Eosinophil Count and Neutrophil-to-Lymphocyte Count Ratio as Biomarkers for Prediction of Early-onset Neonatal Sepsis

(Running title: Eosinophil Count and Neutrophil-to-Lymphocyte Count Ratio for Early-onset Neonatal sepsis)

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Despite advances in neonatal intensive care, sepsis is still a major causes of neonatal death and morbidity. Culture-confirmed early-onset neonatal sepsis (EONS) that is defined as occurring within 48-72 hours after birth, is diagnosed 0.4 to 0.8 per 1000 live-born term infants through culture study in developed countries. However, the use of systemic antibiotics in infants with culture-negative EONS has been reported to be 6- to 16-times higher than that in infants with culture-confirmed EONS.

Many biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), and interleukins have been used to identify infants with sepsis and in clinical decision-making for their management. CRP is a widely used biomarker in clinical setting and extensively studied in research for newborn infants, although it is highly nonspecific as it has been reported to increase up to 40-50 mg/L in infants who are born via vaginal delivery. PCT, a promising biomarker for sepsis in newborn infants, has the advantage of not being affected by maternal fever during labor because of its inability to cross the placenta. However, few studies have reported the clinical usefulness of PCT for early diagnosis of EONS.

Eosinopenia, a historical biomarker for infection, has been investigated to differentiate sepsis with non-infectious condition in some studies. Shaaban et al. reported that eosinopenia <50 cells/mm$^3$ showed a sensitivity of 81%, a specificity of 65%, a positive predictive value (PPV) of 66%, and a negative predictive value (NPV) of 80% for predicting sepsis in adults and concluded that eosinopenia is a very sensitive but not specific marker of sepsis in the intensive care setting. Wibrow et al. reported that eosinophil counts had very little overall predictive ability (area under receiver operating characteristic curve [AUROC] 0.448, 95% confidence interval [CI]: 0.363-0.533, P = 0.237) for sepsis, while sensitivity (54%, 95% CI: 47-61%) and specificity (56%, 95% CI: 49-63) of eosinopenia <10/mm$^3$ to predict bloodstream infection in pediatric patients were both low.
The neutrophil to lymphocyte count ratio (NLCR), a simple marker of inflammation, has been considered useful to many diseases including sepsis in adults. Dursun et al.\textsuperscript{8}) reported that NLCR had a sensitivity of 75.6%, a specificity of 38.4%, a PPV of 35.6%, and a NPV of 77.8\% to predict sepsis in children. Westerdijk et al.\textsuperscript{9}) reported that the NLCR in adults with sepsis was significantly higher than in those without sepsis (15.3\{10.8-38.2\} (median [25-75%]) vs. 9.3 [6.2-14.5]; \textit{P}<0.001) but AUROC was significantly higher for CRP (0.89, 95\% CI: 0.87-0.92) and PCT (0.88, 95\% CI: 0.86-0.91) than NLCR (0.66, 95\% CI: 0.62-0.71).

Recently, the study evaluating the diagnostic value of eosinopenia and the NLCR as biomarkers of EONS indicated that eosinopenia of <140 cells/mm\(^3\) had a sensitivity of 60.0\%, a specificity of 90.0\%, a PPV of 94.7\% and a NPV of 42.9\% while a NLCR with a 1.245 cutoff value had a sensitivity of 83.3\%, a specificity of 93.3\%, a PPV of 94.7\% and a NPV of 65.2\%.\textsuperscript{10}) However, this study should be interpreted with caution in some aspect. First, bacteria were identified only in 20% (18/90) of patients in EONS group, which differs from the diagnostic criteria for EONS, whereby EONS is defined exclusively by culture-positive cases in many developed countries. Second, this study did not compare basic patient characteristics including perinatal factors for the EONS and non-EONS groups. In addition, this study excluded infants with neonatal respiratory diseases such as respiratory distress syndrome, transient tachypnea of the newborn and congenital pneumonia, and included only a small number of preterm infants in the study population.

In conclusion, further study of the clinical utility of eosinopenia and the NLCR as early biomarkers of EONS should be performed focusing on invasive bacterial infections leading to critical status and therapeutic decision-making strategy.
References


10. Wilar R. Diagnostic Value of Eosinopenia and Neutrophil to Lymphocyte Ratio on Early