosis, peripheral edema, or 4) respiratory failure using respiratory muscles or accompanying mental changes [19].

CAP was diagnosed when the following conditions were met; 1) cough and at least one other lower respiratory tract symptom; 2) new focal chest signs on examination; 3) at least one systemic feature of sweating, fevers, aches and and/or temperature ≥ 38°C [20]. The causative organism was recognized when detected in sputum or bronchoalveolar lavage fluid and/or blood. Sputum specimens were recognized when > 25 leukocytes and < 10 epithelial cells per high power field [21]. We performed peripheral blood sampling within 1 hour of admission to verify white blood cell (WBC) counts, delta neutrophil index (DNI), hemoglobin, high sensitive C-reactive protein (hs-CRP) and procalcitonin. Oxygen saturation, partial pressure of oxygen (PaO2) and carbon dioxide (PaCO2) were measured on day 1.

**Treatments and endpoint**

We treated enrolled patients with nebulized salbutamol, ipratropium bromide, Budesonide and intravenous prednisolone in a dosage of 30 to 40 mg daily, according to GOLD guidelines [1]. Systemic corticosteroid was given during 10–14 days, and switched to an oral prednisolone on day 4–7. Antibiotics were used in patients with CAP and adjusted according to antimicrobial susceptibilities on sputum or blood culture analysis. Antibiotic therapy was initiated in basic accordance with the ATS/IDSA guidelines [22].

We investigated the mortality rate of AECOPD patients with or without CAP who were readmitted within 6 months after discharge from the hospital. We analyzed cumulative survival rate according to serum DNI level (< 3.5 vs ≥ 3.5%) and readmission duration (≤ 30 vs > 30 days) in AECOPD patients.
Statistical analysis
SPSS 24.0 (SPSS Inc.; Chicago, IL, USA) were used for statistical analysis. Chi-square or Fisher’s exact test were used for categorical variables and Student t or Mann-Whitney U test used for continuous variables. We used Cox proportional hazards regression model to estimate the survival rate during 6 months between two groups. Relative risks were expressed as hazard ratio (HR) and 95% confidence interval (CI). Cumulative survival rates were expressed using a Kaplan–Meier approach and the log-rank test. Univariate and multivariate analysis was performed to evaluate prognostic factors associated with mortality of the patients. The receiver operating characteristic (ROC) curve was utilized to assess the accuracy of different indicators for mortality of AECOPD. We compared the area under the ROC curve (AUC) according to 1) readmission duration, 2) DNI, 3) readmission duration + DNI, and 4) readmission duration + CAP. The cut-off value for DNI was set at 3.5%. Pearson’s correlation coefficients (r value) test was used for evaluating the relationship between two variables. Descriptive statistics were expressed as mean value ± standard deviation for continuous data and number (%) for categorical data. P-value less than 0.05 were considered to be statistically significant.

Results
Total subjects
During study period, 827 severe AECOPD patients were admitted to a respiratory center, and 726 patients were eligible for inclusion criteria. Eighty-five patients (47

Fig. 1 Flowchart shows identification of severe AECOPD patients who were admitted to a respiratory center. AECOPD = acute exacerbation of chronic obstructive pulmonary disease; CAP = community-acquired pneumonia; DNI = delta neutrophil index
patients with CAP and 38 patients without CAP) were dropped out because were referred to other hospitals. Finally, 140 AECOPD patients with CAP (19 patients who were readmitted within 30 days and 121 patients who were readmitted after 30 days) and 174 AECOPD patients without CAP (22 patients who were readmitted within 30 days and 152 patients who were readmitted after 30 days) were enrolled during 6 months, respectively (Fig. 1). The mean age was 72.2 ± 9.4 year-old, and 240 patients (76.4%) were male. The demographic characteristics of AECOPD patients who were readmitted between ≤30 days and >30 days are shown in Table 1. Underlying comorbid conditions except hypertension \((P = 0.042)\), the regular inhaled medications and spirometric results before an admission were not significantly different among four groups (Table 1).

The mortality rates for AECOPD patients who were readmitted

When we investigated the mortality rate of AECOPD patients readmitted between ≤30 days and >30 days, the mortality rate during 6 months was the highest in AECOPD with CAP group who were readmitted ≤30 days (78.9% vs. 15.7% vs. 40.9% vs. 9.2%, \(P < 0.001\)) (Table 1). The causes of mortality were as follows; 30 patients with AECOPD (5 patients with CAP readmitted ≤30 days vs. 13 with CAP readmitted >30 days vs. 3 patients without CAP readmitted ≤30 days vs. 9 AECOPD without CAP readmitted >30 days), 18 pneumonias (10 vs. 3 vs. 2 vs. 3), 7 sepsis (0 vs. 3 vs. 1 vs. 3) and 2 pneumothoraces (0 vs. 0 vs. 2 vs. 2).

**Laboratory and microbiologic findings**

At the time of admission, oxygen saturation, \(\text{PaO}_2\), \(\text{PaCO}_2\), hemoglobin, and procalcitonin were not significantly different among four groups (Table 1).

### Table 1 Characteristics of AECOPD patients with and without CAP

| Characteristics                        | AECOPD with CAP | P-value | AECOPD without CAP | P-value |
|----------------------------------------|-----------------|---------|--------------------|---------|
|                                       | Readmission ≤ 30 days |        | Readmission > 30 days |        |
| Age, y, mean (SD)                      | 76.2 ± 7.4      | 0.055   | 72.8 ± 11.1        | 0.655   |
| Male sex, n (%)                        | 14 (73.7)       | 0.627   | 15 (68.2)          | 0.329   |
| CAT score, mean (SD)                   | 25.4 ± 6.8      | 0.107   | 25.2 ± 5.9         | 0.044   |
| mMRC dyspnea scale, n (%)              | 2–4             | 0.869   | 18 (81.8)          | 0.787   |
| GOLD stage, A/B/C/D, n                 | 1/7/3/8         | 0.332   | 0/9/4/9           | 0.095   |
| GOLD C, D ratio, n (%)                 | 11 (57.9)       | 0.379   | 13 (59.1)         | 0.134   |
| Long-term oxygen therapy               | 7 (36.8)        | 0.117   | 6 (9.1)            | 0.380   |
| Smoking amount, py, mean (SD)          | 43.1 ± 17.4     | 0.506   | 45.0 ± 13.4        | 0.604   |
| BMI, kg/m\(^2\)                        | 21.9 ± 2.6      | 0.481   | 21.5 ± 2.8         | 0.666   |
| Underlying comorbid conditions, n (%)  |                 |         |                    |         |
| Hypertension                           | 7 (36.8)        | 0.140   | 15 (68.2)          | 0.969   |
| Diabetes mellitus                      | 12 (63.2)       | 0.190   | 8 (36.4)           | 0.362   |
| Congestive heart failure               | 5 (26.3)        | 0.855   | 8 (36.4)           | 0.965   |
| Chronic kidney disease                 | 1 (5.3)         | 0.726   | 1 (4.5)            | 0.421   |
| Hepatobiliary disease                  | 0 (0.0)         | 0.306   | 1 (4.5)            | 0.421   |
| Medications before an admission, n (%) |                 |         |                    |         |
| Inhaled corticosteroids                | 11 (57.9)       | 0.951   | 13 (59.1)          | 0.824   |
| Long-acting muscarinic antagonists      | 10 (52.6)       | 0.598   | 12 (54.5)          | 0.690   |
| Long-acting beta\(_2\) agonists       | 11 (57.9)       | 0.943   | 9 (40.9)           | 0.229   |
| Functional parameters, %, mean (SD)    |                 |         |                    |         |
| Post-bronchodilator FEV\(_1\)/FVC     | 49.0 ± 10.3     | 0.962   | 48.3 ± 13.8        | 0.093   |
| Post-bronchodilator \(\text{FEV}_1\)  | 58.7 ± 23.9     | 0.606   | 55.5 ± 29.8        | 0.217   |
| Post-bronchodilator FVC                | 78.8 ± 23.2     | 0.387   | 75.3 ± 24.7        | 0.554   |
| Mortality within 6 months, n (%)       | 15 (78.9)       | < 0.001 | 9 (40.9)           | < 0.001 |

AECOPD acute exacerbations of chronic obstructive pulmonary disease, BMI body mass index, CAP community-acquired pneumonia, CAT Chronic obstructive pulmonary disease assessment test, \(\text{FEV}_1\) forced expiratory volume in 1 s, FVC forced vital capacity, GOLD Global Initiative for Chronic Obstructive Lung Disease, mMRC modified Medical Research Council, n number, py pack-years, SD standard deviation, y years old

\(^{a}\)mMRC dyspnea scale consists in five statements that describe almost the entire range of dyspnea from none (grade 0) to almost complete incapacity (grade 4)
different, but WBC count ($P < 0.001$), serum DNI ($P < 0.001$) and hs-CRP levels ($P < 0.001$) showed significant differences among four groups (Table 2). Mean DNI values were 9.5 ± 9.2, 5.0 ± 4.6, 2.9 ± 2.6, and 1.7 ± 2.6% respectively, and were significantly higher in AECOPD with CAP (readmitted ≤ 30 days) than without CAP (Fig. 2).

We identified causative organisms in 72.9% (102 out of 140) of AECOPD with CAP. *Streptococcus pneumoniae* was the most frequently isolated pathogen (38.6%); *Staphylococcus aureus* (13.6%), *Pseudomonas aeruginosa* (12.1%), *Klebsiella pneumoniae* (5.0%) and other pathogens (3.6%) were isolated, respectively (Table 2).

**Cumulative survival rates according to readmission duration and serum DNI level**

When we compared the cumulative survival rate of AECOPD patients according to readmission duration (≤ 30 vs > 30 days), AECOPD patients with readmission ≤ 30 days and CAP showed the lowest cumulative survival rate compared to other groups ($P < 0.001$) (Fig. 3a). When we compared the cumulative survival rate of AECOPD patients according to readmission duration (≤ 30 vs > 30 days) and DNI level (< 3.5 vs ≥ 3.5%), AECOPD patients with readmission ≤ 30 days and DNI ≥ 3.5% showed the lowest cumulative survival rate compared to other groups ($P < 0.001$) (Fig. 3b). Thus, the cumulative survival rate was lower as a serum DNI level (≥ 3.5%) was higher and readmission duration (≤ 30 days) was shorter.

**Prognostic factors associated with the mortality and ROC curve**

To identify risk factors associated with the mortality of AECOPD patients who were readmitted, multivariate logistic regression analysis was performed using significant variables with $P$ value < 0.05 by univariate analysis. Multivariate analysis using factors that were found to be significant by univariate analysis revealed that readmission duration ≤ 30 days (HR 7.879, 95% CI 4.554–13.632, $P < 0.001$); and serum DNI level (HR 1.086, 95% CI 1.043–1.131, $P < 0.001$) were significantly associated with the mortality of AECOPD patients during 6 months (Table 3). Pearson’s correlation coefficient (r value) of DNI (%) with hs-CRP was 0.433 ($P < 0.001$), DNI with PCT: 0.419 ($P < 0.001$), % DNI with PCO$_2$: -0.062 ($P = 0.276$), respectively.

The AUC for readmission duration (≤ 30 days) + DNI level (≥ 3.5%) was 0.753 (95% CI 0.676–0.830, $P < 0.001$) with a sensitivity of 73.7% and a specificity of 67.3%; AUC for readmission duration + CAP 0.678 (95% CI 0.597–0.758), readmission duration 0.677 (95% CI 0.590–0.765), and DNI 0.654 (95% 0.573–0.735), respectively (Fig. 4).

**Table 2** Laboratory and microbiologic findings between AECOPD with and without CAP

| Variables (at the time of admission) | AECOPD with CAP | P-value | AECOPD without CAP | P-value |
|-------------------------------------|-----------------|---------|-------------------|---------|
|                                     | Readmission     |         | Readmission       |         |
|                                     | ≤ 30 days       | > 30 days| ≤ 30 days         | > 30 days|
| Oxygen saturation, %                | 88.3 ± 8.7      | 88.5 ± 10.0| 0.926            | 86.8 ± 10.6| 0.153|
| PaO$_2$, mm Hg                      | 62.6 ± 15.1     | 62.5 ± 15.4| 0.973            | 61.2 ± 16.5| 0.104|
| PaCO$_2$, mmHg                      | 46.9 ± 30.1     | 38.2 ± 12.7| 0.231            | 43.3 ± 18.5| 0.438|
| WBC, × 10$^3$/μL                    | 14.7 ± 6.9      | 13.0 ± 5.7| 0.239            | 11.6 ± 6.4| 0.205|
| DNI, %                              | 9.5 ± 9.2       | 5.0 ± 4.6| 0.049            | 2.9 ± 2.6 | 0.039|
| Hemoglobin, g/dL                    | 12.0 ± 1.8      | 13.0 ± 1.8| 0.029            | 12.6 ± 1.5| 0.198|
| hs-CRP, mg/dL                       | 16.4 ± 8.3      | 15.9 ± 9.4| 0.839            | 2.3 ± 2.3 | 0.472|
| $^a$Procalcitonin, mg/dL            | 8.1 ± 21.2      | 3.8 ± 7.4| 0.467            | 1.3 ± 3.7 | 0.753|

| Microbiologic findings, n (%)       |                |         |                  |         |
|-------------------------------------|----------------|---------|-----------------|---------|
| *Streptococcus pneumoniae*          | 7 (36.8)       | 47 (38.8)| 0.868            | 1 (4.5) | 2 (1.3) | 0.335|
| *Staphylococcus aureus*             | 3 (15.8)       | 16 (13.2)| 0.724            | 2 (9.1) | 18 (11.8)| 1.000|
| *Pseudomonas aeruginosa*            | 1 (5.3)        | 16 (13.2)| 0.468            | 1 (4.5) | 15 (9.9)| 0.697|
| *Klebsiella pneumoniae*             | 2 (10.5)       | 5 (4.1)| 0.297            | 1 (4.5) | 10 (6.6)| 1.000|
| $^b$Others                          | 0 (0.0)        | 5 (4.1)| 1.000            | 0 (0.0) | 2 (1.3)| 1.000|

AECOPD acute exacerbations of chronic obstructive pulmonary disease, CAP community-acquired pneumonia, DNI delta neutrophil index, hs-CRP high sensitive C-reactive protein, $n$ number, PaCO$_2$ arterial carbon dioxide partial pressure, PaO$_2$ arterial oxygen partial pressure, SD standard deviation, WBC white blood cell

$^a$Initial procalcitonin results were available for 81 patients in AECOPD with CAP and 94 patients in AECOPD without CAP

$^b$Others were included *Mycoplasma pneumoniae* (2), *Legionella pneumophila* (1), *Haemophilus influenzae* (1) and *Acinetobacter baumannii* (1) in AECOPD with CAP, and *Legionella pneumophila* (1) and *Haemophilus influenzae* (1) in AECOPD without CAP, respectively
Discussion
The most important point in this study was that AECOPD with CAP group who were readmitted ≤30 days and DNI ≥ 3.5% showed the lowest cumulative survival rate compared to the other groups. ROC curve demonstrated that DNI (≥ 3.5%) with readmission duration (≤ 30 days) can affect the mortality of AECOPD patients who were readmitted.

Currently, initial DNI with serum WBC and CRP which are commonly used markers is known to be useful for predicting inflammation and infection [23]. DNI, the difference between the leukocyte differentials measured in cytochemical myeloperoxidase channel and those assayed in the nuclear lobularity channel, reflects the fraction of circulating immature granulocytes [24, 25]. Previous study reported that granulocyte precursors less mature than bands can be a better predictor of infection than band neutrophil counts [26]. The diagnostic value of DNI (reflecting the fraction of circulating immature granulocytes) was superior to WBC, absolute neutrophil count or other widely available laboratory markers for severe sepsis/septic shock [25].

Many clinicians have studied the usefulness of blood biomarkers such as CRP and procalcitonin for early assessment of sepsis. Recently, systematic review and meta-analysis showed that the DNI has prognostic value in adults with sepsis and high DNI values tend to be associated with mortality in septic patients [15]. Several studies have been reported to use DNI for the diagnosis or prognosis of other infectious diseases including pneumonia, pulmonary tuberculosis, and acute prostatitis [23, 27, 28]. However, there are no reports on the usefulness of DNI in COPD patients. In our paper, we focused on the AECOPD patients who readmitted within 180 days of discharge.

The observational study showed that the readmission for AECOPD within 30 days is associated with a progressive increased long-term risk of death [5]. In this study, ROC curve showed that DNI was a useful biologic marker for predicting the mortality rate of AECOPD in addition to readmission within 30 days. DNI levels were higher in AECOPD with CAP patients than without CAP. This indicates that DNI levels are associated with infection even in AECOPD. However, the mortality rate was the highest in patients readmitted within 30 days, suggesting that readmission within 30 days had a greater impact on prognosis than DNI level.

Readmission within 30 days and serum DNI level were significantly associated with the mortality of readmitted AECOPD patients when we analyzed the risk factors using multivariate analysis. And when the cut off value of DNI level is set to 3.5%, readmission duration (≤ 30 days) and serum DNI level (≥ 3.5%) have shown to be more useful in predicting mortality than readmission duration (≤ 30 days) and CAP in ROC curve analysis.

Unfortunately, there are no studies showing the usefulness of DNI in AECOPD patients so far and it was a problem to determine the cutoff value of DNI to predict prognosis. Previous study [29] have shown that the DNI value of sepsis patients was 3.4% and our study confirmed that mean DNI value of AECOPD patients was 3.5%, so we set the cutoff value of DNI to 3.5%. Figure 3 also showed that AECOPD patients with readmission
Fig. 3 Fig. 3 shows cumulative survival rates during 6 months of AECOPD patients according to (a) readmission duration (< 30 vs > 30 d) and CAP, (b) readmission duration (≤ 30 vs > 30 d) and serum DNI level (< 3.5 vs ≥ 3.5%). a It shows the lowest cumulative survival rate in AECOPD with readmission ≤30 d and CAP (HR 23.549, 95% CI 11.234–49.364, P < 0.001). b It shows also the lowest cumulative survival rate in AECOPD with readmission ≤30 d and serum DNI ≥ 3.5% according to readmission duration and serum DNI level (HR 26.642, 95% CI 10.129–42.067, P < 0.001). AECOPD = acute exacerbation of chronic obstructive pulmonary disease; CAP = community-acquired pneumonia; DNI = delta neutrophil index; d = days.

Table 3 Prognostic factors associated with the mortality of AECOPD patients readmitted within 6 months

| Variables                      | Univariate (mortality) | Multivariate (mortality) |
|--------------------------------|------------------------|--------------------------|
|                                | 95% CI                  | HR                       | P-value    | 95% CI                  | HR                       | P-value    |
| **Demographic**                |                        |                          |            |                        |                          |            |
| GOLD group C-D                 | 1.195, 3.549           | 2.060                    | 0.009*     | 0.792, 2.863           | 1.506                    | 0.212      |
| Smoking amounts, py            | 0.995, 1.024           | 1.009                    | 0.218      |                          |                          |            |
| Long-term oxygen therapy       | 0.261, 0.775           | 0.450                    | 0.004*     | 0.303, 1.107           | 0.580                    | 0.098      |
| Readmission ≤30 d              | 6.679, 27.005          | 13.430                   | < 0.001*   | 4.554, 13.632          | 7.879                    | < 0.001*   |
| **Functional & laboratory**    |                        |                          |            |                        |                          |            |
| Post-bronchodilator FEV1       | 0.977, 1.003           | 0.990                    | 0.120      |                          |                          |            |
| WBC, /μL                       | 1.000, 1.000           | 1.000                    | 0.085      |                          |                          |            |
| DNI, %                         | 1.064, 1.133           | 1.098                    | < 0.001*   | 1.043, 1.131           | 1.086                    | < 0.001*   |
| hs-CRP, mg/dL                  | 1.003, 1.048           | 1.025                    | 0.029*     | 0.978, 1.032           | 1.005                    | 0.736      |

*Indicates significance in univariate and multivariate analysis (P < 0.05).

AECOPD = acute exacerbations of chronic obstructive pulmonary disease, CI = confidence interval, DNI = delta neutrophil index, d = days, GOLD = Global Initiative for Chronic Obstructive Lung Disease, FEV1 = forced expiratory volume in 1 s, hs-CRP = high sensitive C-reactive protein, HR = hazard ratio, py = pack-years, WBC = white blood cell.
≤30 days and DNI ≥ 3.5% showed significantly lower cumulative survival rate compared to other groups. We considered why DNI levels are associated with mortality in AECOPD patients who were rehospitalized. Another study showed that DNI level at 72 h significantly correlated with mortality in patients with bacteremia [30], and increased DNI values at the time admission were significantly associated with severe sepsis/septic shock and overt disseminated intravascular coagulation (DIC) and the elevation of DNI value preceded the onset of organ/circulatory failure [25]. Our study showed that DNI levels were higher in AECOPD patients with CAP although we couldn’t confirm whether sepsis was associated with CAP. Patients with CAP are expected to have more patients with DIC, systemic inflammatory response syndrome or sepsis, which may have affected early readmission and mortality after discharge. However, there is no definitive study of the mechanism by which DNI affects mortality, and additional studies are needed.

We have some limitations in this study. First, the present study was performed in a single institution, selection bias may have influenced the significance of the present findings although the criteria of hospitalization were established, and thus a multicenter study is required to validate the results. Second, we did not accurately assess the patients with SIRS or sepsis in this study so could not clearly explain the reason for increased DNI in patients with CAP. In addition, there is no clear reason for why mortality is higher in the increased-DNI group in patients with early readmission and further research is needed. Third, DNI alone has weak predictive power against mortality in AUC curve and increases predictability when accompanied by early readmission in AECOPD patients. These results suggest that biologic markers such as DNI still have difficulties in predicting the mortality of AECOPD patients and should be considered with clinical factors such as early readmission.

However, this study is meaningful to confirm the higher mortality rate in the increased DNI group with early readmission among AECOPD patients who were readmitted.

Conclusions
Our study showed that AECOPD with CAP group who were readmitted ≤30 days and DNI ≥ 3.5% showed higher mortality during 6 months compared to the other groups. DNI level can be used as a predictor of prognosis in AECOPD patients who were readmitted after discharge, further investigation will be necessary.

Abbreviations
AECOPD: Acute exacerbations of chronic obstructive pulmonary disease; BMI: Body mass index; CAP: Community-acquired pneumonia; CAT: Chronic obstructive pulmonary disease assessment test; CI: Confidence interval; DNI: Delta neutrophil index; d: days; ROC: Receiver operating characteristic

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Authors’ contributions
SMP designed this investigation and wrote the manuscript. SHK and SJL contributed to study design. WCK was responsible for radiologic evaluation of community-acquired pneumonia. SJJ and BSS collected the data. JHK conducted statistical analysis and revision of the manuscript. MLK designed this investigation and reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate
Research was conducted in compliance with the requirements and under the authorization of the Yonsei University Wonju Severance Christian Hospital Institutional Review Board (IRB No. CR312009).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.
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