

Can venous cord blood neutrophil to lymphocyte ratio and platelet to lymphocyte ratio predict early-onset sepsis in preterm infants?

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Background: To explore the predictive value of venous cord blood neutrophil-to-lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) for Early-onset sepsis (EOS) in preterm infants. **Methods:** A prospective cohort of neonates with gestational ages <32 weeks in a single hospital from January 2017 to January 2020 were enrolled. Multivariable logistic regression was used to determine independent risk factors for EOS. ROC curves were created to estimate the predictive capacity. **Results:** A total of 427 neonates were included in the study. 176 neonates were exposed to chorioamnionitis including 89 EOS and 87 without EOS, and the venous cord blood white blood cell (WBC), (neutrophil) N, (platelet) P, NLR and PLR in the EOS infants were significantly increased. 251 infants were unexposed to chorioamnionitis including 63 EOS and 188 without EOS, and N and NLR were significantly increased in EOS infants. After adjustment for covariates, multivariable logistic regression analysis demonstrated high NLR was independently associated with the subsequent risk of EOS in the infants both exposed and unexposed to chorioamnionitis. The most accurate discriminatory NLR for EOS threshold in infants exposed to chorioamnionitis was 2.68 (AUC = 0.949, sensitivity = 0.839, specificity = 0.933). The most accurate discriminatory NLR for EOS threshold in infants unexposed to chorioamnionitis was 2.01 (AUC = 0.852, sensitivity = 0.830, specificity = 0.762). The cutoff value of the PLR for predicting EOS in the preterm infants exposed to chorioamnionitis was 55.051, the sensitivity was 82%, the specificity was 36.7%, and the AUC was 0.579. **Conclusions:** Venous cord blood NLR seems to be an early, sensitive and convenient marker for preterm infants with EOS, especially in those exposed to chorioamnionitis. Meanwhile, venous cord blood PLR is not an accurate predictor of EOS in preterm infants.

Keywords

Venous cord blood; Early-onset sepsis; Preterm infants; Chorioamnionitis; Neutrophil to lymphocyte ratio; Platelet to lymphocyte ratio

1. Introduction

Neonatal sepsis is one of the major causes of morbidity and mortality worldwide. It is estimated that about 22 per 1000 live births develop neonatal sepsis, and the mortality rate is between 11% and 19% [1]. Neonatal sepsis is divided into

early-onset sepsis (EOS) and late-onset sepsis (LOS) according to the time of symptom onset. Based on National Institute of Child Health and Human Development (NICHD) Neonatal Research Network [2], the definition of neonatal proven EOS is bacterial and fungal pathogens cultured from blood or cerebrospinal fluid (CSF) within 72 hours after birth. EOS, affects 0.98 infections per 1000 live births [3], and with an incidence around of 17 per 1000 live births of infants 401–1500 g [2]. EOS is often associated with serious and long-term complications, including bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), neurodevelopmental impairments, and death [4]. However, making a definitive diagnosis is a challenge, especially in preterm babies, because the clinical signs are often unreliable. Blood or CSF bacterial culture may be delayed and early biological markers are not sensitive or specific. Meanwhile, prophylactic antibiotics were used in most premature babies after birth even if the babies are at low risk for EOS. This may result in substantial antibiotic overtreatment, which leads to a dramatic increase in the emergence of antibiotic-resistant bacteria, an increased risk of LOS, NEC and long-term adverse consequences [5].

Chorioamnionitis is a common complication in pregnancy and is strongly linked to preterm birth and EOS. However, studies found strictly following the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics' Committee on the Fetus and Newborn (COFN) guidelines for management of neonates born to mothers with clinical chorioamnionitis leads to the overtreatment of many uninfected infants [6, 7]. In an attempt to accurately and rapidly diagnose EOS in preterm infants born to mothers with or without chorioamnionitis, and decrease the use of empiric antibiotics, it is essential to seek earlier, more reliable indicators to predict EOS.

In recent years, studies demonstrated that combining neutrophils and lymphocytes or platelet and lymphocytes rather than the absolute counts may be clinically useful. The neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) are

phocyte ratio (PLR), have been considered as useful systemic inflammatory markers and prognostic indicators in EOS of term neonates [8], as well as in various diseases of adult such as pneumonia [9], coronavirus disease-19 [10], appendicitis [11], cancers [12, 13] and cardiovascular diseases [14, 15]. In the previous study, we also found that NLR at 72 hours after birth could be as an early significant predictor of BPD in infants at gestational age <32 weeks [16].

Detection of biological markers from cord blood is an early, non-invasive, and inexpensive approach, however, to date, no prospective study has specifically assessed cord blood NLR and PLR as early markers of EOS in preterm infants. The primary objective of this research was to evaluate the predictive value of the NLR and the PLR in venous cord blood for EOS in preterm infants whether or not exposed to chorioamnionitis.

2. Methods

2.1 Study population

A prospective, observational study was performed to evaluate newborns born at gestational age <32 weeks in a single hospital from January 2017 to January 2020. Consistent with the World Medical Association Declaration of Helsinki, this study was approved by the Medical Ethics Committee of Yiwu Maternity and Children Hospital (No. 0000033). Informed consent was obtained from the parents of each enrolled newborn. The study process is described in Fig. 1. Exclusion criteria included complex congenital heart disease, congenital gastrointestinal malformation, genetic abnormality, congenital metabolic diseases, and insufficient plasma quantity to measure complete blood count (CBC). 9 preterm infants were excluded in the 436 initially enrolled babies.

2.2 Laboratory measurements

Blood samples were obtained from umbilical venous blood at the time of delivery. Blood samples were taken into standardized vacuum tubes containing dipotassium ethylene dinitro tetraacetic acid (EDTA) for CBC analysis by UniCel DxH 800 (Beckman coulter Inc., Hialeah, FL, USA). The NLR was calculated as the absolute neutrophil (N) count divided by the absolute lymphocyte (L) count. The PLR was calculated as the absolute Platelet (P) count divided by the absolute L count.

2.3 Data collection

Data on the following were recorded: the information of maternal pregnancy and delivery, infant outcome from birth until death, hospital discharge or transfer, or six months after birth, whichever occurred first. Variables included maternal age, maternal complications, vaginitis, antenatal antibiotics, antenatal corticosteroids, preterm premature rupture of membranes more than 18 hours, chorioamnionitis, vaginal delivery, birth weight, gestational age, sex, delivery room resuscitation, Apgar scores, newborn respiratory distress syndrome (NRDS), BPD, duration of NICU stay, and other comorbidities. Histopathological chorioamnionitis

was recorded if chorioamnionitis was noted on the placental pathology report, and the definition was according with the Stillbirth Collaborative Research Network Pathology Protocol [17]. Clinical chorioamnionitis [18] was recorded as clinical signal (typically characterized by 2 or more) of maternal fever, uterine tenderness, malodorous amniotic fluid, maternal or fetal tachycardia, or evidence of maternal leukocytosis $\geq 15 \times 10^9/L$, or C-reactive protein (CRP) $>8 \text{ mg/L}$. The cases were excluded if clinical chorioamnionitis was noted without histopathological confirmation.

2.4 EOS classification

To date, there is no unified definition of neonatal sepsis [19]. The definition of proven EOS in most neonatal research and surveillance networks is as follows [2]: within the first 72 hours of life, the neonate presented clinical and laboratory signs of sepsis, with a positive blood or CSF bacterial culture. Due to the low positive rate of bacterial culture, the neonate who were considered to have clinical EOS would receive antibiotic treatment. The neonate who presented with clinical signs (≥ 2 items) and laboratory signs (≥ 2 items) with a negative blood or CSF culture, not otherwise explained by prematurity and pregnancy induced hypertension, was defined as clinical EOS [20]. Clinical signs including: (a) respiratory symptoms (apnea, tachypnea, respiratory distress, increased oxygen requirements or need for ventilation support); (b) GI symptoms (abdominal distension, bloody stool); (c) cardiac symptoms (bradycardia [heart rate $<100/\text{minute}$], tachycardia [heart rate $>180/\text{minute}$], hypotension); (d) neurological symptoms (irritability, lethargy, seizures); (e) unstable temperature (rectal $<36.0 \text{ }^\circ\text{C}$ or $>38.0 \text{ }^\circ\text{C}$); and (f) poor peripheral circulation or prolonged capillary refilling time (>3 seconds). Laboratory signs at 12–24 hours of life including: (a) leukopenia $<5000 \times 10^9 \text{ cells/L}$ or hyperleukocytosis $>21,000 \times 10^9 \text{ cells/L}$; (b) Immature to total neutrophil ratio (I/T) greater than 0.2; (c) Thrombocytopenia $<100,000 \times 10^9 \text{ cells/L}$; (d) CRP $>10 \text{ mg/L}$ or PCT $\geq 2 \text{ ng/mL}$.

2.5 Statistical analysis

Statistical analyses were performed using the statistical package SPSS for Windows version 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as the mean \pm SD or medians (interquartile range: 1st quartile–3rd quartile) and categorical variables were expressed as frequencies (percentages). The independent sample *t*-test or Kruskal-Wallis test was used for continuous variables. The Pearson χ^2 test or Fisher's exact test was applied to analyze categorical variables. Multivariable logistic regression analysis was performed to determine the effect of cord blood parameters on the risk of EOS. Additionally, an area under the receiver-operating characteristic (ROC) curve was assessed to determine the best cutoff value, sensitivity and specificity of the cord blood parameters in predicting EOS in preterm infants. Statistical significance was defined as a *P* value < 0.05 .

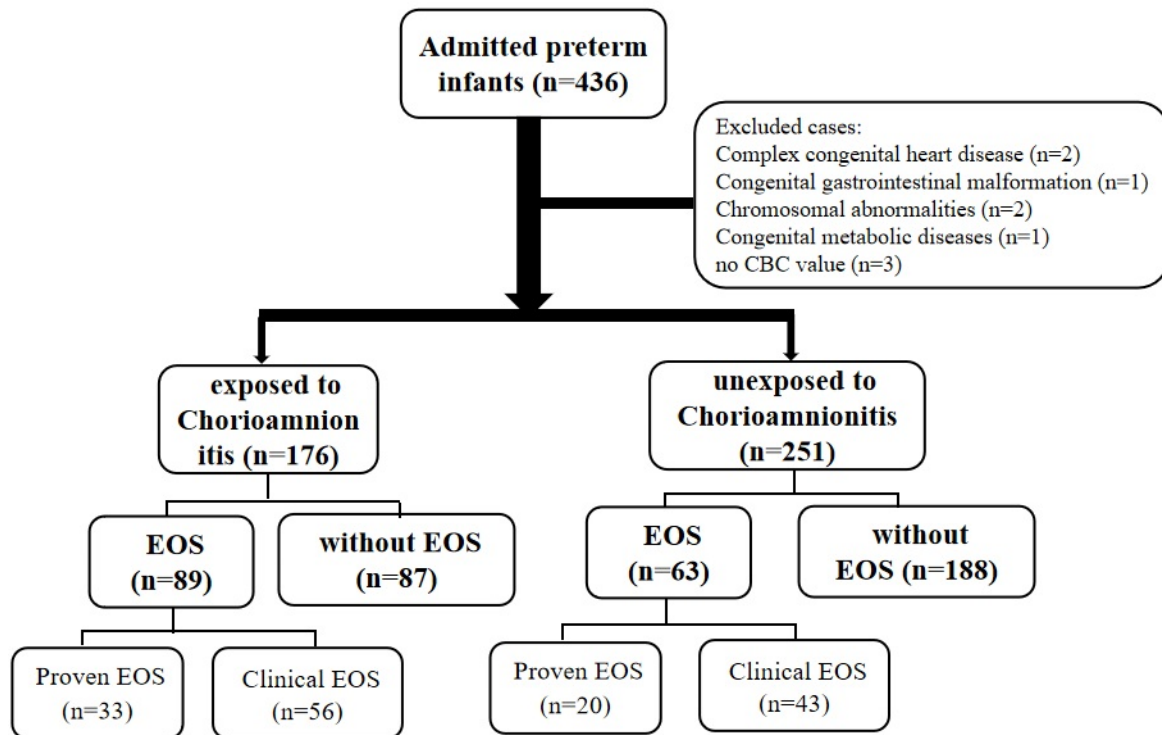


Fig. 1. Flowchart of the study process.

3. Results

3.1 Patients characteristics

Baseline demographic and clinical characteristics of patients were summarized in Table 1. Neonates exposed to chorioamnionitis had lower gestational age and higher rates of EOS. Of the admitted 427 preterm infants, 176 exposed to chorioamnionitis including 89 EOS and 87 without EOS, and 251 unexposed to chorioamnionitis including 63 EOS and 188 without EOS. Among the preterm infants with EOS, 53 (34.86%) patients had positive blood or CSF cultures: *Escherichia coli* (11 patients), *Klebsiella pneumoniae* (9 patients), *Streptococcus agalactiae* (10 patients), *Enterobacter cloacae* (5 patients), *Staphylococcus epidermidis* (5 patients), and *Staphylococcus warneri* (3 patients), other *Streptococcus* (4 patients), other *Gram-negative bacilli* (6 patients). The infants with EOS had lower gestational age and birthweight than those without EOS. Preterm infants born to a mother with vaginitis and vaginal delivery had increased rates of EOS in the chorioamnionitis group. The infants with EOS had higher risk for newborn respiratory distress syndrome (NRDS), BPD, NEC and longer days of intravenous nutrition therapy and duration of NICU stay in the exposed to chorioamnionitis group.

3.2 Cord blood parameters and EOS

Comparison of cord blood parameters from CBC between the EOS group and the without EOS group was summarized in Table 2. Of the preterm infants exposed to chorioamnionitis, relative to the without EOS group, the cord blood white blood cell (WBC) (17.47 ± 8.20 vs 13.35 ± 6.71 , $P =$

0.003), N (10.71 ± 8.59 vs 3.21 ± 2.32 , $P = 0.000$), P (221.87 ± 81.31 vs 186.18 ± 59.69 , $P = 0.009$), NLR (4.65 ± 2.36 vs 1.33 ± 0.98 , $P = 0.000$) and PLR (93.17 ± 57.60 vs 78.58 ± 44.00 , $P = 0.021$) in the EOS group were increased significantly. Of the preterm infants unexposed to chorioamnionitis, relative to the without EOS group, N (7.85 ± 4.09 vs 4.66 ± 4.14 , $P = 0.011$) and NLR (2.94 ± 2.0 vs 1.68 ± 1.14 , $P = 0.007$) were significantly increased. There is no significant difference of PLR between EOS and without EOS group in the preterm infants unexposed to chorioamnionitis. However, the differences in values of WBC, N and P remained within the normal range for preterm infants.

3.3 Cord blood NLR to predict EOS

After adjustment for covariates, multivariable logistic regression analysis demonstrated high cord blood NLR was independently associated with the subsequent risk of EOS in the preterm infants with (OR = 3.843 [95% CI: 2.173–6.797]; $P = 0.000$) or without (OR = 1.221 [95% CI: 1.074–1.387]; $P = 0.002$) maternal chorioamnionitis.

In order to evaluate the ability of cord blood parameters to predict the EOS of prematurity, we constructed ROC curves and obtained the sensitivities, specificities and thresholds. The ROC curves were displayed in Figs. 2,3. Of the preterm infants exposed to chorioamnionitis, the most accurate discriminatory cord blood NLR for EOS threshold was 2.68 (AUC = 0.949, sensitivity = 0.839, specificity = 0.933). Of the preterm infants unexposed to chorioamnionitis, the most accurate discriminatory cord blood NLR for EOS threshold was

Table 1. Baseline demographic and clinical characteristics of study population.

	Exposed to chorioamnionitis (n = 176)		P	Unexposed to chorioamnionitis (n = 251)		P
	EOS (n = 89)	without EOS (n = 87)		EOS (n = 63)	without EOS (n = 188)	
Male, N (%)	49 (55.1)	52 (59.8)	0.064	43 (68.3)	100 (53.2)	0.080
Gestational age (weeks)						
Median (IQR)	27.78 (26.82, 28.57)	29.29 (28.86, 29.57)	0.000*	30.43 (30.14, 31)	31.29 (30.57, 31.71)	0.000*
Min, max	24.43, 29.71	27.00, 29.71		29.86, 31.71	29.86, 31.86	
Birthweight (grams)	1036.29 ± 204.09	1289.75 ± 184.68	0.000*	1376.98 ± 267.76	1626.04 ± 246.09	0.000*
Maternal age (years)	30.96 ± 4.58	29.59 ± 5.53	0.135	29.14 ± 4.56	30.67 ± 4.70	0.061
Antenatal antibiotics exposure, N (%)	122 (69.3)	65 (74.7)	0.453	10 (15.9)	42 (22.3)	0.331
Vaginitis, N (%)	53 (59.5)	26 (29.9)	0.038*	15 (23.8)	37 (19.6)	0.060
Prolonged rupture of membranes >18 h, N (%)	30 (33.7)	31 (35.6)	0.799	21 (33.3)	59 (31.4)	0.754
Hypertensive disorders in pregnancy, N (%)	6 (6.7)	8 (9.2)	0.492	4 (6.3)	15 (8.0)	0.331
preeclampsia	3 (3.4)	5 (5.7)	0.491	3 (4.8)	9 (4.8)	0.647
Gestational diabetes mellitus, N (%)	22 (24.7)	19 (21.8)	0.557	13 (20.6)	42 (22.3)	0.581
Multiple pregnancy, N (%)	34 (38.2)	34 (39.1)	0.942	21 (33.3)	66 (35.1)	0.604
IVF, N (%)	41 (46.1)	30 (34.5)	0.163	20 (31.7)	70 (37.2)	0.498
Vaginal delivery, N (%)	53 (59.6)	30 (34.5)	0.038*	34 (53.9)	79 (42.1)	0.109
Apgar score at 1 min <7, N (%)	44 (49.4)	35 (40.2)	0.315	16 (25.4)	52 (27.7)	0.708
Apgar score at 5 min <7, N (%)	8 (8.9)	43 (4.9)	0.054	3 (4.8)	66 (3.5)	0.651
NRDS, N (%)	80 (89.9)	60 (68.9)	0.017*	39 (61.9)	74 (39.4)	0.012*
BPD, N (%)	66 (74.2)	35 (40.2)	0.000*	26 (41.3)	74 (39.3)	0.130
PDA, N (%)	22 (24.7%)	13 (14.9)	0.104	8 (12.7%)	17 (9.0%)	0.269
NEC, N (%)	8 (9.0%)	2 (2.3%)	0.031*	5 (7.9%)	3 (1.6%)	0.026*
IVH, N (%)	9 (10.1%)	3 (3.4%)	0.132	6 (9.5%)	16 (8.5%)	0.490
CPL, N (%)	2 (2.2%)	1 (1.1%)	0.509	1 (1.6%)	0	-
ROP, N (%)	9 (10.1%)	4 (4.6%)	0.133	3 (4.8%)	2 (1.1%)	0.102
mortality, N (%)	3 (3.4%)	2 (2.3%)	0.511	2 (3.2%)	1 (0.5%)	0.156
Intravenous nutrition therapy (d)	23.92 ± 11.32	18.21 ± 11.84	0.007*	20.71 ± 10.26	18.02 ± 10.75	0.147
duration of NICU stay (d)	66.05 ± 22.56	51.08 ± 21.53	0.000*	52.64 ± 19.60	48.55 ± 18.76	0.219

Continuous variables are expressed as mean ± SD, median with interquartile range or count with percentage, as appropriate. * $P < 0.05$. BPD, Bronchopulmonary dysplasia; CPL, cystic periventricular leukomalacia; IVF, In vitro fertilization; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRDS, newborn respiratory distress syndrome; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

2.01 (AUC = 0.852, sensitivity = 0.830, specificity = 0.762). The cutoff value of the PLR for predicting EOS in the preterm infants exposed to chorioamnionitis was 55.051, the sensitivity was 82%, the specificity was 36.7%, and the AUC was 0.579.

4. Discussion

EOS is a serious and potentially life-threatening disease in preterm infants. Early diagnosis and therapy are crucial to prevent morbidity and mortality. Chorioamnionitis is a major risk factor for EOS. Neonates exposed to chorioamnionitis had a lower gestational age and higher rates of EOS compared with unexposed neonates in our study. However, the 49.4% (87/176) of the preterm infants exposed to chorioamnionitis were still without EOS. Studies have showed that the risk of EOS is significantly decreased with the use of intrapartum antibiotics [21, 22]. Furthermore, empiric antibiotic use in newborns may alter the microbiome in gut, increasing the risk of LOS, and autoimmune disorders [5, 21].

Neutrophils are activated first during inflammation because they are the first cellular defense of the natural im-

mune system, whereas lymphocytes are the primary cells of the adaptive immune system. Bacterial infection leads to a raise of the total leukocyte and neutrophil counts, which quickly migrate to the influenced region. Meanwhile, neutrophils play an active role in phagocytosis, release of cytokine, and T-cell activation, resulting in an inflammatory reaction [23]. In the present study, we found WBC and N increased in EOS patients compared to that without EOS when exposed to chorioamnionitis. The N also increased significantly in EOS patients when unexposed to chorioamnionitis. However, the differences in values of WBC and N remained within the normal range for preterm infants. There was no difference in L between preterm infants with and without EOS. Additionally, we found cord blood N had the capacity to predict BPD, performing better in the preterm infants with chorioamnionitis.

The NLR, combining neutrophils and lymphocytes in the calculation, is suggested to be more useful than the absolute counts. In recent years, the NLR has been reported as a widely available marker and prognostic indicator of inflammatory diseases. NLR increases as a consequence of sever-

Table 2. Cord blood parameters from CBC between the EOS group and the without EOS group.

	Exposed to chorioamnionitis (n = 176)		P	Unexposed to chorioamnionitis (n = 251)		P
	EOS (n = 89)	without EOS (n = 87)		EOS (n = 63)	without EOS (n = 188)	
WBC, 10 ⁹ /L	17.47 ± 8.2	13.35 ± 6.71	0.003*	11.95 ± 5.36	11.51 ± 6.31	0.671
N, 10 ⁹ /L	10.71 ± 8.59	3.21 ± 2.32	0.000*	7.85 ± 4.09	4.66 ± 4.14	0.011*
L, 10 ⁹ /L	3.11 ± 2.85	2.85 ± 1.44	0.091	3.21 ± 1.33	3.36 ± 1.21	0.508
P, 10 ⁹ /L	221.87 ± 81.31	186.18 ± 59.69	0.009*	254.55 ± 54.34	236.78 ± 60.13	0.085
NLR	4.65 ± 2.36	1.33 ± 0.00	0.000*	2.94 ± 2.0	1.68 ± 1.14	0.007*
PLR	93.17 ± 57.60	78.58 ± 44.00	0.021*	94.67 ± 47.40	81.16 ± 55.52	0.151

Continuous variables are expressed as mean ± SD. L, lymphocytes; N, neutrophils; NLR, neutrophil to lymphocyte ratio; P, platelets; PLR, platelet-to-lymphocyte ratio; WBC, white Blood Cell. *P < 0.05.

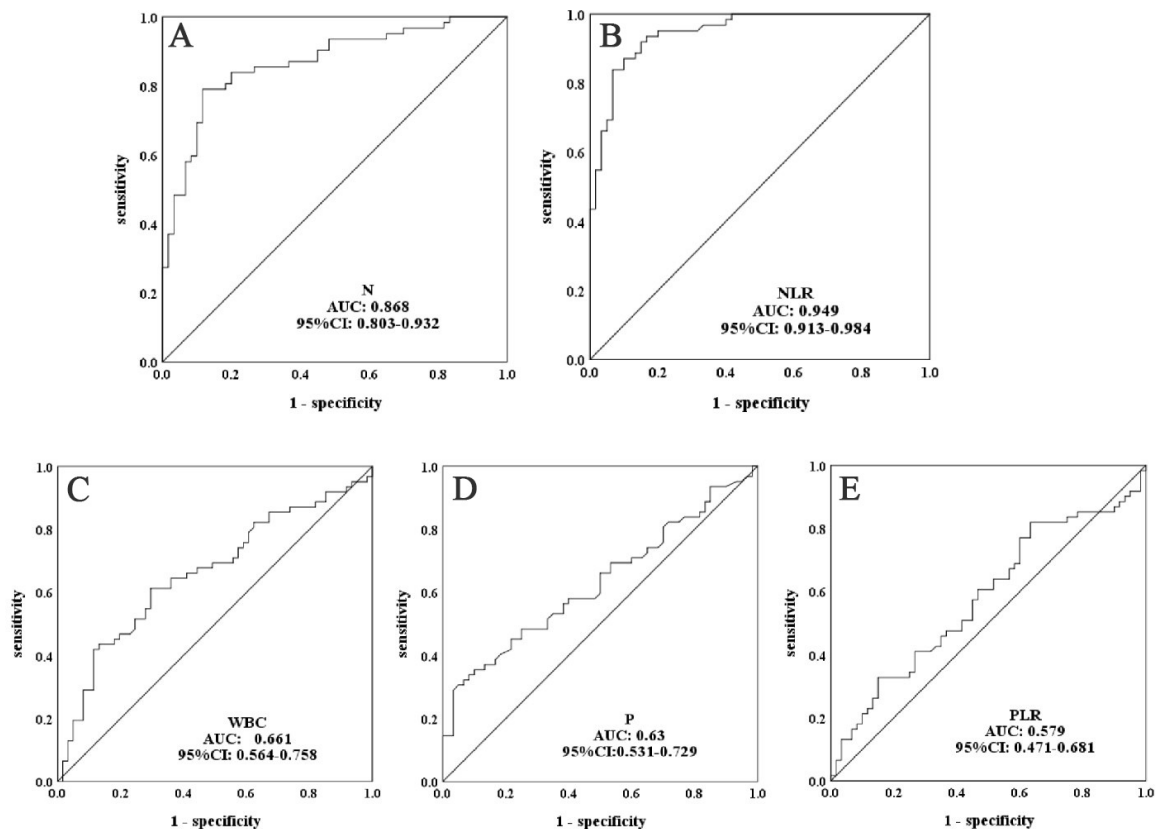


Fig. 2. The ROC curves of venous cord blood parameters for the prediction of EOS in the preterm infants exposed to chorioamnionitis. (A) The ROC curves of N. (B) The ROC curves of NLR. (C) The ROC curves of WBC. (D) The ROC curves of P. (E) The ROC curves of PLR.

ity of clinical status and clinical outcomes such as exacerbation and mortality of COPD [24], 30-day mortality in elderly adults with community-acquired pneumonia [9]. In the research of neonates, Alkan *et al.* [25] found that the prediction of NLR was more effective than CRP in detecting culture-proven LOS in preterm infants with birth weights ≤ 1500 g and/or ≤ 32 gestational weeks. Can *et al.* [8] suggested that there was a positive association between NLR and EOS in term neonates, and the predictive cutoff value of NLR was 6.76. In our study, preterm infants with EOS had higher venous cord blood NLR than those without EOS, regardless of exposure to chorioamnionitis. The AUC of the NLR (0.949) in preterm infants with chorioamnionitis was significantly

higher than those without chorioamnionitis. Therefore, the venous cord blood NLR performed more accurately for BPD in the preterm infants with chorioamnionitis with threshold 2.68 (sensitivity = 0.839, specificity = 0.933).

Platelets are involved in many physiological and pathological functions as well as some of the platelet parameters associated with disease. Platelet count and average size may increase with inflammation and thromboembolism [26]. Sreeramkumar *et al.* [23] observed numerous interactions of platelets with the leading edge of adherent neutrophils in an inflammatory model, and demonstrated that recruited neutrophils scan for activated platelets to initiate inflammation in the early phase. Chen *et al.* [27] suggested that the platelets

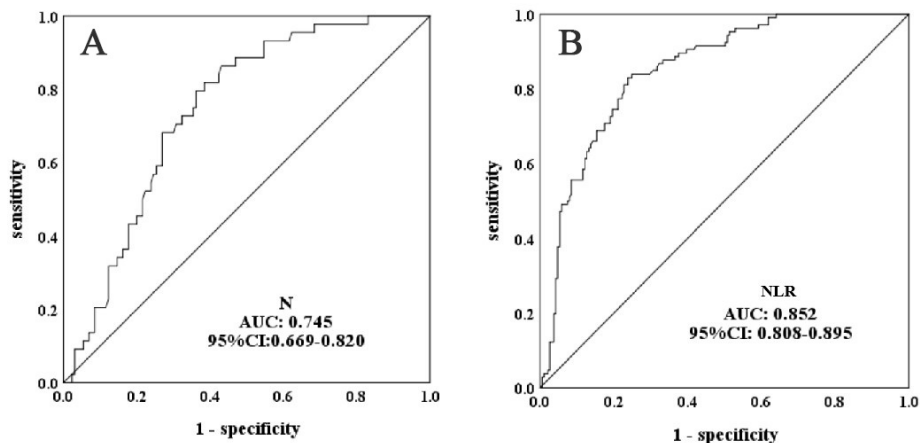


Fig. 3. The ROC curves of venous cord blood parameters for the prediction of EOS in the preterm infants unexposed to chorioamnionitis. (A) The ROC curves of N. (B) The ROC curves of NLR.

at birth were significantly higher in extremely premature infants developing moderate-severe BPD. We also found the P increased in EOS patients compared to that without EOS when exposed to chorioamnionitis. However, the differences in value of P remained within the normal range for preterm infants.

Recently, PLR is reported as a significant marker revealing shifts in platelet and lymphocyte counts in inflammatory and prothrombotic disease. Studies demonstrated that the PLR as an inflammatory marker in evaluating and predicting the occurrence and prognosis of diseases such as COPD [24], cardiovascular diseases [14], rheumatic diseases [28], and coronavirus disease-19 [10]. Arcagok *et al.* [29] suggested that PLR can be used as a parameter in the prediction of EOS in term infants. In our study, preterm infants with EOS had higher venous cord blood PLR than those without EOS when born to maternal chorioamnionitis, but venous cord blood PLR is not an appropriate predictor of EOS in preterm infants with a low AUC in ROC analysis.

There are some limitations in this study. The potential for residual confounding could not be eliminated due to this being a single-center study. Larger numbers of subjects and multicenter studies are required to confirm the findings. Secondly, due to the limited number of cases, there was no comparison of the predictive value of indicators for proven EOS and clinical EOS, which needs further research.

To summarize, the venous cord blood NLR demonstrated strong association with EOS in regression analyses and demonstrated high AUC, sensitivity and specificity in ROC analysis. This seems to be an early, sensitive and convenient marker for identification of EOS in preterm infants, especially in those with maternal chorioamnionitis. Therefore, distinguishing patients with EOS by increased venous cord blood NLR value could help guide antibiotic management decisions and reduce unnecessary antibiotic use. Meanwhile, venous cord blood PLR is not an appropriate predictor of EOS in preterm infants.

Author contributions

SJC and XXZ managed the experiments, analyzed the results. HXJ collected the data and analyzed the results. JHC collected the data. TFH analyzed the results. CEC designed the research study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee (Yiwu Maternity and Children, No. 0000033). Informed consent was obtained from the parents of each enrolled newborn.

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Conflict of interest

The authors declare no competing interests.

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