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Prognostic Usefulness of Eosinopenia in the Pediatric Intensive Care Unit

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Eosinopenia, a biomarker for infection, has recently been shown to be a predictor of adult mortality in the intensive care unit (ICU). Our study assessed the usefulness of eosinopenia as a mortality and an infection biomarker in the pediatric ICU (PICU). We compared the PICU mortality scores, eosinophil count and percentage at ICU admission between children who survived and those who did not survive and between children with infection and those without infection. A total of 150 patients were evaluated. The initial eosinophil count and percentage were significantly lower in the group that did not survive when compared to those that did survive ($P < 0.001$; $P < 0.001$). However, there was no significant difference in the eosinophil count and percentage seen in patients with and without infection. Eosinopenia, defined as an eosinophil count < 15 cells/μL and an eosinophil percentage $< 0.25\%$, (hazard ratio [HR]: 2.96; $P = 0.008$) along with a Pediatric Index of Mortality (PIM) 2 (HR: 1.03; $P = 0.004$) were both determined to be independent predictors of mortality in the PICU. The presence of eosinopenia at the ICU admission can be a useful biomarker for mortality in children, but is not useful as a biomarker for infection.

Key Words: Biomarkers; Child; Eosinophils; Infection; Intensive Care Units; Prognosis

INTRODUCTION

The prediction of mortality in the intensive care units (ICUs) is more intricate in children than in adults because a precise and complete assessment of consciousness in non-verbal children is limited, despite the fact that such an assessment is the most important factor for predicting mortality (1). Vital signs are also crucial factors, but they are difficult to measure precisely in children. This is due to both the variations in normal ranges that are dependent upon age, weight, and height and the difficulty in performing invasive procedures to measure them, such as establishing arterial and central vein access. The difficulty in obtaining blood samples in children is another potential obstacle to properly predicting their mortality, since most mortality scoring systems require broad laboratory data (2).

There have been many trials to assess several pediatric mortality scores (including the Pediatric Index of Mortality [PIM] 2) with satisfactory results (2-6). However, these scores still require an assessment of consciousness, vital signs, and numerous laboratory data. Therefore, a simpler prognostic biomarker is desperately needed in the pediatric ICU (PICU).

Recently, many researchers have suggested various biomarkers to predict the outcome in patients with critical illnesses (7, 8). C-reactive protein (CRP), pro-calcitonin, and thrombocytopenia are some of the suggested biomarkers that have already been utilized in the clinical arena (9). Eosinopenia has also gained an interest as a sensitive, specific, easy-to-measure, and inexpensive biomarker in the adult ICU (10, 11).

Sepsis, a systemic inflammatory response syndrome (SIRS) associated with infection, is strongly associated with mortality in the ICU (12). Acute infection can cause eosinopenia (13) through several mechanisms, such as peripheral sequestration of eosinophils in inflammatory sites, suppression of the egress of mature eosinophils from the bone marrow, and suppression of eosinophil production (14). Acute stress also involves eosinopenia, which is mediated by adrenal glucocorticoids and epinephrine. Severe, stressful conditions in the ICU are directly linked to mortality (15). Eosinopenia can reflect increased mortality in the ICU as a result of both acute infections and severe, stressful conditions.

There are few studies on eosinopenia as a mortality biomarker in children. Additionally, it has not yet been clarified as to wheth-

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er eosinopenia is a useful infection biomarker in children. This study was conducted to evaluate the usefulness of eosinopenia in predicting mortality and infection in the PICU.

MATERIALS AND METHODS

Study subjects and classification

We evaluated all pediatric patients admitted to the ICU of Severance Hospital, Seoul, Korea from January 2009 to March 2012. Patients who were discharged or died within 24 hr after ICU admission, as well as those who were treated with systemic steroids within one week of admission to the ICU were excluded (16). Infant cases and cardiac cases were treated in separate specialized units.

All ICU admissions were classified into two sets of separate groups (survivor vs non-survivor group, non-infection vs infection group). Survivors were defined as patients who were discharged from the ICU after recovery, while the patients who died during their ICU care were classified as non-survivors. Infection cases were classified according to criteria from the International Pediatric Sepsis Consensus Conference (17). Infection was diagnosed by the presence of a pathogen-proven infection (positive culture, tissue stain, or polymerase chain reaction test) or a clinical syndrome associated with a high probability of infection, such as positive findings on clinical examination, imaging, or laboratory tests (e.g., white blood cells [WBCs] in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans) (17).

Data collection

All patients were evaluated in terms of their age, gender, principal diagnosis for ICU care, infection status, and infection site at the time of ICU admission. CRP and WBC, with neutrophil and eosinophil counts and percentages of total WBC, were measured. Blood samples were obtained from indwelling arterial catheters or by venipuncture within the first 24 hr of ICU admission. Blood samples were drawn from each patient into EDTA tubes and were immediately transported to the chemical laboratory department at room temperature. The assays were performed within one hour of blood sampling. The WBC count and the eosinophil count were determined using an automated analyzer (ADVIA 2120 Hematology System, Siemens Healthcare Diagnostics, Forchheim, Germany). The plasma CRP concentration was measured by direct immunoturbidimetry (CA400, Beckman Coulter, CA, USA). The Pediatric RISk of Mortality (PRISM) III, PIM 2, and Pediatric Logistic Organ Dysfunction (PELOD) scores were recorded in all cases (3-5).

Statistical analysis

Parametrically distributed values in the text and tables are expressed as means ± standard deviations (SDs). Non-parametrically distributed values are expressed as median values with inter-quartile ranges. The survivor and non-survivor groups were compared in terms of patient characteristics, PICU mortality scores, and laboratory data by Student's t-test for continuous variables and the chi-square test for categorical variables (if the data was parametrically distributed). The non-infection and infection groups were compared in the same manner as the survivor and non-survivor groups. The Mann-Whitney test was utilized to analyze the non-parametrically distributed data.

The receiver operating characteristic (ROC) curves and the areas under the curves (AUCs) were determined for eosinophil counts and eosinophil percentages at ICU admission. The best cutoff values for eosinophil count and eosinophil percentage were chosen based on the Younden's index and the AUC. We calculated the sensitivity and specificity at the best cutoff points for the eosinophil count and eosinophil percentage, as well as at the point where both the eosinophil count and percentage were taken into account.

According to the best cutoff point where both eosinophil count and percentage were taken into account, two groups of patients with and without eosinopenia were compared in terms of survival rate. Survival curves were determined by the Kaplan-Meier method and the differences in survival between the subgroups were analyzed using the log-rank test. We used Cox proportional-hazard regression models to determine hazard ratios (HRs). All variables with P values < 0.1 on univariate analysis were included in the multivariate analysis.

A P value < 0.05 was considered statistically significant. The Statistical Package for the Social Sciences (version 18.0, SPSS Inc., Chicago, IL, USA) was used for all analyses.

Ethics statement

All data were collected and analyzed retrospectively in this study. This study was approved by the institutional review board of Severance Hospital (Seoul, Korea, IRB No. 4-2012-0369), and exempted from an informed consent form.

RESULTS

A total of 150 patients were evaluated in this study. The main health problems at ICU admission were respiratory problems, such as respiratory infection or airway obstruction, in 71 patients (47%); neurologic problems, such as status epilepticus or brain hemorrhage, in 31 patients (21%); gastrointestinal problems, such as gastrointestinal bleeding or fulminant hepatitis, in 9 patients (6%); nephrogenic problems, such as renal failure, in 10 patients (7%); hemato-oncologic problems, such as tumor lysis syndrome or neutropenic fever during chemotherapy, in 16 patients (10%); metabolic disorders in 4 patients (3%); postoperative care in 6 patients (4%); and other problems in 3 patients (2%).

Clinical characteristics of the survivor and non-survivor groups

The ICU mortality rate was 21% (n = 31). The primary health problems at the time of ICU admission in the non-survivor group were respiratory problems in 11 patients (35%), neurologic problems in 7 patients (23%), gastrointestinal problems in 3 patients (10%), nephrogenic problems in 3 patients (10%), hemato-oncologic problems in 5 patients (16%), and metabolic disorders in 2 patients (6%). Clinical characteristics, PICU mortality scores, and laboratory data were compared between the survivor and non-survivor groups (Table 1). PICU mortality scores were significantly higher, while eosinophil counts, eosinophil percentages, and platelet counts were significantly lower in the non-survivor groups. There was no significant difference in infection status or mechanical ventilation rate between the groups. With regard to the other laboratory data, CRP, WBC, neutrophil count, and neutrophil percentage were not statistically different.

Clinical characteristics of the non-infection and infection groups

At the time of admission, 103 patients (69%) were classified into the infection group. The sites of infection were the respiratory tract in 68 patients (66%), central nervous system in 13 patients (13%), gastrointestinal tract in 6 patients (6%), urinary tract in 4 patients (4%), and other locations in 12 patients (11%). Clinical characteristics, PICU mortality scores, and laboratory data were compared between the non-infection group and the infection group in Table 2. Among the patients who survived, those with infection stayed longer in the ICU than those without. There was no statistically significant difference in age, sex, survival rate, or PRISM III, PIM 2 and PELOD scores. In terms of laboratory data, eosinophil count and eosinophil percentage were not statistically different.

Eosinophil count and eosinophil percentage in predicting ICU mortality

We tested the diagnostic performance of eosinophil count and

Table 1. Clinical characteristics, PICU mortality scores, and laboratory data between the survivor and non-survivor groups

Parameters	Survivor (n = 119)	Non-survivor (n = 31)	*P* value
Age (yr)	3.2 (0.9-9.7)	3.1 (1.1-8.4)	0.926
Male sex, No (%)	73 (61)	22 (71)	0.322
Infection case, No (%)	84 (71)	19 (61)	0.320
Mechanical ventilation, No (%)	67 (56)	23 (74)	0.070
PRISM III score	8.0 (5.0-11.0)	15.0 (9.0-17.0)	< 0.001
PIM 2 score	3.3 (1.4-7.1)	26.6 (6.4-51.6)	< 0.001
PELOD score	2.0 (1.0-12.0)	12.0 (10.0-22.0)	< 0.001
C-reactive protein (mg/dL)	7.07 (2.10-45.50)	11.20 (4.48-72.91)	0.468
WBC (cells/μL)	11,590 (5,795-20,670)	11,310 (9,033-21,950)	0.492
Neutrophil (cells/μL)	6,170 (3,545-13,675)	9,050 (4,990-13,625)	0.772
Neutrophil (% of WBC)	64.5 (55.1-83.8)	66.6 (43.9-85.4)	0.508
Eosinophil (cells/μL)	80.0 (30.0-204.5)	45.0 (0-72.5)	< 0.001
Eosinophil (% of WBC)	0.60 (0.25-1.65)	0.20 (0.00-0.70)	< 0.001
Platelet (10^3/μL)	288.0 (165.0-431.5)	217.0 (89.3-380.3)	0.011

PICU, pediatric intensive care unit; PRISM, pediatric risk of mortality; PIM, pediatric index of mortality; PELOD, pediatric logistic organ dysfunction, WBC, white blood cell.

Table 2. Clinical characteristics, PICU mortality scores, and laboratory data between the non-infection and infection groups

Parameters	Non-infection (n = 47)	Infection (n = 103)	*P* value
Age (yr)	3.2 (0.6-10.1)	2.9 (1.1-8.3)	0.985
Male sex, No (%)	34 (72)	61 (59)	0.122
Survivor case, No (%)	35 (75)	84 (82)	0.320
ICU length in survivors (days)	5.0 (3.0-13.0)	8.0 (5.0-15.0)	0.016
PRISM III score	11.0 (5.0-16.0)	8.0 (5.0-12.0)	0.109
PIM 2 score	6.8 (1.9-13.8)	3.9 (1.5-9.1)	0.090
PELOD score	11.0 (1.0-20.0)	10.0 (1.0-12.0)	0.216
C-reactive protein (mg/dL)	6.35 (1.76-24.92)	11.50 (2.59-57.89)	0.355
WBC (cells/μL)	11,190 (6,345-22,725)	11,500 (6,775-20,110)	0.471
Neutrophil (cells/μL)	6,670 (3,545-18,395)	6,620 (4,125-13,100)	0.870
Neutrophil (% of WBC)	65.1 (54.9-81.9)	64.4 (52.9-85.5)	0.247
Eosinophil (cells/μL)	85.0 (30.0-215.0)	60.0 (20.0-185.0)	0.882
Eosinophil (% of WBC)	0.75 (0.28-2.00)	0.50 (0.20-1.25)	0.981
Platelet (10^3/μL)	238.0 (160.3-405.8)	296.0 (159.5-425.5)	0.657

PICU, pediatric intensive care unit; PRISM, pediatric risk of mortality; PIM, pediatric index of mortality; PELOD, pediatric logistic organ dysfunction, WBC, white blood cell.

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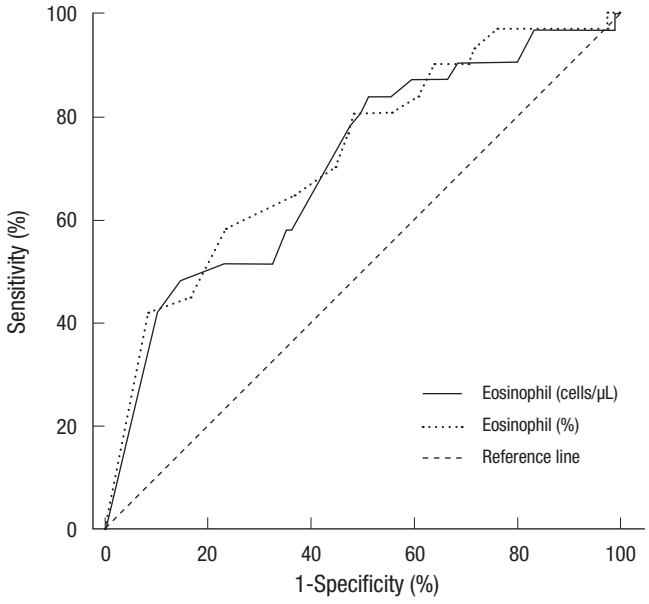

Fig. 1. Receiver operating curves (ROC) of eosinophil counts and eosinophil percentages used to distiguish survivors from non-survivors. The area under the curve is 0.705 for eosinophil count ($P < 0.001$) and 0.725 for eosinophil percentage ($P < 0.001$).

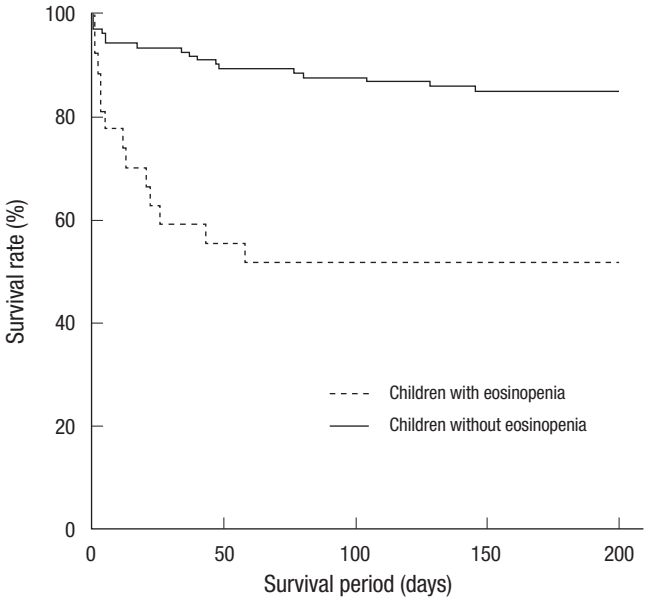

Fig. 2. Survival curves for the children with eosinopenia and without eosinopenia. The eosinopenia was defined by an eosinophil count < 15 cells/μL and an eosinophil percentage < 0.25% ($P < 0.001$ by log-rank test).

eosinophil percentage taken at the time of ICU admission. The areas under the ROC curves of the eosinophil count and eosinophil percentage used to distinguish between the survivor and non-survivor groups were 0.705 ($P < 0.001$) and 0.725 ($P < 0.001$), respectively (Fig. 1). The best eosinophil count and eosinophil percentage cutoff values were 15 cells/μL and 0.25%, respectively. At the cutoff of 15 cells/μL, the sensitivity of the eosinophil count was 48.4%, the specificity was 84.9%, and the AUC was 0.667. At the cutoff of 0.25%, the sensitivity of the eosinophil percentage was 58.1%, the specificity was 76.5%, and the AUC was 0.673. When we considered both the eosinophil count and percentage together, both the specificity and the AUC increased to 92.4% and 0.732, respectively, while the sensitivity remained at 58.1%.

Since the platelet count at the time of ICU admission was significantly lower in non-survivors than in survivors, we also generated a ROC curve for the platelet count. We determined that the best cutoff value for platelet count (90×10^3/μL) resulted in an AUC of 0.614, with a sensitivity of 38.7% and a specificity of 84.0%.

At ICU admission, the children with eosinopenia (eosinophil count < 15 cells/μL and an eosinophil percentage < 0.25%) had a significantly lower survival rate, as determined by the log-rank test and the Kaplan-Meier survival curves ($P < 0.001$) (Fig. 2). Univariate analysis utilizing the Cox regression model revealed that eosinopenia (HR, 4.34; $P < 0.001$), PRISM III (HR, 1.13; $P < 0.001$), PIM 2 (HR, 1.03; $P < 0.001$), PELOD (HR, 1.08; $P < 0.001$), mechanical ventilator (HR, 2.03; $P = 0.084$), and platelet count $< 90 \times 10^3$/μL (HR, 2.93; $P = 0.004$) were correlated with ICU mortality. In multivariate analysis, only eosinopenia (HR, 2.96; $P = 0.008$) and PIM 2 (HR, 1.03; $P = 0.004$) were found to be independent predictors of ICU mortality (Table 3).

Table 3. Multivariate analysis using Cox model of prognosis markers of mortality in the PICU

Variables	Hazard ratio	95% Confidence interval	*P* value
Eosinopenia	2.96	1.33-6.61	0.008
PRISM III score	1.04	0.97-1.12	0.225
PIM 2 score	1.03	1.01-1.04	0.004
PELOD score	0.99	0.94-1.05	0.835
Mechanical ventilation	1.65	0.63-4.31	0.310
Platelet $< 90 \times 10^3$/μL	1.99	0.89-4.46	0.096

PICU, pediatric intensive care unit; PRISM, pediatric risk of mortality; PIM, pediatric index of mortality; PELOD, pediatric logistic organ dysfunction.

DISCUSSION

This is the first study to assess eosinopenia at the time of ICU admission as a prognostic biomarker in children. This study suggests that, along with PIM 2, eosinopenia is a reliable marker that is able to predict ICU mortality in children. However, it was not found to be valuable in diagnosing infection at PICU admission.

A prognostic biomarker of mortality is currently needed because the prediction of mortality would enable physicians to make better treatment decisions (9). Until now, the most acceptable way to predict mortality in the ICU is through the use of a composite scoring system that consists of mainly physiologic variables. In the PICU, PRISM III and PIM 2 are frequently used as scoring systems to predict the severity of illness at the time of

ICU admission, while PELOD is used for serial measurements during the length of the ICU stay (2). In this study, the utility of the PICU mortality score in predicting ICU mortality was verified. Specifically, PIM 2 was an independent predictor even after adjustment for other factors (Table 3).

Thrombocytopenia has been accepted as a useful prognostic factor in children as well as in adults, which was further supported in our study (18). Thrombocytopenia serves as a reasonable predictor of mortality both because it develops from a seriously impaired condition and it may lead to a more severe situation, such as increased bleeding and transfusion requirements (18, 19).

Our study demonstrated that eosinophil counts and eosinophil percentages were significantly lower in non-surviving children, which is similar to prior studies performed in adults (10, 11). While the most acceptable cutoff for the eosinophil count in adults as a predictor of mortality is 40-50 cells/μL (10, 11, 20), our study suggested a lower level of 15 cells/μL in pediatric patients. This lower value can potentially be explained by either the greater vulnerability of children during severe inflammation and stress or the greater proportion of children who were medical, rather than surgical, ICU patients (medical vs surgical patients: 144 [95%] vs 6 [5%]) (21).

While most studies addressed only absolute eosinophil count (10, 11), our study evaluated both eosinophil count and percentage. When the eosinophil count and percentage were considered together, the predictive power for ICU mortality increased, with higher values for both the specificity and the AUC. Considering the fact that specificity might be more informative than sensitivity for the prediction of mortality (9), this combination may be more reasonable. The children with eosinopenia who had an eosinophil count < 15 cells/μL and an eosinophil percentage $< 0.25\%$ had a lower rate of survival (Fig. 2). Eosinopenia increased the risk of mortality by a HR of 2.96 according to multivariate analysis using a Cox regression model (Table 3).

Eosinopenia has been studied as an infection biomarker. However, our study showed that it was not useful in the prediction of infection status. The median eosinophil count and eosinophil percentage were lower in the infection group than in the non-infection group, but the difference was not statistically significant (Table 2). There are several studies that illustrate the value of eosinopenia in children suffering from infectious diseases, while another study concluded that eosinopenia was of limited use as a biomarker in pediatric patients with infections (22-24). On the other hand, eosinopenia has been consistently considered a useful diagnostic marker of infection in adults (25, 26). The greater ambiguity in the signs and symptoms of infection in children might contribute to the difference seen between adults and children. A shorter prodrome in children, which may not be long enough to decrease the level of eosinophils, can also explain this difference (24).

Eosinopenia is more representative of mortality than of an infection because it can develop from acute infection or acute, severe stress, both of which are strongly correlated with mortality (12, 13, 15). Infection is known to be the most common cause of ICU mortality (12). However, infection status alone is not enough to predict ICU mortality. Recently, many clinics have been trying to initially control infection, emphasizing early antimicrobial therapy (27). The study at our center demonstrated that there was no difference in the survival rate or pediatric mortality scores based upon the infectious status (Table 2). Nonetheless, the children with infections had longer ICU courses than the children without infections amongst the surviving cases. Although infection status may not directly relate to ICU mortality, it can affect the clinical course in the ICU.

The limitations of this study should be considered. First, this was a single-center study, which excluded infant and cardiac cases and included limited surgical cases. Therefore, our conclusions cannot be generalized to all PICU patients. Second, we should have evaluated the serial change in eosinophil counts and percentages for a certain period of time after ICU admission. Since many of the children were treated with systemic corticosteroids after ICU admission, we were unable to evaluate serial changes. Third, the infection group was defined according to the International Pediatric Sepsis Consensus Conference in our study, while it was classified as sepsis or bloodstream infection in most other studies (17, 24-26). Because sepsis is a SIRS associated with an infection, it can induce a more severe systemic inflammation than infection without SIRS. Thus, the level of eosinopenia in our study might have been underestimated.

In conclusion, eosinopenia in the PICU can be useful as a mortality biomarker, but not as an infection biomarker. Eosinopenia (eosinophil count < 15 cells/μL and eosinophil percentage $< 0.25\%$) can increase the risk of ICU mortality in children and may help ICU pediatricians determine the right treatment plan, in conjunction with other pediatric mortality scoring systems.

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The authors have no conflicts of interest to disclose.

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