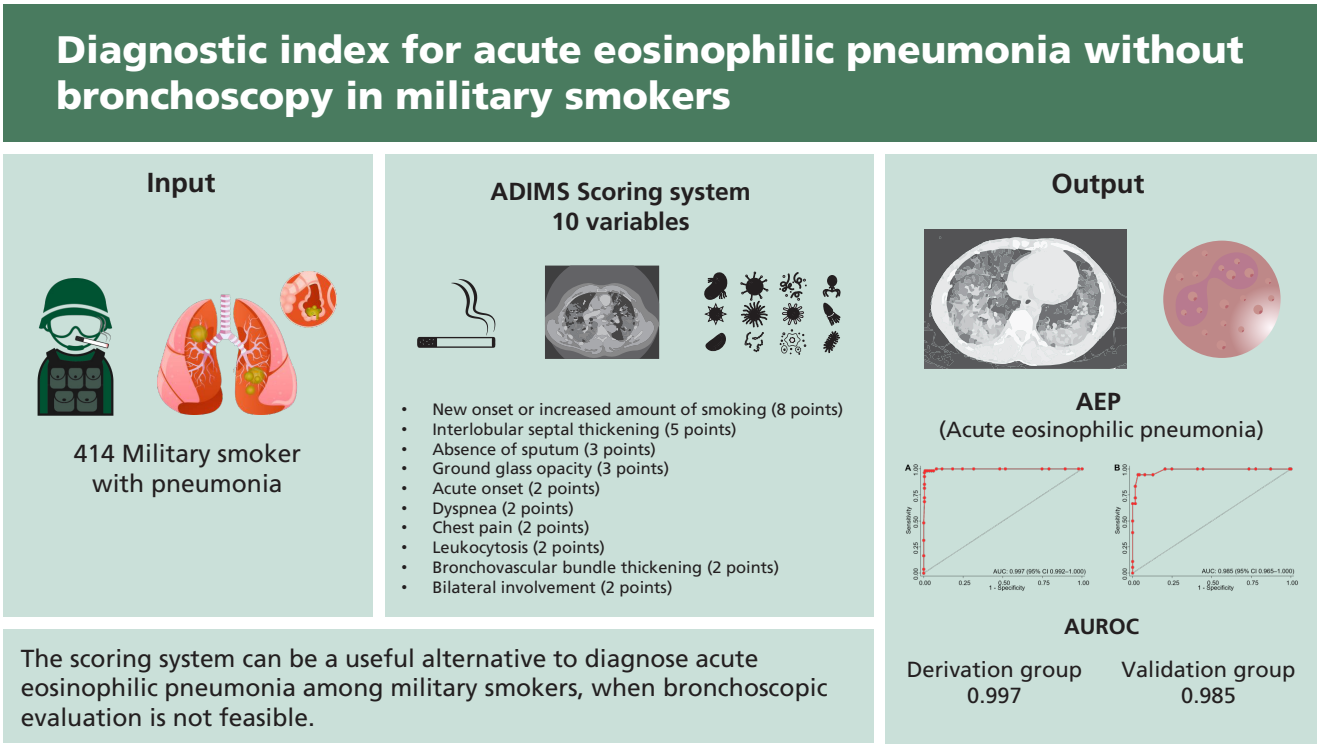
ORIGINAL ARTICLE

Korean J Intern Med 2022;37:377-386
https://doi.org/10.3904/kjim.2021.069

# Diagnostic index for acute eosinophilic pneumonia without bronchoscopy in military smokers

Sunmin Park*, Deokjae Han*, Ji Eun Lee, Duck Hyun Ryu, and Hyung-Jun Kim

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Armed Forces Capital Hospital, Seongnam, Korea




Received : February 4, 2021
Revised : March 3, 2021
Accepted: March 5, 2021

Correspondence to Hyung-Jun Kim, M.D.
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Armed Forces Capital Hospital, 81 Saemaeul-ro 177 beon-gil, Bundang-gu, Seongnam 13574, Korea
Tel: +82-31-725-6250, Fax: +82-31-706-0987, E-mail: hyung405@gmail.com
https://orcid.org/0000-0003-1984-8864

* These authors contributed equally to this work.



pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

**Background/Aims:** Acute eosinophilic pneumonia (AEP) is common among military smokers; however, bronchoscopy is required for the diagnosis. We aimed to derive and validate a scoring system to diagnose AEP without bronchoscopy.
**Methods:** We conducted a retrospective study including patients diagnosed with AEP or any other pneumonia among military smokers hospitalized in the Armed Forces Capital Hospital from 15 November 2016 through 25 December 2019. The patients were divided into derivation and validation groups according to their admission day. Patient symptoms, laboratory findings, and computed tomography findings were candidate variables. Least absolute shrinkage and selection operator (LASSO) regression was used to calculate the scores for each variable.
**Results:** Among 414 patients, AEP was confirmed in 54 of 279 patients (19.4%) in the derivation group and in 18 of 135 patients (13.3%) in the validation group. Ten variables were selected using LASSO regression: new-onset or a recently increased smoking (≤ 4 weeks) (8 points), interlobular septal thickening (5 points), absence of sputum (3 points), ground glass opacity (3 points), acute onset (≤ 3 days) (2 points), dyspnea (2 points), chest pain (2 points), leukocytosis (2 points), bronchovascular bundle thickening (2 points), and bilateral involvement (2 points). The area under the receiver-operating characteristic curve of the score to diagnose AEP was 0.997 (95% confidence interval, 0.992 to 1.000) in the derivation group and 0.985 (95% confidence interval, 0.965 to 1.000) in the validation group.
**Conclusions:** We introduce a scoring system that can distinguish AEP from other types of pneumonia in military smokers without the need for bronchoscopy.

**Keywords:** Pulmonary eosinophilia; Diagnosis; Validation study; Eosinophilic pneumonia; Smokers

## INTRODUCTION

Acute eosinophilic pneumonia (AEP) is a relatively rare respiratory disease, characterized by acute-onset dyspnea, fever, bilateral lung involvement, and lung eosinophilia [1]. The underlying pathophysiology of this disease is not fully known; it can be caused by various agents including smoking and medication [2]. AEP can progress rapidly and result in acute respiratory failure, which is life-threatening [3]. Fortunately, it responds well to systemic steroids [4,5].

Although certain computed tomography (CT) findings are recognised as key characteristics of AEP [6], it is difficult to fully distinguish AEP from other types of pneumonia in its early phase [4]. For an accurate diagnosis, bronchoscopic evaluation with bronchoalveolar lavage fluid is necessary to fulfil the diagnostic criteria [7]. Although systemic steroids may be considered for treatment in urgent settings without bronchoscopy, they must be used with caution in patients without an accurate diagnosis. In the recently published community-acquired pneumonia (CAP) guidelines [8], the use of systemic steroids is not recommended in patients with CAP.

Compared to the general setting, AEP was more commonly reported among military personnel [9-11]. Most of these patients were smokers [9,11,12]. However, early bronchoscopy may not be feasible in certain situations, such as in cases involving a shortage of medical equipment, unavailable medical staff, or acute deterioration of the patient [13]. Furthermore, bronchoscopy has become a high-risk procedure during the coronavirus disease pandemic as it provokes droplet formation [14]. Therefore, we aimed to derive and validate a scoring system that can distinguish AEP from other types of pneumonia without bronchoscopy in military smokers.

## METHODS

### Study subjects and definition of AEP

Patients hospitalized in the Armed Forces Capital Hospital from 15 November 2016 through 25 December 2019 were screened. The Armed Forces Capital Hospital is the highest-level referral center among 17 military hospitals in South Korea, and is the only center capable of performing bronchoscopy. Therefore, all patients suspected to have AEP are transferred to our center [10,12,15]. For this study, patients diagnosed with either AEP or pneumonia were selected. Because the aim of our study was to aid the diagnosis of AEP among military smokers, those who did not smoke at the time of admission were excluded. We also excluded patients


https://doi.org/10.3904/kjim.2021.069

without CT results, because chest CT findings are one of the key characteristics of AEP [6,16].

The diagnosis of AEP was confirmed according to the modified Philit criteria [7]: (1) acute respiratory illness (≤ 1 month); (2) pulmonary infiltrates on chest imaging; (3) pulmonary eosinophilia (> 25% eosinophils in the bronchoalveolar lavage fluid); and (4) absence of other specific pulmonary eosinophilic diseases. Some patients could not undergo bronchoscopy due to their urgent medical condition, unavailability of emergent bronchoscopy, or a temporary shortage of medical staff. Therefore, they were clinically suspected to have AEP and were treated accordingly. These patients were excluded because the fulfilment of the modified Philit criteria could not be assessed, nor could they be classified as having other pneumonias. Thus, we excluded patients whose diagnosis was inconclusive, who were transferred to other hospitals, and who died before the final diagnosis. The patients who were hospitalized from 15 November 2016 through 31 December 2018 were assigned to the derivation group, and those hospitalized after this period were assigned to the validation group.

## Data collection

Data were collected retrospectively from the patients' medical records; these included data on patient demographics, smoking history, comorbidities, and symptoms. Smoking history included conventional cigarettes only. We evaluated the duration (weeks), quantity (packs per day), and any change in habits of smoking. Patients who restarted smoking in the preceding 4 weeks after quitting for longer than 4 weeks were considered new-onset smokers, and patients who doubled their quantity of daily smoking within the preceding 4 weeks were considered to have increased their quantity of smoking. The comorbidities inspected were hypertension, diabetes mellitus, chronic lung disease (asthma, chronic obstructive pulmonary disease, bronchiectasis, or tuberculosis-destroyed lung), chronic liver disease, history of tuberculosis, history of AEP, and any type of allergy. Symptoms consisted of dyspnea, fever, chills, night sweats, cough, sputum, chest pain, rhinorrhea, myalgia, fatigue, palpitation, and sore throat, along with the onset of the chief complaint. Laboratory findings that could be commonly evaluated were extracted: white blood cell count, neutrophil count, lymphocyte count, eosinophil count, platelet count, and C-reactive protein levels.

The included chest CT findings were ground glass opacity, interlobular septal thickening, bronchovascular bundle thickening, pleural effusion, bilateral involvement, consolidation, and centrilobular nodules [6,17,18]. The CT findings were independently inspected by two blinded researchers (S.P. and D.H.) and any discrepancy was resolved by another researcher (H.J.K.).

Our study was conducted in accordance with the amended Declaration of Helsinki and was approved by the Institutional Review Board of the Armed Forces Capital Hospital (protocol number: AFCH-20-IRB-025). The requirement for

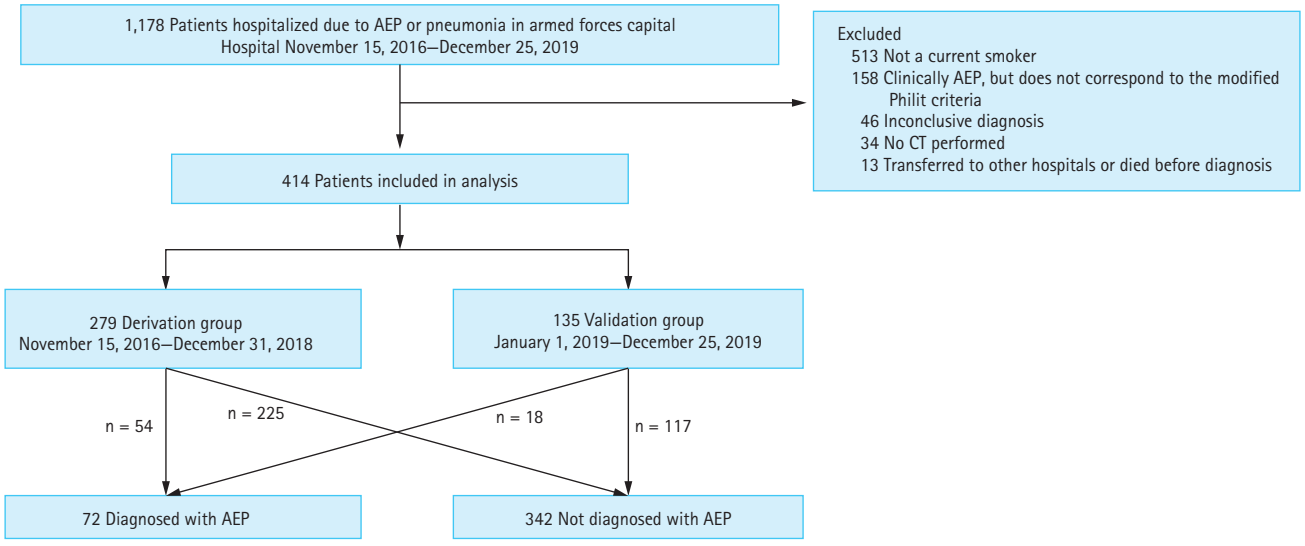



**Figure 1.** Flowchart of the patient selection process. AEP, acute eosinophilic pneumonia; CT, computed tomography.

informed consent was waived because of the retrospective design of the study, but the records were anonymized prior to the analyses. There were no relevant missing data found during the data collection process.

### Construction of the scoring system

The scoring system was constructed according to the recent recommendation for the development and reporting of prediction models in respiratory medicine [19]. The candidate variables included the majority of the inspected characteristics. Since this scoring system was designed for bedside use, continuous variables were transformed into generally acceptable forms. The white blood cell count was transformed to leukocytosis (≥ 10,000/μL) or not, platelet count to thrombocytopenia (≤ 150,000/μL) or not, eosinophil count to eosinophilia (≥ 500/μL) or not, and neutrophil and lymphocyte counts to the neutrophil-to-lymphocyte ratio. The smoking history was simplified to 'new-onset or a recent increase in the quantity of smoking (≤ 4 weeks)' [20,21]. The onset of the chief complaint was simplified as acute onset (≤ 3 days) or otherwise. Consequently, a total of 36 candidate variables were included to construct the scoring system (Supplementary Table 1).

For variable selection and score derivation, the least absolute shrinkage and selection operator (LASSO) regression was used [22]. With LASSO regression, a simplified list of variables was derived with 10-fold cross-validation, and the penalized coefficients were calculated. To simplify the coefficients for use in the scoring system, they were multiplied by 5 and rounded to the nearest integer.

### Validation of the score

Each patient's total score was calculated using the derived scoring system. The total score was used to evaluate its performance by calculating the area under the receiver-operating characteristics curve (AUC) to predict the diagnosis of AEP for the derivation and validation groups. To evaluate the goodness-of-fit of our model, a calibration plot was obtained and the Hosmer-Lemeshow test was performed for both groups.

Our study was performed in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement [23]. The TRIPOD checklist is available in Appendix 1.

## RESULTS

### Patient selection and characteristics

During the study period, 1,178 patients were screened. After excluding the non-eligible patients, 414 patients were included in our study and were divided into the derivation (n = 279) and validation groups (n = 135); 54 of 279 patients (19.4%) and 18 of 135 patients (13.3%) were diagnosed with AEP in the two groups, respectively (Fig. 1).

All the patients were male, with a median age of 20 years (interquartile range, 20 to 21). The median duration of smoking was 37.5 months (interquartile range, 12.0 to 62.5), which was shorter for those diagnosed with AEP than for those diagnosed with other types of pneumonia (median 0.8 months vs. 48.0 months, $p < 0.001$). Fifty-seven of 72 patients (79.2%) diagnosed with AEP were classified as new-onset smokers, as compared to 13 of 342 patients (3.8%) diagnosed with other types of pneumonia ($p < 0.001$). The distribution of comorbidities did not differ between patients diagnosed with AEP and those without. The patients diagnosed with AEP had a higher white blood cell count (median 14,015/μL vs. 7,260/μL, $p < 0.001$), neutrophil count (median 10,940/μL vs. 5,175/μL, $p < 0.001$), lymphocyte count (median 1,375/μL vs. 1,230/μL, $p = 0.042$), platelet count (median 241 × 103/μL vs. 189 × 103/μL, $p < 0.001$), and higher levels of C-reactive protein (median 7.9 mg/dL vs. 5.4 mg/dL, $p = 0.006$). Radiographic findings differed significantly according to the diagnosis of AEP. Among the patients with AEP, ground glass opacity (100.0% vs. 77.5%, $p < 0.001$), interlobular septal thickening (94.4% vs. 6.1%, $p < 0.001$), pleural effusion (36.1% vs. 7.6%, $p < 0.001$), bronchovascular bundle thickening (33.3% vs. 1.5%, $p < 0.001$), and bilateral involvement (98.6% vs. 37.1%, $p < 0.001$) were more commonly found than in patients diagnosed with other types of pneumonia. The prevalence of consolidation (40.3% vs. 87.1%, $p < 0.001$) was lower in patients with AEP. Results from microbiological evaluation were less likely to be positive in patients with AEP compared to those without AEP in both bacterial (56.9% vs. 75.0%, $p = 0.002$) and viral origin (19.3% vs. 73.4%, $p < 0.001$) from respiratory specimens (Table 1). Details of the microbiological evaluation are presented in Supplementary Table 2.

Patients in the derivation and validation groups revealed similar characteristics, although there were several differ-


https://doi.org/10.3904/kjim.2021.069

**Table 1. Comparison of patients according to the diagnosis of acute eosinophilic pneumonia**

| Variable | Total (n = 414) | AEP (n = 72) | Not AEP (n = 342) | *p* value |
|---|---|---|---|---|
| Male sex | 414 (100.0) | 72 (100.0) | 342 (100.0) | NA |
| Age, yr | 20 (20–21) | 20 (20–21) | 20 (20–21) | 0.139 |
| Body mass index, kg/m$^2$ | 23.4 (21.6–25.9) | 23.9 (21.7–25.8) | 23.3 (21.6–25.9) | 0.865 |
| Smoking history | | | | |
| New-onset smoking (≤ 4 weeks) | 70 (16.9) | 57 (79.2) | 13 (3.8) | < 0.001 |
| Increase in quantity of smoking (≤ 4 weeks) | 3 (0.7) | 3 (4.2) | 0 | 0.005 |
| Duration of smoking, months | 37.5 (12.0–62.5) | 0.8 (0.5–1.0) | 48.0 (24.0–72.0) | < 0.001 |
| Packs of cigarettes smoked per day | 0.5 (0.4–0.8) | 0.4 (0.3–0.5) | 0.5 (0.4–0.8) | < 0.001 |
| Comorbidities | | | | |
| Allergy | 33 (8.0) | 6 (8.3) | 27 (7.9) | 0.901 |
| Chronic lung disease[a] | 8 (1.9) | 0 | 8 (2.3) | 0.361 |
| History of tuberculosis | 3 (0.7) | 0 | 3 (0.9) | > 0.999 |
| Hypertension | 2 (0.5) | 0 | 2 (0.6) | > 0.999 |
| Symptoms | | | | |
| Onset, day | 3 (2–4) | 2 (1–3) | 3 (2–5) | < 0.001 |
| Fever | 376 (90.8) | 64 (88.9) | 312 (91.2) | 0.532 |
| Cough | 376 (90.8) | 69 (95.8) | 307 (89.8) | 0.120 |
| Sputum | 318 (76.8) | 40 (55.6) | 278 (81.3) | < 0.001 |
| Chills | 220 (53.1) | 35 (48.6) | 185 (54.1) | 0.397 |
| Sore throat | 171 (41.3) | 7 (9.7) | 164 (48.0) | < 0.001 |
| Rhinorrhea | 119 (28.7) | 7 (9.7) | 112 (32.8) | < 0.001 |
| Dyspnea | 95 (23.0) | 54 (75.0) | 41 (12.0) | < 0.001 |
| Chest pain | 93 (22.5) | 28 (38.9) | 65 (19.0) | < 0.001 |
| Myalgia | 60 (14.5) | 12 (16.7) | 48 (14.0) | 0.564 |
| Fatigue | 9 (2.2) | 2 (2.8) | 7 (2.1) | 0.659 |
| Night sweats | 6 (1.5) | 0 | 6 (1.8) | 0.596 |
| Palpitation | 2 (0.5) | 0 | 2 (0.6) | > 0.999 |
| Laboratory findings | | | | |
| White blood cell count, /μL | 7,915 (5,510–11,430) | 14,015 (11,480–16,875) | 7,260 (5,220–9,570) | < 0.001 |
| Neutrophil count, /μL | 5,695 (3,730–8,880) | 10,940 (8,810–14,335) | 5,175 (3,370–7,230) | < 0.001 |
| Lymphocyte count, /μL | 1,240 (920–1,610) | 1,375 (995–1,755) | 1,230 (890–1,590) | 0.042 |
| Eosinophil count, /μL | 40 (10–160) | 250 (155–425) | 20 (0–80) | < 0.001 |
| Platelet count, × 10$^3$/μL | 198 (158–244) | 241 (210–284) | 189 (151–231) | < 0.001 |
| C-reactive protein, mg/dL | 5.6 (3.2–9.6) | 7.9 (4.4–11.1) | 5.4 (3.1–9.0) | 0.006 |
| Chest CT findings | | | | |
| Ground glass opacity | 337 (81.4) | 72 (100.0) | 265 (77.5) | < 0.001 |
| Consolidation | 327 (79.0) | 29 (40.3) | 298 (87.1) | < 0.001 |
| Centrilobular nodules | 89 (21.5) | 14 (19.4) | 75 (21.9) | 0.641 |
| Interlobular septal thickening | 89 (21.5) | 68 (94.4) | 21 (6.1) | < 0.001 |

**Table 1. Continued**

| Variable | Total (n = 414) | AEP (n = 72) | Not AEP (n = 342) | *p* value |
|---|---|---|---|---|
| Pleural effusion | 52 (12.6) | 26 (36.1) | 26 (7.6) | < 0.001 |
| Bronchovascular bundle thickening | 29 (7.0) | 24 (33.3) | 5 (1.5) | < 0.001 |
| Bilateral involvement | 198 (47.8) | 71 (98.6) | 127 (37.1) | < 0.001 |
| Positive results from microbiological evaluation | | | | |
| Gram stain and culture of respiratory specimens | 226/314 (72.0) | 37/65 (56.9) | 189/249 (75.9) | 0.002 |
| Respiratory virus PCR | 251/384 (65.4) | 11/57 (19.3) | 240/327 (73.4) | < 0.001 |
| *Streptococcus pneumoniae urinary* antigen | 4/343 (1.2) | 0/51 (0.0) | 4/292 (1.4) | > 0.999 |

Values are presented as number (%) or median (interquartile range). *p* values were calculated according to the chi-square test, Fisher's exact test, or the Wilcoxon rank sum test.
AEP, acute eosinophilic pneumonia; NA, not applicable; CT, computed tomography; PCR, polymerase chain reaction.
[a]Chronic lung disease refers to asthma, chronic obstructive pulmonary disease, bronchiectasis, and tuberculosis-destroyed lung.

**Table 2. Calculated penalized coefficients of variables selected by least absolute shrinkage and selection operator**

| Variable | Penalized coefficient | Score |
|---|---|---|
| New-onset or a recent increase in quantity of smoking (≤ 4 weeks) | 1.512 | 8 |
| Interlobular septal thickening | 0.902 | 5 |
| Ground glass opacity | 0.550 | 3 |
| Sputum | –0.531 | –3 |
| Bronchovascular bundle thickening | 0.452 | 2 |
| Dyspnea | 0.410 | 2 |
| Chest pain | 0.400 | 2 |
| Leukocytosis (> 10,000/μL) | 0.383 | 2 |
| Bilateral involvement | 0.366 | 2 |
| Acute onset (≤ 3 days) | 0.330 | 2 |
| Fever | 0.089 | 0 |
| Fatigue | –0.087 | 0 |
| Pleural effusion | 0.024 | 0 |
| Neutrophil-to-lymphocyte ratio | 0.017 | 0 |

**Table 3. ADIMS to diagnose acute eosinophilic pneumonia without bronchoscopy**

| ADIMS scoring system |
|---|
| 8 Points |
| New-onset or a recent increase in the quantity of smoking (≤ 4 weeks) |
| 5 Points |
| Interlobular septal thickening |
| 3 Points |
| Absence of sputum |
| Ground glass opacity |
| 2 Points |
| Acute onset (≤ 3 days) |
| Dyspnea |
| Chest pain |
| Leukocytosis (> 10,000/μL) |
| Bronchovascular bundle thickening |
| Bilateral involvement |

ADIMS, Acute Eosinophilic Pneumonia Diagnostic Index in Military Smokers.

ences. Patients in the derivation group had a higher incidence of interlobular septal thickening (24.4% vs. 15.6%, $p = 0.041$) and bilateral involvement (51.3% vs. 40.7%, $p = 0.045$). Patient symptoms and laboratory findings did not differ between the two groups (Supplementary Table 3).

## Derivation of the score

After LASSO regression, 14 variables were selected from the 36 candidate variables. The selected variables were new-onset or a recent increase in the quantity of smoking (≤ 4 weeks), interlobular septal thickening, ground glass opacity, the presence of sputum, bronchovascular bundle thickening, dyspnea, chest pain, leukocytosis (≥ 10,000/μL), bilateral involvement, acute onset (≤ 3 days), fever, fatigue, pleural effusion, and a higher neutrophil-to-lymphocyte ratio. The penalized coefficients were calculated, multiplied


https://doi.org/10.3904/kjim.2021.069

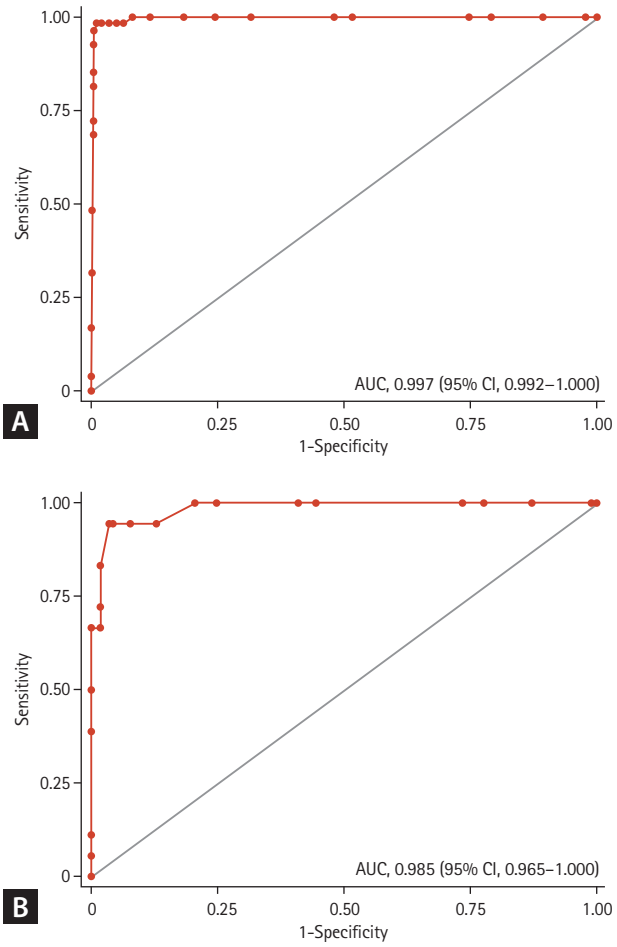



**Figure 2.** Receiver-operating characteristics curve of the acute eosinophilic pneumonia (AEP) Diagnostic Index for Military Smokers (ADIMS) (A) in the derivation group and the (B) validation group. AUC, area under the receiver-operating characteristics curve; CI, confidence interval.

by 5, and subsequently rounded off to the nearest integer. After this process, the coefficients of four variables (fever, fatigue, pleural effusion, and the neutrophil-to-lymphocyte ratio) became zero and were excluded from the final score (Table 2).

The scores were organized as follows: 8 points for new-onset or a recent increase in the quantity of smoking (≤ 4 weeks); 5 points for interlobular septal thickening; 3 points for both the absence of sputum and ground glass opacity; and 2 points each for acute onset (≤ 3 days), dyspnea, chest pain, leukocytosis (≥ 10,000/μL), bronchovascular bundle thickening, and bilateral involvement (Table 3). The score distribution ranged from 0 to 31 points. We named this scoring system 'AEP Diagnostic Index for Military Smokers,' which was abbreviated as ADIMS. The ADIMS score was calculated for each patient and showed a similar distribution among the derivation and validation groups (Supplementary Fig. 1).

### Validation of the score

The AUC of the ADIMS to distinguish AEP from other types of pneumonia was 0.997 (95% confidence interval [CI], 0.992 to 1.000) in the derivation group, and 0.985 (95% CI, 0.965 to 1.000) in the validation group, which refers to an excellent performance (Fig. 2). We evaluated the calibration plots and Hosmer-Lemeshow tests, which revealed that the ADIMS fit well (Supplementary Fig. 2).

### Sensitivities and specificities

Various cut-off values were used to calculate the sensitivities and specificities to correctly diagnose AEP. With cut-off values of ≥ 18, 96.30% of patients could be correctly classified. The cut-off of ≥ 18 points showed a sensitivity of 94.44% and a specificity of 96.58% (Supplementary Table 4).

## DISCUSSION

This is the first study to introduce a scoring system, the ADIMS, which can distinguish AEP from other types of pneumonia without bronchoscopy. The ADIMS showed excellent discrimination performance in both the derivation and validation groups. The cut-off of ≥ 18 points showed a high sensitivity and specificity in distinguishing AEP from other types of pneumonia in young male military smokers.

The presenting manifestations of the patients with AEP in our study were similar to those reported previously among other study populations [2,9,10,20,24]. Symptoms of dyspnea, cough, chest pain, fever, and fatigue, along with bilateral parenchymal infiltrates were commonly observed in studies from the United States [2,9]. A study from Japan reported that the symptoms of fever, dyspnea, and cough were common, while sputum was not [20]. Previous reports from our center at a different time period also confirmed similar characteristics, including cough, dyspnea, fever, diffuse ground glass opacity, interlobular septal thickening, pleural effusion, and leukocytosis [10,24].

The excellent discrimination performance of the ADIMS can be explained by the distinct features of AEP compared to those of other types of pneumonia. Primarily, AEP is well

known to be associated with a recent change in smoking habits [25,26]. New-onset smoking, along with restarting or increasing the amount of smoking, was commonly observed among patients with AEP [20]. In a previous study, patients who smoked a cigarette every hour for a duration of 4 hours suffered from cough and dyspnea within 12 hours of exposure, along with a decline in the partial pressure of oxygen and vital capacity [20]. On the other hand, the association between a recent change in smoking habits and CAP has not been established, despite the higher risk of CAP among smokers and ex-smokers [27].

The recognizable radiographic features of AEP also play an important role in enhancing the performance of the ADIMS. As previously reported [17], among 29 patients with AEP, ground glass opacities and interlobular septal thickening were present in more than 90%, with more than 70% presenting with bilateral involvement. Such diffuse bilateral lung involvement along with pleural effusion was also emphasized in an earlier study [18]. This differs from other commonly encountered pneumonia types such as CAP. Focal airspace consolidation is the most common radiographic abnormality found in CAP [28], especially in cases of bacterial origin [29].

Dyspnea, chest pain, and the absence of sputum were selected as key symptoms in the ADIMS. Since our study population included young military patients (median age 20) with minimum underlying comorbidities, the risk of deterioration due to CAP was very low [28]. Therefore, dyspnea, which implies extensive involvement of the lungs, was relatively rare in patients with other types of pneumonia compared to that in patients with AEP. This was also true for chest pain, which implies chest tightness or discomfort resulting from acute respiratory difficulty. The presence of pleural effusion may induce pleuritic chest pain, which is common in AEP but only observed in approximately 20% of hospitalized patients with CAP [30]. This is in accordance with the incidence of chest pain related to other types of pneumonia found in our study (19.0%). The absence of sputum was another important aspect. Although sputum can be present in any type of respiratory disease, the purulence and color may imply an infectious origin [31,32].

Leukocytosis was the only laboratory parameter selected in the ADIMS. Peripheral neutrophilic leukocytosis in the early course of disease is a well-known characteristic of AEP [5,7,33-35]. The exact cause for this phenomenon is not fully understood; however, the increased production of interleukin-8 by bronchial epithelial cells following cigarette exposure may be associated with such peripheral neutrophilic leukocytosis [35].

We would like to make some recommendations in order to utilize the ADIMS wisely. First, the ADIMS should be considered in young military smokers with suspected lower respiratory tract disease. Second, it should be an alternative diagnostic method when bronchoscopic evaluation is not possible. When bronchoscopy is feasible, the modified Philit criteria should be the gold standard for diagnosing AEP. Third, an ADIMS score of ≥ 18 seems to be an appropriate cut-off value considering the high sensitivity (94.44%) and specificity (96.58%) at that point. When the cut-off is achieved, the administration of systemic steroids should be considered in these patients.

Several limitations should be recognised. First, a detailed history regarding heat-not-burn and electronic cigarettes was not included in our study. Although both smoking products can be possible causes for AEP [36], they were excluded because it was not possible to assess the relative importance of each agent. In addition, the standardized quantification of electronic cigarettes is impossible, considering the diverse ingredients in the devices [37]. Second, our study was confined to young male military smokers and could not evaluate exposure to certain drugs or toxins. This was inevitable due to the single center retrospective design in a military hospital. Although AEP is common in young military smokers, future studies are required to validate the ADIMS in other populations.

In conclusion, we developed and validated the ADIMS, a simple scoring system that can efficiently distinguish AEP from other types of pneumonia without bronchoscopy in military smokers. The model was well-fit and revealed excellent performance. The ADIMS can be used as a reasonable alternative to diagnose AEP when bronchoscopic evaluation is not feasible.

## KEY MESSAGE

1. Among 414 patients with suspected acute eosinophilic pneumonia or other types of pneumonia, acute eosinophilic pneumonia was confirmed in 62 (15.0%) patients.
2. Recent change in smoking habits, chest computed tomographic findings, patient symptoms, and some laboratory findings could distinguish acute


https://doi.org/10.3904/kjim.2021.069

eosinophilic pneumonia from other types of pneumonia in military smokers.
3. The scoring system can be a useful alternative to diagnose acute eosinophilic pneumonia among military smokers, when bronchoscopic evaluation is not feasible.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

## Acknowledgments

This work was supported by the Korean Military Medical Research Project funded by the ROK Ministry of National Defense (ROK-MND-2020-KMMRP-024). The sponsor had no role in the study.

## REFERENCES

1. De Giacomi F, Vassallo R, Yi ES, Ryu JH. Acute eosinophilic pneumonia. causes, diagnosis, and management. Am J Respir Crit Care Med 2018;197:728-736.
2. De Giacomi F, Decker PA, Vassallo R, Ryu JH. Acute eosinophilic pneumonia: correlation of clinical characteristics with underlying cause. Chest 2017;152:379-385.
3. Akkanti B, Gentry B, Kesavan R, Kar B. Acute eosinophilic pneumonia. BMJ Case Rep 2016;2016:bcr2015212899.
4. Allen JN, Pacht ER, Gadek JE, Davis WB. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. N Engl J Med 1989;321:569-574.
5. Rhee CK, Min KH, Yim NY, et al. Clinical characteristics and corticosteroid treatment of acute eosinophilic pneumonia. Eur Respir J 2013;41:402-409.
6. Jeong YJ, Kim KI, Seo IJ, et al. Eosinophilic lung diseases: a clinical, radiologic, and pathologic overview. Radiographics 2007;27:617-639.
7. Philit F, Etienne-Mastroianni B, Parrot A, Guerin C, Robert D, Cordier JF. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. Am J Respir Crit Care Med 2002;166:1235-1239.
8. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019;200:e45-e67.
9. Shorr AF, Scoville SL, Cersovsky SB, et al. Acute eosinophilic pneumonia among US military personnel deployed in or near Iraq. JAMA 2004;292:2997-3005.
10. Yoon CG, Kim SJ, Kim K, Lee JE, Jhun BW. Clinical characteristics and factors influencing the occurrence of acute eosinophilic pneumonia in Korean military personnel. J Korean Med Sci 2016;31:247-253.
11. Sine CR, Hiles PD, Scoville SL, et al. Acute eosinophilic pneumonia in the deployed military setting. Respir Med 2018;137:123-128.
12. Choi JY, Lim JU, Jeong HJ, Lee JE, Rhee CK. Association between peripheral blood/bronchoalveolar lavage eosinophilia and significant oxygen requirements in patients with acute eosinophilic pneumonia. BMC Pulm Med 2020;20:22.
13. Johnston AM, Batchelor NK, Wilson D. Evaluation of a disposable sheath bronchoscope system for use in the deployed field hospital. J R Army Med Corps 2014;160:217-219.
14. Wahidi MM, Shojaee S, Lamb CR, et al. The use of bronchoscopy during the coronavirus disease 2019 pandemic: CHEST/AABIP guideline and expert panel report. Chest 2020;158:1268-1281.
15. Jhun BW, Kim SJ, Son RC, et al. Clinical outcomes in patients with acute eosinophilic pneumonia not treated with corticosteroids. Lung 2015;193:361-367.
16. Cheon JE, Lee KS, Jung GS, Chung MH, Cho YD. Acute eosinophilic pneumonia: radiographic and CT findings in six patients. AJR Am J Roentgenol 1996;167:1195-1199.
17. Daimon T, Johkoh T, Sumikawa H, et al. Acute eosinophilic pneumonia: thin-section CT findings in 29 patients. Eur J Radiol 2008;65:462-467.
18. King MA, Pope-Harman AL, Allen JN, Christoforidis GA, Christoforidis AJ. Acute eosinophilic pneumonia: radiologic and clinical features. Radiology 1997;203:715-719.
19. Leisman DE, Harhay MO, Lederer DJ, et al. Development and reporting of prediction models: guidance for authors from editors of respiratory, sleep, and critical care journals. Crit Care Med 2020;48:623-633.
20. Uchiyama H, Suda T, Nakamura Y, et al. Alterations in smoking habits are associated with acute eosinophilic pneumonia. Chest 2008;133:1174-1180.
21. Takeuchi A, Nelson C, Yamamoto I, Yamashiro S, Myers J. Acute eosinophilic pneumonia after resumption of cigarette smoking. Mil Med 2016;181:e613-e615.
22. Tibshirani R. Regression shrinkage and selection via the lasso.

J R Stat Soc Series B Methodol 1996;58:267-288.
23. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015;350:g7594.
24. Jhun BW, Kim SJ, Kim K, Lee JE. Outcomes of rapid corticosteroid tapering in acute eosinophilic pneumonia patients with initial eosinophilia. Respirology 2015;20:1241-1247.
25. Watanabe K, Fujimura M, Kasahara K, et al. Acute eosinophilic pneumonia following cigarette smoking: a case report including cigarette-smoking challenge test. Intern Med 2002;41:1016-1020.
26. Thakur LK, Jha KK. Acute eosinophilic pneumonia following recent cigarette smoking. Respir Med Case Rep 2016;19:103-105.
27. Baskaran V, Murray RL, Hunter A, Lim WS, McKeever TM. Effect of tobacco smoking on the risk of developing community acquired pneumonia: a systematic review and meta-analysis. PLoS One 2019;14:e0220204.
28. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243-250.
29. Vilar J, Domingo ML, Soto C, Cogollos J. Radiology of bacterial pneumonia. Eur J Radiol 2004;51:102-113.
30. Falguera M, Carratala J, Bielsa S, et al. Predictive factors, microbiology and outcome of patients with parapneumonic effusion. Eur Respir J 2011;38:1173-1179.
31. Miravitlles M, Kruesmann F, Haverstock D, Perroncel R, Choudhri SH, Arvis P. Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis. Eur Respir J 2012;39:1354-1360.
32. Chen K, Pleasants KA, Pleasants RA, et al. A systematic review and meta-analysis of sputum purulence to predict bacterial infection in COPD exacerbations. COPD 2020;17:311-317.
33. Pope-Harman AL, Davis WB, Allen ED, Christoforidis AJ, Allen JN. Acute eosinophilic pneumonia: a summary of 15 cases and review of the literature. Medicine (Baltimore) 1996;75:334-342.
34. Hayakawa H, Sato A, Toyoshima M, Imokawa S, Taniguchi M. A clinical study of idiopathic eosinophilic pneumonia. Chest 1994;105:1462-1466.
35. Miki K, Miki M, Nakamura Y, et al. Early-phase neutrophilia in cigarette smoke-induced acute eosinophilic pneumonia. Intern Med 2003;42:839-845.
36. Chaaban T. Acute eosinophilic pneumonia associated with non-cigarette smoking products: a systematic review. Adv Respir Med 2020;88:142-146.
37. Dinakar C, O'Connor GT. The health effects of electronic cigarettes. N Engl J Med 2016;375:1372-1381.


https://doi.org/10.3904/kjim.2021.069

**Supplementary Table 1. Included variables for the least absolute shrinkage and selection operator analysis**

| Demographic | Symptoms | Comorbidities | Laboratory findings | CT findings |
|---|---|---|---|---|
| Age | Acute onset (≤ 3 days) | Hypertension | Leukocytosis (> 10,000/μL) | Ground glass opacity |
| Body mass index, kg/m$^2$ | Dyspnea | History of tuberculosis | Thrombocytopenia (< 150,000/μL) | Consolidation |
| New-onset or a recent increase in the quantity of smoking (≤ 4 weeks) | Fever | Chronic lung disease | Eosinophilia (> 500/μL) | Interlobular septal thickening |
| Smoking amount, packs/day | Chills | Any type of allergy | Neutrophil-to-lymphocyte ratio | Bronchovascular bundle thickening |
| | Night sweats | Chronic liver disease | C-reactive protein (mg/dL) | Centrilobular nodules |
| | Cough | History of AEP | | Pleural effusion |
| | Sputum | Allergy | | Bilateral involvement |
| | Rhinorrhoea | | | |
| | Chest pain | | | |
| | Myalgia | | | |
| | Fatigue | | | |
| | Palpitation | | | |
| | Sore throat | | | |

CT, computed tomography; AEP, acute eosinophilic pneumonia.

**Supplementary Table 2. Microbiological results from respiratory specimens of patients according to the diagnosis of acute eosinophilic pneumonia**

| Variable | Total | AEP | Not AEP | *p* value |
|---|---|---|---|---|
| Gram stain and culture | | | | |
| Any bacteria | 226/314 (72.0) | 37/65 (56.9) | 189/249 (75.9) | 0.002 |
| α-Hemolytic Streptococcus | 181/314 (57.6) | 32/65 (49.2) | 149/249 (59.8) | 0.123 |
| Gram negative rod | 9/314 (2.9) | 1/65 (1.5) | 8/249 (3.2) | 0.691 |
| MSSA | 8/314 (2.6) | 1/65 (1.5) | 7/249 (2.8) | > 0.999 |
| *Haemophilus influenzae* | 7/314 (2.2) | 1/65 (1.5) | 6/249 (2.4) | > 0.999 |
| *Klebsiella pneumoniae* | 2/314 (0.6) | 0/65 (0.0) | 2/249 (0.8) | > 0.999 |
| *Pseudomonas aeruginosa* | 2/314 (0.6) | 0/65 (0.0) | 2/249 (0.8) | > 0.999 |
| Gram negative diplococci | 2/314 (0.6) | 0/65 (0.0) | 2/249 (0.8) | > 0.999 |
| *Branhamella catarrhalis* | 1/314 (0.3) | 0/65 (0.0) | 1/249 (0.4) | > 0.999 |
| *Streptococcus pneumoniae* | 1/314 (0.3) | 0/65 (0.0) | 1/249 (0.4) | > 0.999 |
| MRSA | 1/314 (0.3) | 0/65 (0.0) | 1/249 (0.4) | > 0.999 |
| Other unusual bacteria[a] | 15/314 (4.8) | 2/65 (3.1) | 13/249 (5.2) | 0.744 |
| Respiratory virus polymerase chain reaction | | | | |
| Any virus | 251/384 (65.4) | 11/57 (19.3) | 240/327 (73.4) | < 0.001 |
| Adenovirus | 208/384 (54.2) | 5/57 (8.8) | 203/327 (62.1) | < 0.001 |
| Rhinovirus | 33/384 (8.6) | 4/57 (7.0) | 29/327 (8.9) | 0.801 |
| Coronavirus | 7/384 (1.8) | 0/57 (0.0) | 7/327 (2.1) | 0.600 |
| Influenza virus A | 6/384 (1.6) | 0/57 (0.0) | 6/327 (1.8) | 0.598 |
| Influenza virus B | 6/384 (1.6) | 1/57 (1.8) | 5/327 (1.5) | > 0.999 |
| Respiratory syncytial virus | 6/384 (1.6) | 1/57 (1.8) | 5/327 (1.5) | > 0.999 |
| Metapneumovirus | 5/384 (1.3) | 0/57 (0.0) | 5/327 (1.5) | > 0.999 |
| Parainfluenza virus | 3/384 (0.8) | 0/57 (0.0) | 3/327 (0.9) | > 0.999 |

Values are presented as number (%).
AEP, acute eosinophilic pneumonia; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a]Includes *Eikenella corrodens*, *Klebsiella aerogenes*, *Enterobacter cloacae*, *Rothia muilaginosa*, *Staphylococcus haemolyticus*, Gram positive rod, and *Neisseria* species.


https://doi.org/10.3904/kjim.2021.069

**Supplementary Table 3. Comparison of patient characteristics between the derivation and validation groups**

| Variable | Derivation group (n = 279) | Validation group (n = 135) | *p* value |
|---|---|---|---|
| Male sex | 279 (100.0) | 135 (100.0) | NA |
| Age, yr | 20 (20–21) | 20 (19–21) | < 0.001 |
| Body mass index, kg/m$^2$ | 23.5 (21.8–25.7) | 23.3 (21.4–26.2) | 0.797 |
| Duration of smoking, mo | 37.5 (12.0–62.5) | 36.0 (6.0–62.5) | 0.373 |
| Packs of cigarettes smoked, /day | 0.5 (0.4–0.8) | 0.5 (0.3–0.6) | 0.258 |
| Comorbidities | | | |
| Allergy | 17 (6.1) | 16 (11.9) | 0.043 |
| Chronic lung disease | 3 (1.1) | 5 (30.7) | 0.120 |
| History of tuberculosis | 2 (0.7) | 1 (0.7) | > 0.999 |
| Hypertension | 2 (0.7) | 0 | > 0.999 |
| Symptom | | | |
| Onset | 3 (2–4) | 3 (2–4) | 0.289 |
| Fever | 257 (92.1) | 119 (88.2) | 0.190 |
| Cough | 254 (91.0) | 122 (90.4) | 0.825 |
| Sputum | 209 (74.9) | 109 (80.7) | 0.188 |
| Chills | 149 (53.4) | 71 (52.6) | 0.877 |
| Sore throat | 118 (42.3) | 53 (39.3) | 0.557 |
| Rhinorrhoea | 77 (27.6) | 42 (31.1) | 0.459 |
| Dyspnea | 68 (24.4) | 27 (20.0) | 0.321 |
| Chest pain | 66 (24.7) | 27 (20.0) | 0.403 |
| Myalgia | 39 (14.0) | 21 (15.6) | 0.669 |
| Fatigue | 8 (2.9) | 1 (0.7) | 0.282 |
| Night sweats | 3 (1.1) | 3 (2.2) | 0.397 |
| Palpitation | 1 (0.4) | 1 (0.7) | 0.546 |
| Laboratory findings | | | |
| White blood cell count, /μL | 7,870 (5,450–11,510) | 8,160 (5,770–11,340) | 0.611 |
| Neutrophil count, /μL | 5,570 (3,650–9,090) | 6,000 (3,840–8,520) | 0.700 |
| Lymphocyte count, /μL | 1,270 (920–1,630) | 1,230 (890–1,540) | 0.266 |
| Eosinophil count, /μL | 30 (10–150) | 50 (10–170) | 0.763 |
| Platelet count, × 10$^3$/μL | 196 (157–244) | 202 (165–244) | 0.313 |
| C-reactive protein, mg/dL | 5.9 (3.4–10.1) | 50.2 (20.9–90.6) | 0.398 |
| Chest CT findings | | | |
| Ground glass opacity | 232 (83.2) | 105 (77.8) | 0.188 |
| Consolidation | 221 (79.2) | 106 (78.5) | 0.871 |
| Centrilobular nodules | 64 (22.9) | 25 (18.5) | 0.305 |
| Interlobular septal thickening | 68 (24.4) | 21 (15.6) | 0.041 |
| Pleural effusion | 36 (12.9) | 16 (11.9) | 0.762 |
| Bronchovascular bundle thickening | 21 (7.5) | 8 (5.9) | 0.550 |
| Bilateral involvement | 143 (51.3) | 55 (40.7) | 0.045 |

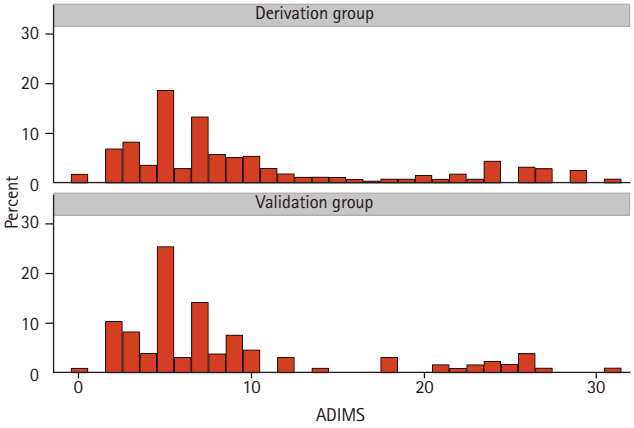
Values are presented as number (%) or median (interquartile range). *p* values were calculated according to the chi-square test, Fisher's exact test, or Wilcoxon rank sum test.
NA, not applicable; CT, computed tomography.

**Supplementary Table 4. Sensitivities and specificities according to various cut-off values of ADIMS in the validation group**

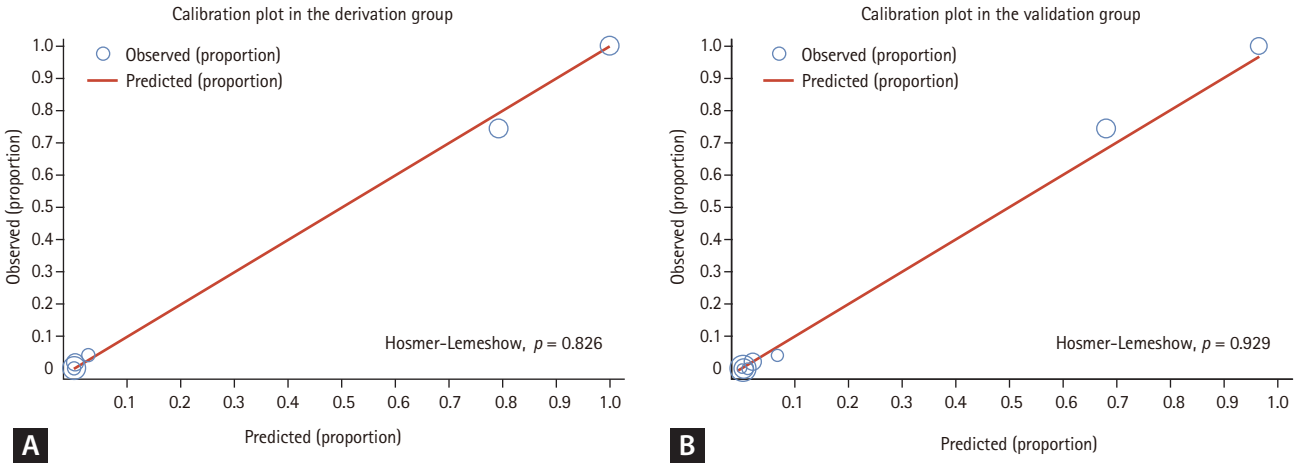
| Cut-off | Sensitivity, % | Specificity, % | Correctly classified, % |
|---|---|---|---|
| ≥ 7 | 100.00 | 58.97 | 64.44 |
| ≥ 8 | 100.00 | 75.21 | 78.52 |
| ≥ 9 | 100.00 | 79.49 | 82.22 |
| ≥ 10 | 94.44 | 87.18 | 88.15 |
| ≥ 12 | 94.44 | 92.31 | 92.59 |
| ≥ 14 | 94.44 | 95.73 | 95.56 |
| ≥ 18 | 94.44 | 96.58 | 96.30 |
| ≥ 21 | 83.33 | 98.29 | 96.30 |
| ≥ 22 | 72.22 | 98.29 | 94.81 |
| ≥ 23 | 66.67 | 98.29 | 94.07 |
| ≥ 24 | 66.67 | 100.00 | 95.56 |
| ≥ 25 | 50.00 | 100.00 | 93.33 |

ADIMS, Acute Eosinophilic Pneumonia Diagnostic Index in Military Smokers.


https://doi.org/10.3904/kjim.2021.069




**Supplementary Figure 1.** Distribution of Acute Eosinophilic Pneumonia Diagnostic Index in Military Smokers (ADIMS) in the derivation and validation groups. The distribution of ADIMS is largely similar in the derivation and validation groups.




**Supplementary Figure 2.** Calibration plots of Acute Eosinophilic Pneumonia Diagnostic Index in Military Smokers (ADIMS) according to the (A) derivation and (B) validation groups. The calibration plots show that the model fitted well in both the derivation and validation groups.


https://doi.org/10.3904/kjim.2021.069

**Appendix 1. TRIPOD checklist: prediction model development and validation**

| Section/Topic | Item | | Checklist item | Page |
|---|---|---|---|---|
| Title and abstract | | | | |
| Title | 1 | D;V | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted. | 1 |
| Abstract | 2 | D;V | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. | 2 |
| Introduction | | | | |
| Background and objectives | 3a | D;V | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | 4 |
| | 3b | D;V | Specify the objectives, including whether the study describes the development or validation of the model or both. | 4 |
| Methods | | | | |
| Source of data | 4a | D;V | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. | 5 |
| | 4b | D;V | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. | 5 |
| Participants | 5a | D;V | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. | 5 |
| | 5b | D;V | Describe eligibility criteria for participants. | 5 |
| | 5c | D;V | Give details of treatments received, if relevant. | NA |
| Outcome | 6a | D;V | Clearly define the outcome that is predicted by the prediction model, including how and when assessed. | 5 |
| | 6b | D;V | Report any actions to blind assessment of the outcome to be predicted. | 6 |
| Predictors | 7a | D;V | Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured. | 6-7 |
| | 7b | D;V | Report any actions to blind assessment of predictors for the outcome and other predictors. | 6 |
| Sample size | 8 | D;V | Explain how the study size was arrived at. | NA |
| Missing data | 9 | D;V | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. | 6 |
| Statistical analysis methods | 10a | D | Describe how predictors were handled in the analyses. | 7 |
| | 10b | D | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. | 7-8 |
| | 10c | V | For validation, describe how the predictions were calculated. | 7-8 |
| | 10d | D;V | Specify all measures used to assess model performance and, if relevant, to compare multiple models. | 7-8 |
| | 10e | V | Describe any model updating (e.g., recalibration) arising from the validation, if done. | NA |
| Risk groups | 11 | D;V | Provide details on how risk groups were created, if done. | NA |
| Development vs. validation | 12 | V | For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors. | 5 |
| Results | | | | |
| Participants | 13a | D;V | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | 8 |
| | 13b | D;V | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. | 8-9 |
| | 13c | V | For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome). | 9 |

**Appendix 1. Continued**

| Section/Topic | Item | | Checklist item | Page |
|---|---|---|---|---|
| Model development | 14a | D | Specify the number of participants and outcome events in each analysis. | 8 |
| | 14b | D | If done, report the unadjusted association between each candidate predictor and outcome. | NA |
| Model specification | 15a | D | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). | 9-10 |
| | 15b | D | Explain how to use the prediction model. | 10 |
| Model performance | 16 | D;V | Report performance measures (with CIs) for the prediction model. | 10 |
| Model-updating | 17 | V | If done, report the results from any model updating (i.e., model specification, model performance). | NA |
| Discussion | | | | |
| Limitations | 18 | D;V | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data). | 13 |
| Interpretation | 19a | V | For validation, discuss the results with reference to performance in the development data, and any other validation data. | 11-13 |
| | 19b | D;V | Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence. | 11-13 |
| Implications | 20 | D;V | Discuss the potential clinical use of the model and implications for future research. | 13 |
| Others | | | | |
| Supplementary information | 21 | D;V | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. | NA |
| Funding | 22 | D;V | Give the source of funding and the role of the funders for the present study. | 14 |

Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.
NA, not applicable; CI, confidence interval.


https://doi.org/10.3904/kjim.2021.069