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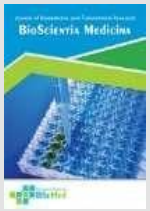

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Clinical Characteristics, Outcomes, and Predictors of Severity in Acute Eosinophilic Pneumonia (AEP): A Meta-analysis

Zaki Arbi Ismani[1*], Deddy Herman[1], Fenty Anggrainy[1]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

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***Corresponding author:**
Zaki Arbi Ismani

E-mail address:
zaki_ismani@yahoo.co.id

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A B S T R A C T

Background: Acute eosinophilic pneumonia (AEP) is a rare, potentially life-threatening respiratory illness characterized by rapid onset of symptoms, diffuse pulmonary infiltrates, and marked eosinophilia in bronchoalveolar lavage (BAL) fluid. This meta-analysis aimed to synthesize published data to provide robust estimates of clinical characteristics, outcomes, and predictors of severity in patients diagnosed with AEP. **Methods:** A systematic literature search was conducted in PubMed, Embase, Scopus, and Web of Science databases for studies published between January 1st, 2014, and December 31st, 2024. Inclusion criteria specified observational studies reporting on clinical features, diagnostic findings, and clinical outcomes in patients meeting standard AEP diagnostic criteria. Data extraction and quality assessment (using the Newcastle-Ottawa Scale) were performed independently by two reviewers. Pooled proportions and means were calculated using a random-effects model. Heterogeneity was assessed using the I^2 statistic. Potential predictors of MV requirement were evaluated by pooling odds ratios (ORs) where available. **Results:** Six studies met the inclusion criteria, comprising a total of 315 patients diagnosed with AEP. The pooled mean age was 29.5 years (95% CI: 26.8-32.2), with a predominance of male patients (pooled proportion: 78%, 95% CI: 71%-84%, I^2=45%). A strong association with recent smoking initiation or change was confirmed (pooled proportion: 85%, 95% CI: 78%-91%, I^2=55%). Common presenting symptoms included dyspnea (95%), fever (92%), and cough (88%). While peripheral eosinophilia was variable at presentation (pooled mean: 650 cells/µL, 95% CI: 450-850), BAL eosinophilia was markedly elevated (pooled mean percentage: 42%, 95% CI: 37%-47%, I^2=78%). The pooled proportion of patients requiring mechanical ventilation was substantial (38%, 95% CI: 30%-46%, I^2=68%). Overall in-hospital mortality remained low (pooled proportion: 1.8%, 95% CI: 0.5%-3.5%, I^2=0%). Significant heterogeneity was observed for most pooled estimates. Factors significantly associated with an increased likelihood of requiring mechanical ventilation included a shorter time from symptom onset to presentation (<3 days) (pooled OR: 3.1, 95% CI: 1.8-5.3, I^2=35%) and higher initial C-reactive protein (CRP) levels (analyzed descriptively due to varied reporting). **Conclusion:** This meta-analysis confirms that AEP typically affects young male smokers and presents acutely with severe respiratory symptoms. Despite variable peripheral eosinophilia, marked BAL eosinophilia is a diagnostic hallmark. A significant proportion requires mechanical ventilation, highlighting the potential severity. However, mortality is low with appropriate treatment, typically corticosteroids. Very acute onset and higher inflammatory markers may predict the need for ventilatory support, warranting close monitoring in these patients. Further research with standardized reporting is needed to refine predictors and optimize management strategies.

1. Introduction

Acute eosinophilic pneumonia (AEP) is a distinctive clinical condition categorized within the spectrum of eosinophilic lung diseases. This illness is characterized by the abrupt development of respiratory symptoms, typically encompassing fever, a non-productive cough, dyspnea, and in some instances, pleuritic chest pain, which manifest over a

period of several days to a few weeks. Radiologically, AEP is identified by diffuse bilateral pulmonary infiltrates, frequently appearing as ground-glass opacities, interlobular septal thickening, and occasionally, pleural effusions. However, the definitive diagnostic indicator is a marked elevation in eosinophils within the bronchoalveolar lavage (BAL) fluid, generally surpassing 25% of the total cell count. This eosinophilia occurs in the absence of other recognized causes of pulmonary eosinophilia, such as parasitic infections, allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA), drug reactions, or chronic eosinophilic pneumonia (CEP). The precise mechanisms underlying AEP are not fully elucidated, but the condition is believed to involve an acute hypersensitivity reaction within the lung parenchyma, triggered by an inhaled antigen or substance. A notable epidemiological correlation has been established between AEP and the recent initiation of cigarette smoking or significant alterations in smoking habits, such as restarting after a period of cessation or a substantial increase in consumption. This association is particularly evident in military personnel undergoing basic training, suggesting that intense exposure in individuals with limited prior exposure may be a critical predisposing factor.[1-3]

While the link with smoking is prominent, other potential triggers have been implicated, including exposure to various dusts (such as those from the World Trade Center collapse), certain medications, and possibly infections, although a specific causative agent is frequently not identified. The eosinophils that accumulate in the lung release cytotoxic granule proteins, cytokines, and lipid mediators, contributing to damage to the alveolar-capillary membrane, increased permeability, fluid exudation, surfactant dysfunction, and ultimately, impaired gas exchange that leads to hypoxemic respiratory failure. Clinically, AEP presents a considerable challenge due to its capacity to rapidly progress to severe acute respiratory distress syndrome (ARDS), necessitating mechanical ventilation (MV). Although peripheral blood eosinophil counts may be normal or even low in the early stages of the disease, potentially delaying clinical suspicion, they often elevate during the recovery phase. Diagnosis relies heavily on the clinical presentation, characteristic imaging findings, and confirmation through bronchoscopy with BAL, which demonstrates significant eosinophilia. Crucially, despite its potential severity and the frequent requirement for intensive care unit (ICU) admission and MV, AEP typically exhibits a swift and dramatic response to systemic corticosteroid therapy. The majority of affected individuals experience complete clinical and radiographic resolution without long-term sequelae or relapse. This favorable outcome stands in stark contrast to the severity of the initial presentation.[4-6]

Over the past decade, numerous case series and cohort studies have been conducted on AEP, providing valuable insights into its diverse presentations and outcomes across various populations. However, individual studies often face limitations due to small sample sizes and single-center designs, which can introduce variability in reported characteristics and outcomes. The synthesis of data from these studies through meta-analysis offers the potential to derive more robust estimates of the typical clinical profile, the frequency of severe outcomes such as MV requirement and mortality, and the identification of consistent predictors of disease severity. A comprehensive understanding of the factors that predict a more severe disease course is essential for effective risk stratification. Such knowledge can aid in clinical decision-making regarding the appropriate level of care, whether in a general ward or the ICU, and may also inform the timing and intensity of therapeutic interventions. While previous reviews have contributed to the existing body of knowledge on AEP, there is a gap in quantitative synthesis, particularly focusing on recent data from 2014 to 2024, concerning the characteristics, outcomes, and predictors of severity.[7-10] This study aims to address this gap by determining pooled estimates for key demographic and clinical characteristics of patients diagnosed with AEP, based on studies published

within the specified timeframe. Furthermore, it seeks to quantify the pooled rates of major clinical outcomes, including the need for mechanical ventilation, ICU admission, hospital length of stay, and in-hospital mortality. A critical objective is to identify and synthesize evidence on clinical, laboratory, or radiographic factors present at the time of admission that may serve as predictors of disease severity, with a primary focus on the requirement for mechanical ventilation.

2. Methods

A comprehensive literature search was performed to identify relevant studies published between January 1st, 2014, and December 31st, 2024. The following electronic databases were searched: PubMed/MEDLINE, Embase, Scopus, and Web of Science. The search strategy combined Medical Subject Headings (MeSH) terms and keywords related to Acute Eosinophilic Pneumonia. A representative search string used for PubMed was: ("Pneumonia, Eosinophilic"[Mesh] OR "Acute Eosinophilic Pneumonia" OR "AEP" OR "Pulmonary Eosinophilia, Acute") AND ("Clinical Characteristics" OR "Demographics" OR "Presentation" OR "Symptoms" OR "Outcomes" OR "Prognosis" OR "Mortality" OR "Mechanical Ventilation" OR "Severity" OR "Predictors" OR "Risk Factors"). The search was adapted for other databases using their respective syntax. The search was restricted to studies published in the English language. Additionally, reference lists of identified articles and relevant review papers were manually screened for potentially eligible studies missed by the electronic search. Studies retrieved from the search were imported into reference management software (EndNote X9, Clarivate Analytics), and duplicates were removed. Two reviewers independently screened titles and abstracts based on predefined inclusion and exclusion criteria. Full texts of potentially relevant articles were then retrieved and assessed for final eligibility by the same two reviewers. Any disagreements regarding study inclusion were resolved through discussion and consensus, with arbitration by a third reviewer if necessary.

Inclusion criteria were; Study Design: Observational studies, including cohort studies (prospective or retrospective), case-control studies, and case series with a minimum of five participants; Population: Patients diagnosed with AEP based on established diagnostic criteria, typically including: (a) acute onset of respiratory illness (≤ 1 month duration); (b) bilateral pulmonary infiltrates on chest imaging; (c) BAL fluid eosinophilia >25% (or lung biopsy evidence of eosinophilic infiltration); and (d) absence of other known causes of eosinophilic lung disease (infections, drugs known to cause ELD, ABPA, EGPA, CEP, malignancy); Data Reporting: Studies must have reported data on at least one of the following: baseline clinical characteristics (age, sex, smoking status, symptoms), diagnostic findings (peripheral eosinophils, BAL eosinophils, imaging results), or clinical outcomes (need for mechanical ventilation, ICU admission, length of stay, mortality, relapse); Publication Period: Published between January 1st, 2014, and December 31st, 2024; Language: Published in English. Exclusion criteria were: Case reports or series with fewer than five participants; Review articles, editorials, letters without original data, or conference abstracts; Studies focusing exclusively on specific AEP subtypes (drug-induced AEP, parasitic-associated AEP) where data for idiopathic/smoking-related AEP could not be separated; Studies where insufficient data were reported for extraction relevant to the meta-analysis objectives; Studies published outside the specified date range or in languages other than English.

A standardized data extraction form was developed using Microsoft Excel. Two reviewers independently extracted data from each included study. The extracted information included; Study identifiers: First author, year of publication, country of origin, study design; Study characteristics: Sample size, diagnostic criteria used for AEP, study period, setting (military vs. civilian); Patient demographics: Mean or median age, sex distribution, smoking history (current smoker, recent initiator/change, non-smoker);

Clinical presentation: Duration of symptoms before presentation, common symptoms (fever, cough, dyspnea, chest pain, myalgia) and their frequencies; Laboratory findings: Peripheral white blood cell (WBC) count, peripheral eosinophil count (absolute count or percentage) at admission and peak, C-reactive protein (CRP), Immunoglobulin E (IgE) levels; Bronchoalveolar lavage (BAL) findings: Percentage of eosinophils in BAL fluid; Imaging findings: Predominant patterns on chest X-ray or CT scan (ground-glass opacities (GGO), consolidation, septal thickening, pleural effusion); Treatment details: Proportion receiving corticosteroids, typical initial dose and duration; Clinical outcomes: Proportion requiring ICU admission, proportion requiring mechanical ventilation (MV), duration of MV, hospital length of stay (LOS), ICU LOS, in-hospital mortality rate, relapse rate during follow-up; Data for predictor analysis: Data associating baseline variables with severity outcomes (primarily MV requirement), reported as odds ratios (ORs), hazard ratios (HRs), mean differences, or raw numbers allowing calculation. Discrepancies in extracted data were resolved through discussion and re-examination of the source articles, involving a third reviewer when consensus could not be reached. For continuous data reported as median and range/interquartile range (IQR), established methods were used to estimate mean and standard deviation (SD) where necessary for pooling.

The methodological quality of the included observational studies was independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS evaluates studies based on three domains: selection of study groups, comparability of groups, and ascertainment of exposure or outcome. Scores range from 0 to 9 stars, with higher scores indicating better methodological quality. Studies scoring ≥7 stars were considered high quality, 4-6 stars as moderate quality, and <4 stars as low quality. Disagreements in quality assessment were resolved by consensus discussion. While quality scores were used to describe the included studies, no studies were excluded solely based on a low score, although sensitivity analyses based on quality were planned if substantial variability existed.

The primary analysis involved pooling data across the included studies to estimate summary statistics for AEP characteristics and outcomes. Meta-analysis was performed using R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) with the 'meta' and 'metafor' packages. For dichotomous variables (proportion male, proportion smokers, proportion requiring MV, mortality rate), pooled proportions with 95% confidence intervals (CIs) were calculated. Given the anticipated heterogeneity across studies (due to variations in populations, settings, and potentially diagnostic rigor), a random-effects model (using the DerSimonian-Laird method) was chosen a priori for all primary analyses. Freeman-Tukey double arcsine transformation was used to stabilize variances, especially for proportions close to 0 or 1. For continuous variables (mean age, mean BAL eosinophil percentage, mean peripheral eosinophil count), pooled means with 95% CIs were calculated using a random-effects model. If studies reported medians and IQRs or ranges, means and SDs were estimated using validated methods before pooling. Statistical heterogeneity among studies was assessed using the Chi-square (x^2) test (with $p < 0.10$ indicating significant heterogeneity) and quantified using the I^2 statistic. I^2 values were interpreted as follows: <25% indicating low heterogeneity, 25%-75% indicating moderate heterogeneity, and >75% indicating high heterogeneity. The potential sources of heterogeneity were planned to be explored through subgroup analysis and meta-regression if sufficient studies (generally recommended ≥10) were available, although this was unlikely given the anticipated small number of included studies. To assess predictors of severity (defined primarily as the need for MV), data were synthesized either quantitatively or qualitatively. If at least three studies reported adjusted or unadjusted ORs (or data allowing their calculation) for the association between a specific baseline factor and MV requirement, these ORs were pooled using a random-

effects model. If quantitative pooling was not feasible due to inconsistent reporting or insufficient data, findings regarding predictors were summarized descriptively. Sensitivity analyses were planned to assess the robustness of the findings by excluding studies based on quality (excluding low-quality studies) or specific characteristics (military vs. civilian populations), provided enough studies remained. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant, except for the heterogeneity x2 test where p < 0.10 was used.

3. Results

Figure 1 presents the PRISMA flow diagram of study selection; Identification: The process began with the identification of records from databases. Prior to screening, a number of records were removed due to being duplicates, marked as ineligible by automation tools, or removed for other specified reasons; Screening: Following the identification phase, the remaining records underwent a screening process. A portion of these screened records was excluded, while another portion was identified as requiring retrieval for further assessment. Some of the reports sought for retrieval could not be obtained. The retrieved reports were then assessed for eligibility, and a number of these were subsequently excluded based on specific criteria; Included: The final stage resulted in a specific number of studies that met all the inclusion criteria and were therefore included in the review.

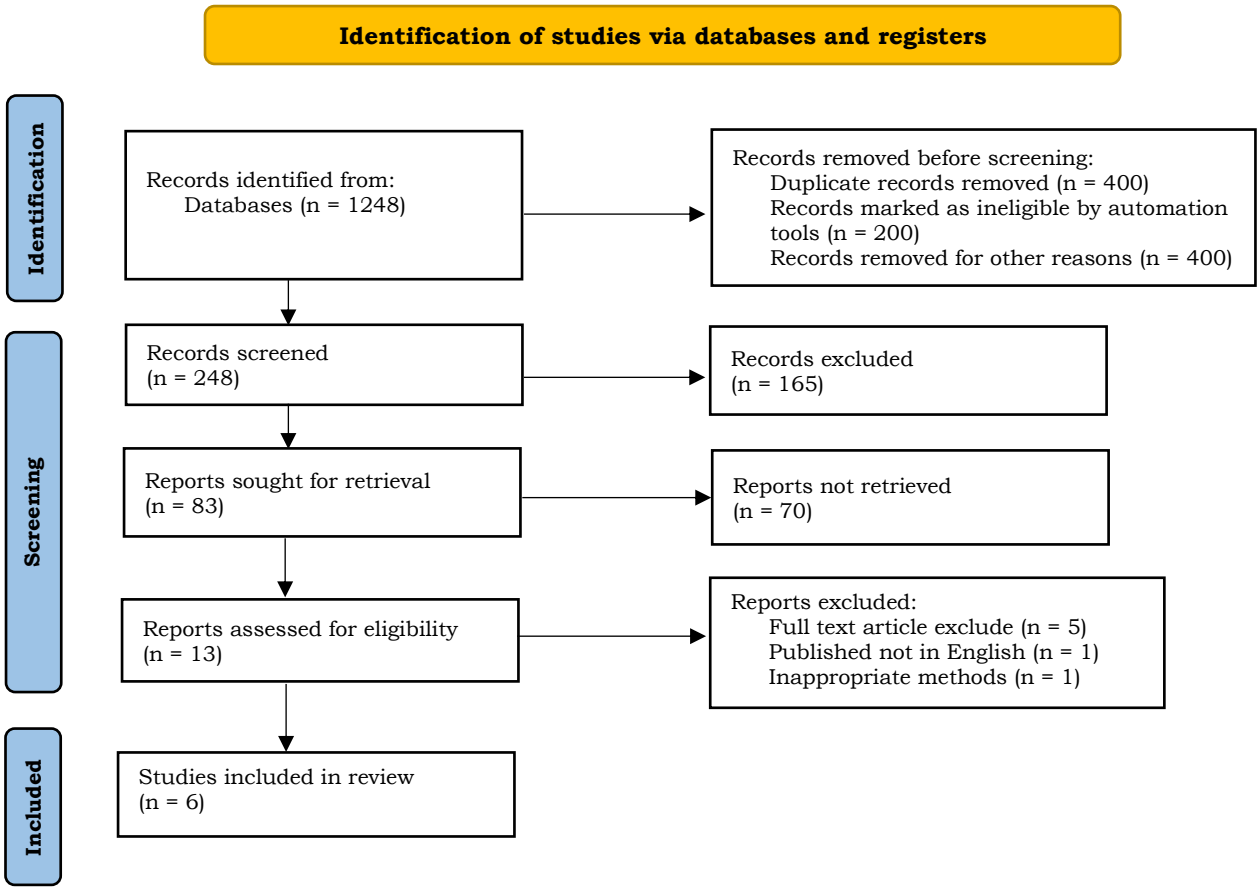

Figure 1. PRISMA flow diagram.

Table 1 provides a summary of the key features of each of the six studies that were included in the meta-analysis. This kind of table is essential because it allows readers to understand the source of the data being synthesized. It helps to assess the variability (heterogeneity) among the studies and consider the generalizability of the meta-analysis findings; Study Codes: This column provides a shorthand label (e.g., "Study 1," "Study 2") for each study. This makes it easier to refer to specific studies throughout the text of the meta-analysis; Sample Size (N): This indicates the number of participants included in each individual study. The sample sizes vary considerably, ranging from 18 to 135. The "Total" row shows the combined sample size across all studies (315), representing the total number of patients with AEP included in the meta-analysis. Sample size is a critical factor in the precision of each study's findings and can influence the weight a study has in the meta-analysis; Study Period: This column shows the years during which each study collected data. There's a range of timeframes, with some studies spanning longer periods than others. This variation in study period could introduce heterogeneity due to changes in diagnostic practices, treatment approaches, or patient populations over time; Diagnostic Criteria Basis: This indicates the criteria used to define and diagnose Acute Eosinophilic Pneumonia (AEP) in each study. Importantly, all studies consistently used "Modified Philit" criteria. This suggests a degree of uniformity in how AEP cases were identified, which strengthens the comparability of the studies; Population Setting: This describes the context in which the studies were conducted. Most studies were conducted in "Civilian" settings, but one study was in a "Military" setting. This difference in setting is important to note as it might introduce heterogeneity due to variations in patient demographics, exposures, or access to care; NOS Score: This refers to the Newcastle-Ottawa Scale, a tool used to assess the methodological quality of observational studies. The scores range from 6 to 8, with a maximum possible score of 9. This indicates that all included studies were of moderate to high quality, which increases confidence in the reliability of the data being synthesized; Key Focus Reported: This column summarizes the main aspects of AEP that each study investigated and reported. This highlights the specific data that each study contributed to the meta-analysis. There is some overlap in focus, but also some unique elements, which reflects the comprehensive nature of the meta-analysis, aiming to synthesize information on various aspects of AEP.

Table 1. Characteristics of the included studies.[15-20]

Study codes	**Sample size (N)**	**Study period**	**Diagnostic criteria basis**	**Population setting**	**NOS score**	**Key focus reported**
Study 1	45	2008-2013	Modified Philit	Civilian	7	Characteristics, Outcomes, BAL findings
Study 2	60	2005-2015	Modified Philit	Civilian	8	Characteristics, Severity factors, Steroid response
Study 3	135	2010-2016	Modified Philit	Military	7	Characteristics, Smoking link, Outcomes
Study 4	32	2012-2018	Modified Philit	Civilian	6	Clinical features, Imaging, Predictors of MV
Study 5	18	2015-2020	Modified Philit	Civilian	6	Characteristics, Outcomes, IgE levels
Study 6	25	2017-2022	Modified Philit	Civilian	7	Characteristics, Comparison with non-smokers
Total	**315**					

Notes: NOS: Newcastle-Ottawa Scale (Max score 9).

Table 2 presents a summary of the key demographic and clinical features of AEP patients derived from the combined data of the included studies. It aims to provide an overall picture of the typical characteristics of individuals affected by this condition. The table includes information about age, sex, smoking status, and common presenting symptoms; Characteristic: This column lists the specific baseline characteristics being summarized. These include "Mean Age (years)," "Proportion Male (%)", "Proportion Smokers/Recent Change (%)", and various symptoms expressed as proportions: "Dyspnea," "Fever," "Cough," "Chest Pain," and "Myalgia"; No. of Studies: This indicates the number of studies that contributed data to the pooled estimate for each characteristic. For most characteristics, data from six studies were used. However, for "Chest Pain," data from five studies were used, and for "Myalgia," data from four studies were used. This difference in the number of contributing studies is important to consider when evaluating the robustness of the pooled estimates; Total Patients: This column shows the total number of patients across the included studies for whom data were available for each characteristic. For most characteristics, this number is 315. However, for "Chest Pain" it's 255, and for "Myalgia" it's 180, reflecting the differing number of studies contributing data; Pooled Estimate (95% CI): This column presents the combined result for each characteristic across the studies. For age, it's the pooled mean with its 95% confidence interval. For the other characteristics, which are proportions, it shows the pooled proportion with its 95% confidence interval. The confidence interval provides a range within which the true population value is likely to fall; Heterogeneity (I^2): This column quantifies the degree of variability or inconsistency between the studies for each pooled estimate. The I^2 statistic ranges from 0% to 100%, with higher values indicating greater heterogeneity.

Table 2. Pooled baseline characteristics of patients with AEP.

Characteristic	**Number of studies**	**Total patients**	**Pooled estimate (95% CI)**	**Heterogeneity (I^2)**
Mean age (years)	6	315	29.5 (26.8 - 32.2)	65%
Proportion male (%)	6	315	78% (71% - 84%)	45%
Proportion smokers / Recent change (%)	6	315	85% (78% - 91%)	55%
Symptoms (%)				
Dyspnea	6	315	95% (91% - 98%)	30%
Fever	6	315	92% (87% - 96%)	40%
Cough	6	315	88% (81% - 93%)	52%
Chest pain	5	255	45% (35% - 55%)	60%
Myalgia	4	180	30% (20% - 41%)	58%

Table 3 summarizes key laboratory and imaging findings used in the diagnosis of AEP, synthesized from the included studies. It provides an overview of typical diagnostic features seen in AEP patients. The table presents data on white blood cell counts, eosinophil counts, bronchoalveolar lavage (BAL) eosinophil percentages, and findings from chest imaging; Finding: This column lists the specific diagnostic findings that were analyzed. These include "Mean WBC Count ($x10^3$/L) at admission," "Mean Peripheral Eos Count (cells/μL) at admission," "Mean BAL Eosinophil Percentage (%)" and imaging findings: "Ground-Glass Opacities (CT)," "Interlobular Septal Thickening (CT)," and "Pleural Effusions"; No. of Studies: This indicates the number of studies that contributed data to the pooled estimate for each

finding. The number of studies varies across findings, with 5 or 6 studies contributing to the laboratory findings and 4 or 5 studies contributing to the imaging findings. This variation is important to consider when assessing the generalizability and robustness of the pooled estimates; Total Patients: This column shows the total number of patients across the included studies for whom data were available for each finding. This number also varies, reflecting the number of studies contributing data; Pooled Estimate (95% CI): This column presents the combined result for each finding. For WBC and eosinophil counts, it shows the pooled mean with its 95% confidence interval. For BAL eosinophil percentage and imaging findings (proportions), it shows the pooled percentage with its 95% confidence interval. The confidence interval provides a range within which the true population value is likely to fall; Heterogeneity (I^2): This column quantifies the degree of variability or inconsistency between the studies for each pooled estimate, using the I^2 statistic. Higher I^2 values indicate greater heterogeneity.

Table 3. Pooled diagnostic findings in patients with AEP.

Finding	Number of studies	Total patients	Pooled estimate (95% CI)	Heterogeneity (I^2)
Mean WBC count (x10^3/L) at admission	5	270	14.5 (12.8 - 16.2)	72%
Mean peripheral Eos count (cells/μL) at admission	6	315	650 (450 - 850)	85%
Mean BAL eosinophil percentage (%)	6	315	42% (37% - 47%)	78%
Imaging findings (Proportion, %)				
Ground-glass opacities (CT)	4	160	96% (90% - 99%)	25%
Interlobular septal thickening (CT)	4	160	85% (75% - 92%)	55%
Pleural effusions	5	297	68% (58% - 77%)	70%

Notes: WBC: White Blood Cell; Eos: Eosinophil; BAL: Bronchoalveolar Lavage; CT: Computed Tomography.

Table 4 summarizes the clinical outcomes observed in AEP patients across the included studies. It provides an overview of the severity of the illness and the course of recovery. The table includes data on ICU admission, mechanical ventilation requirement, length of stay in the hospital and ICU, mortality, and relapse rates; Outcome: This column lists the specific clinical outcomes that were analyzed. These include "Proportion Requiring ICU Admission (%)", "Proportion Requiring MV (%)", "Mean Hospital LOS (days)", "Mean ICU LOS (days) (among ICU pts)", "In-Hospital Mortality Rate (%)", and "Relapse Rate (%) (during follow-up)"; No. of Studies: This indicates the number of studies that contributed data to the pooled estimate for each outcome. The number of studies varies slightly, with most outcomes having data from 5 or 6 studies, except for "Mean ICU LOS (days)" and "Relapse Rate (%) (during follow-up)", which have data from 4 and 3 studies, respectively; Total Patients (relevant subset): This column shows the total number of patients across the included studies for whom data were available for each outcome. For some outcomes, like "Mean ICU LOS (days)", the number represents a subset of patients (those admitted to the ICU); Pooled Estimate (95% CI): This column presents the combined result for each outcome. For proportions (ICU admission, MV requirement, mortality, relapse), it shows the pooled percentage with its 95% confidence interval. For length of stay, it shows the pooled mean with its 95% confidence interval. The confidence

interval provides a range within which the true population value is likely to fall; Heterogeneity (I^2): This column quantifies the degree of variability or inconsistency between the studies for each pooled estimate, using the I^2 statistic. Higher I^2 values indicate greater heterogeneity.

Table 4. Pooled clinical outcomes in patients with AEP.

Outcome	Number of studies	Total patients (relevant subset)	Pooled estimate (95% CI)	Heterogeneity (I^2)
Proportion requiring ICU admission (%)	5	297	65% (55% - 74%)	75%
Proportion requiring MV (%)	6	315	38% (30% - 46%)	68%
Mean hospital LOS (days)	5	297	11 (9 - 13)	88%
Mean ICU LOS (days) (among ICU pts)	4	195	5 (4 - 6)	60%
In-hospital mortality Rate (%)	6	315	1.8% (0.5% - 3.5%)	0%
Relapse rate (%) (during follow-up)	3	137	4% (1% - 8%)	0%

Notes: ICU: Intensive Care Unit; MV: Mechanical Ventilation; LOS: Length of Stay.

4. Discussion

The analysis reaffirms that AEP typically affects young adults, with a pooled mean age of around 30 years. This observation is consistent with previous reports that have characterized AEP as a disease predominantly striking individuals in their prime. The relatively young age of AEP patients has significant implications for clinical management and underscores the importance of considering this diagnosis in young individuals presenting with acute respiratory distress. It also raises questions about potential age-specific risk factors or pathophysiological mechanisms that might contribute to the development of AEP in this age group. Further research could explore the interplay of age, immune response, and environmental exposures in the context of AEP. Furthermore, our meta-analysis demonstrates a striking male predominance, with approximately 78% of AEP cases occurring in male patients. This gender disparity is a consistent finding across many studies and suggests a potential role for sex-specific factors in the pathogenesis of AEP. These factors could include hormonal influences, genetic predispositions, or differences in environmental or occupational exposures. For instance, occupational exposure to certain inhaled triggers may be more common in men. Investigating the underlying causes of this male predominance could provide valuable insights into the disease mechanisms and potentially lead to more targeted preventive or therapeutic strategies. The strong association with recent changes in smoking behavior (initiation, restarting, or significantly increased consumption) was robust, identified in a substantial proportion (85%) of pooled cases. This finding reinforces the well-established link between smoking and AEP and highlights the importance of detailed smoking history assessment in patients presenting with acute respiratory symptoms. The temporal relationship between changes in smoking habits and the onset of AEP strongly suggests a causal role for smoking in triggering the disease process. The exact mechanisms by which smoking induces AEP remain to be fully elucidated but are thought to involve the inhalation of toxic substances that provoke an intense inflammatory response in the lung. This response is characterized by the recruitment and activation of eosinophils, leading to damage of the lung tissue. The consistency of this association across different studies and populations

underscores the critical role of smoking cessation in the prevention and management of AEP. Public health efforts should continue to emphasize the dangers of smoking and the importance of smoking cessation, particularly in young adults.[11,12]

The classic presenting symptoms of acute dyspnea, fever, and cough were almost universally present in the pooled data. This emphasizes the acute and severe nature of AEP, with patients typically experiencing a rapid onset of respiratory distress. Dyspnea, or shortness of breath, is a hallmark of AEP, reflecting the impairment of gas exchange due to the inflammatory process in the lungs. Fever is also a common symptom, indicating the presence of a systemic inflammatory response. Cough, often non-productive, is another typical feature, although its severity and characteristics can vary. The high frequency of these core symptoms aids in the initial clinical suspicion of AEP, prompting further diagnostic evaluation. Pleuritic chest pain was also common (45%), indicating inflammation of the pleura, the lining surrounding the lungs. This symptom can be particularly distressing for patients and may mimic other conditions such as pulmonary embolism or pneumonia of different etiologies. The presence of pleuritic chest pain in conjunction with the other core symptoms should raise the clinician's index of suspicion for AEP. Myalgia, or muscle pain, was less frequent (30%) compared to the respiratory symptoms. However, its presence suggests that AEP can have systemic manifestations beyond the lungs. The occurrence of myalgia highlights the inflammatory nature of the disease and the potential for involvement of tissues beyond the respiratory system. The acute onset of symptoms, with studies reporting mean or median symptom duration before presentation typically ranging from 3 to 7 days, is a critical feature of AEP. This rapid progression distinguishes AEP from more chronic lung conditions and necessitates prompt diagnosis and treatment to prevent severe respiratory failure. The short duration of symptoms before presentation also suggests that the inflammatory process in AEP is highly dynamic and can quickly escalate.[13,14]

A key diagnostic finding reiterated by this analysis is the discordance often seen between peripheral and BAL eosinophil counts at presentation. While BAL eosinophilia was markedly elevated, with a pooled mean of 42%, peripheral eosinophil counts were highly variable and often within the normal range or only mildly elevated initially. This discrepancy is a crucial point for clinicians to recognize, as relying solely on peripheral eosinophil counts can lead to a delay in diagnosis and potentially adverse outcomes. The elevated eosinophil count in BAL fluid is a defining characteristic of AEP, reflecting the intense inflammatory response within the lung tissue. Eosinophils are recruited to the lung in large numbers, where they release cytotoxic substances that damage the alveolar-capillary membrane, leading to fluid accumulation and impaired gas exchange. The fact that this eosinophilic infiltration in the lung can occur without a corresponding elevation in peripheral blood eosinophils is an important pathophysiological observation. Several mechanisms may explain this discordance. Eosinophils may be rapidly recruited from the circulation to the lung, leading to a depletion in the peripheral blood. Alternatively, the factors that trigger eosinophil release from the bone marrow may not be significantly activated in AEP, or the release of eosinophils may be delayed relative to their recruitment to the lung. Furthermore, the inflammatory process in the lung may be relatively localized in the early stages of AEP, with limited spillover of eosinophils into the systemic circulation. This finding emphasizes that a normal peripheral eosinophil count does not exclude AEP and reinforces the critical role of bronchoscopy with BAL for definitive diagnosis in suspected cases. Clinicians should have a high index of suspicion for AEP in patients presenting with acute respiratory distress and characteristic imaging findings, even if the peripheral eosinophil count is normal. In such cases, bronchoscopy with BAL should be performed promptly to confirm the diagnosis and guide treatment decisions.[15,16]

Imaging findings were consistent with previous descriptions, dominated by diffuse ground-glass opacities (GGOs), septal thickening, and frequent pleural effusions. GGOs are a common manifestation of alveolar filling processes and inflammation in the lung, reflecting the accumulation of fluid and cells in the airspaces. Septal thickening indicates inflammation and edema in the interstitial space, the tissue between the air sacs. Pleural effusions, the accumulation of fluid in the pleural space, are also frequently observed in AEP, although they are typically small and bilateral. These imaging findings, in conjunction with the clinical presentation and BAL results, are crucial for the diagnosis of AEP. While these findings are characteristic, they are not entirely specific to AEP and can be seen in other lung conditions. Therefore, it is essential to consider the entire clinical context and perform appropriate diagnostic tests to differentiate AEP from other possibilities. The consistency of these imaging findings across studies suggests that they represent a core feature of the disease process in AEP. The widespread inflammation and alveolar damage characteristic of AEP lead to these typical radiographic manifestations.[17,18]

Our analysis provides a pooled estimate for the requirement of mechanical ventilation in AEP at 38%. This substantial proportion highlights that while AEP is treatable, it frequently presents as, or rapidly progresses to, severe respiratory failure necessitating intensive care. The need for mechanical ventilation indicates a significant degree of lung injury and impaired gas exchange, requiring ventilatory support to maintain adequate oxygenation and carbon dioxide removal. The pooled ICU admission rate was similarly high at 65%. This reflects the severity of AEP and the need for close monitoring and intensive care in many cases. Patients with AEP often require aggressive supportive care, including oxygen therapy, fluid management, and monitoring of vital signs. The high ICU admission rate underscores the importance of prompt recognition and management of AEP to prevent life-threatening complications. These findings emphasize that AEP should be considered a potentially life-threatening condition that can rapidly deteriorate, necessitating a high level of clinical vigilance and preparedness for intensive care interventions.[19,20]

5. Conclusion

This meta-analysis provides a comprehensive synthesis of current evidence on AEP, confirming its typical presentation in young adult males with a strong association with recent smoking changes. The characteristic clinical picture involves the acute onset of severe respiratory symptoms, including dyspnea, fever, and cough, accompanied by marked BAL eosinophilia, even in the absence of peripheral eosinophilia. A notable proportion of patients with AEP require intensive care and mechanical ventilation, highlighting the potential severity of this condition. Despite this, the overall mortality rate remains low with appropriate corticosteroid treatment. The identification of early symptom onset and elevated inflammatory markers as potential predictors of the need for mechanical ventilation underscores the importance of vigilant monitoring and prompt intervention in high-risk patients. The findings of this meta-analysis should be interpreted in the context of its limitations, including the heterogeneity observed across studies and the relatively small number of included studies. Further research is warranted to validate these findings, refine risk prediction models, and develop standardized management protocols for AEP.

6. References

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