# Eosinopenia as Predictor of Disease Severity in Patients With Community-Acquired Pneumonia

## An Observational Study

**To the Editor:**

Lower respiratory tract infections, including community-acquired pneumonia (CAP), are a frequent cause of death worldwide.[1] A previous study[2] found that 38% of patients with CAP requiring mechanical ventilation did not survive their hospital stay. Conversely, only 16% of patients with CAP dying in hospital have been mechanically ventilated.[2] Predictors of disease severity are required, because they would help identify high-risk patients with CAP who may benefit from early continuous monitoring to detect complications and reduce mortality. Previous studies found that eosinophil levels $< 50/\mu L$ correlate with an increased mortality in hospitalized patients with CAP in addition to acute exacerbation of COPD.[3] Also, eosinopenia is associated with a higher 4-week mortality in COVID-19 pneumonia.[4] However, the role of eosinopenia for predicting short-term outcome in CAP is poorly understood.

This study therefore analyzed blood eosinopenia $\leq 50/\mu L$ as a predictor of disease severity in patients with CAP.

## Methods

We retrospectively reviewed $\geq$ 18-year-old patients hospitalized with CAP as their primary diagnosis from five university hospitals in Germany between 2009 and 2020. The diagnosis of CAP was based on the International Classification of Diseases Code J10-18 and its subgroups according to the 10th revision, German Modification.[5]

This study analyzed age, sex, and comorbidities including sepsis based on International Classification of Diseases, 10th Revision, German Modification[5] in patients with eosinopenia $\leq 50/\mu L$ and non-eosinopenia ($> 50/\mu L$). Laboratory parameters were measured during the first 24 hours of admission. If multiple laboratory values were available for a single parameter, the first value was used for analysis. Mortality, need for both noninvasive and invasive mechanical ventilation in all patients, length of mechanical ventilation in survivors, date and time of hospital admission in all patients, and discharge in survivors or death of deceased patients were recorded based on the data in the hospital information system.

Data extraction and handling was performed under the umbrella of the Medical Informatics in Research and Care in University Medicine consortium.[6] The study protocol was approved by all five local ethics committees, data privacy advocates, and the use and access committee. Data analysis was performed using DataSHIELD,[7] an open-source software allowing privacy-preserving federated learning and anonymous co-analysis of individual-level data held at multiple locations. Descriptive statistics were reported as sample size-weighted average of the site-specific medians, and 25th and 75th percentiles. Percentages were used to report categorical variables distributions.

Differences in the comorbidity prevalence between the eosinopenia and non-eosinopenia groups were calculated via Fisher exact test in a univariate model. Differences in mortality and the need for mechanical ventilation between the two groups were analyzed using a multivariate general linear model that considered the following variables: age; sex; and blood values for C-reactive protein, creatinine, and hemoglobin in the eosinopenia and non-eosinopenia group.

Differences in length of stay in survivors, time to in-hospital death, and the number of hours of mechanical ventilation in survivors between the two groups were determined using Mann-Whitney *U* test[8] in a univariate model. For reasons of data protection and technical requirements of the analysis software DataSHIELD, Mann-Whitney *U* test was modified as follows: Integer values were exported, decimal places were replaced by uniformly

randomized numbers, and significance was subsequently calculated. This was done with N = 10,000, and the least significant *P* values were reported.

The statistical analysis was conducted using DataSHIELD version 6.1.1 and R versions 4.1.2 and 4.2.0. Nonadjusted $P < .05$ was considered statistically significant.

## Results

Overall, 6,748 (4,060 eosinopenic and 2,688 non-eosinopenic) patient cases were included in the analysis. Demographic data, laboratory parameters, and comorbidities of the eosinopenia and non-eosinopenia group are shown in Table 1.

In-hospital mortality was significantly higher in the eosinopenia vs non-eosinopenia group (13.8% vs 9.1%; relative risk [RR], 1.51; 95% CI, 1.31-1.74; $P < .0001$). In-hospital mortality in the two groups on days 1, 5, 10, 15, and 30 after hospitalization is displayed in Figure 1. The need for mechanical ventilation was significantly elevated in the eosinopenia vs non-eosinopenia group (19.2% vs 14.3%; RR, 1.34; 95% CI, 1.20-1.50; $P < .0001$). Risk of sepsis was significantly elevated in the eosinopenia vs non-eosinopenia group (7.5% vs 5.0%; RR, 1.50; 95% CI, 1.23-1.83; $P < .0001$). Median length of stay in eosinopenic survivors was significantly prolonged compared with non-eosinopenic survivors (8.41 vs 7.64 days; $P < .0001$). Median time to in-hospital death was significantly reduced in the eosinopenia group (6.73 vs 8.92 days; $P = .001$). In survivors, median length of mechanical ventilation in the eosinopenia group was 121.93 hours vs 93.39 hours in the non-eosinopenia group. The difference was not significant ($P = .152$).

## Discussion

The key finding of this study was an association between blood eosinopenia (≤ 50/μL) and an increase in in-hospital mortality, need for mechanical ventilation, risk

**TABLE 1** ] Baseline Characteristics in the Eosinopenia and Non-Eosinopenia Group

| Variable | Eosinopenia Group (n = 4,060) | Non-Eosinopenia Group (n = 2,688) |
|---|---|---|
| Median age in years (25th-75th percentile) | 71.08 (58.2-80.0) | 69.45 (55.78-78.88) |
| Male sex, No. (%) | 2,483 (61.2) | 1,632 (60.7) |
| C-reactive protein, No. (%) | 4,021 (99.0) | 2,637 (98.1) |
| Median (mg/L), 25th-75th percentile (mg/L) | 94.09, 39.61-175.92 | 78.92, 28.12-148.79 |
| Procalcitonin, No. (%) | 1,907 (47.0) | 1,033 (38.4) |
| Median (ng/mL), 25th-75th percentile (ng/mL) | 0.49, 0.23-1.76 | 0.27, 0.12-0.65 |
| Leukocytes, No. (%) | 4,060 (100) | 2,688 (100) |
| Median ($\times 10^9$/L), 25th-75th percentile ($\times 10^9$/L) | 9.76, 6.33-14.35 | 10.19, 7.46-13.61 |
| Hemoglobin, No. (%) | 4,059 (100) | 2,688 (100) |
| Median (g/dL), 25th-75th percentile (g/dL) | 12.43, 10.73-13.94 | 12.14, 10.5-13.7 |
| Hematocrit, No. (%) | 4,059 (100) | 2,688 (100) |
| Median (%), 25th-75th percentile (%) | 36.81, 32.31-40.87 | 36.51, 31.66-40.66 |
| Creatinine, No. (%) | 4,041 (99.5) | 2,662 (99.0) |
| Median (mg/dL), 25th-75th percentile (mg/dL) | 1.04, 0.8-1.49 | 1.02, 0.77-1.52 |
| Asthma, No. (%) | 87 (2.1) | 76 (2.8) |
| COPD[a], No. (%) | 577 (14.2) | 452 (16.8) |
| Congestive heart failure, No. (%) | 801 (19.7) | 503 (18.7) |
| Myocardial infarction[b], No. (%) | 66 (1.6) | 66 (2.5) |
| Peripheral vascular disease[c], No. (%) | 292 (7.2) | 242 (9.0) |
| Cerebrovascular disease, No. (%) | 242 (6.0) | 154 (5.7) |
| Dementia, No. (%) | 340 (8.4) | 190 (7.1) |
| Diabetes mellitus, No. (%) | 966 (23.8) | 634 (23.6) |
| Liver disease, No. (%) | 146 (3.6) | 95 (3.5) |
| Renal disease[d], No. (%) | 880 (21.7) | 697 (25.9) |

Significant differences between eosininopenia and non-eosinopenia group: [a]$P = .004$; [b]$P = .019$; [c]$P = .008$; [d]$P < .0001$.

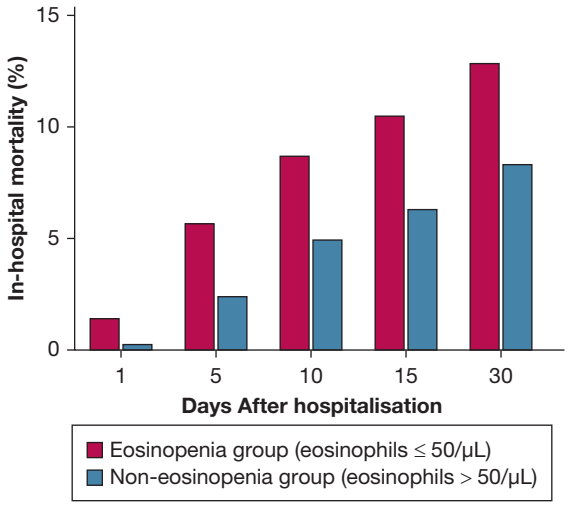


Figure 1 – *In-hospital mortality in the eosinopenia vs non-eosinopenia group on days 1, 5, 10, 15, and 30 after hospitalization.*

of sepsis, length of stay in survivors, and reduced time to in-hospital death in a real-world patient cohort.

Because the prevalence of COPD, myocardial infarction, peripheral vascular disease, and renal disease was lower in the eosinopenia group, whereas the other comorbidities were balanced in the eosinopenia and non-eosinopenia groups, the worse outcomes in eosinopenic patients do not seem to be caused by comorbidities.

In line with our findings, eosinopenia $< 50/\mu L$ correlates with an increased 18-month mortality in hospitalized patients with acute exacerbations of COPD and CAP,[3] and, as part of the Dyspnoea, Eosinopenia, Consolidation, Acidaemia, and Atrial Fibrillation score,[9] elevated short-term mortality in patients with acute exacerbations of COPD. Furthermore, eosinopenia is associated with a higher 4-week mortality in COVID-19 pneumonia.[4]

Solid data about eosinophil numbers as a predictor of short-term outcome in CAP in humans are missing. In a mouse model,[10] after induction of pneumonia with *Staphylococcus aureus*, an IL-33-induced increase in eosinophil levels inhibited acute lung injury as indicated by reduced pulmonary edema and higher oxygen saturations. This was associated with improved survival. Eosinophil reduction prevented IL-33-mediated protection against mortality in mice. Future studies considering eosinophil and IL-33 levels, as well as downstream signaling pathways, are needed to elucidate the mechanism by which eosinophils might benefit survival after CAP.

The strengths of our study relate to the high number of real-world patient cases.

The limitations of this study involve its retrospective design; that its analysis was based on cases instead of patients; the lack of information about the immune status, microbial etiology, and clinical parameters of patients; and the technical restrictions of DataSHIELD, which did not allow for propensity score matching and analyzing eosinophil count as continuous variables.

In conclusion, blood eosinopenia $\leq 50/\mu L$ (vs non-eosinopenia) seems suitable to predict disease severity in patients with CAP. Further prospective studies are required to confirm our findings.

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