

Value of Immune-Inflammatory Markers Derived from complete blood count in Umbilical Cord for the Early Diagnosis of Early-Onset Sepsis Complicated with Purulent Meningitis in Preterm Infants: a single-center prospective study

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Research Article

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Abstract

Background

Neonatal purulent meningitis (NPM) remains one of the leading causes of adverse prognosis and death in neonates, especially preterm infants. Its early diagnosis is challenging because of its nonspecific clinical manifestations and extremely low positive rate of cerebrospinal fluid (CSF) culture.

Objective

To investigate the diagnostic value of inflammatory markers derived from complete blood count (CBC) in umbilical cord blood for early-onset sepsis (EOS) complicated with NPM in preterm infants.

Methods

A prospective nested case–control study was conducted. A total of 112 preterm infants with EOS admitted to the Department of Neonatology of the First People's Hospital of Zunyi from January 2022 to December 2025 were enrolled and divided into a meningitis group (31 patients) and a nonmeningitis group (81 patients) according to the presence of complicated purulent meningitis. Inflammatory markers derived from CBCs in umbilical cord blood, including the white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT), derived neutrophil-to-lymphocyte ratio (dNLR), monocyte-to-lymphocyte ratio (MLR), monocyte count + neutrophil count/lymphocyte count ratio (NMLR), systemic inflammatory response index (SIRI), systemic immune-inflammation index (SII), and neutrophil percentage were recorded for both groups. The Mann–Whitney U test, chi-square test or Fisher's exact test was used to compare the differences between the two groups, and receiver operating characteristic (ROC) curves were plotted to evaluate the predictive value of these indicators for EOS complicated with NPM in preterm infants.

Results

The WBC, NLR, dNLR, MLR, NMLR, SIRI and neutrophil percentage in the meningitis group were significantly greater than those in the nonmeningitis group, indicating that these indicators in umbilical cord blood have certain diagnostic value for EOS complicated with NPM in preterm infants. Among them, the MLR had the highest diagnostic efficiency, with an area under the curve (AUC) of 0.72, a sensitivity of 79% and a specificity of 58%.

Conclusion

The MLR in umbilical cord blood is highly expressed in preterm infants with EOS complicated with NPM and has a relatively high predictive value for this complication. The collection of umbilical cord blood is noninvasive and painless, which can largely compensate for the diagnostic delay of CSF detection. Moreover, WBC detection features mature technology, low cost and short time consumption and is expected to serve as a useful supplement for early diagnostic indicators of EOS complicated with NPM in preterm infants.

Trial registration Clinical trial number: not applicable.

Introduction

Neonatal purulent meningitis (NPM) refers to meningitis caused by bacterial infection during the neonatal period. Approximately 25% of neonates with sepsis develop this complication, with a mortality rate as high as 40%~58% in

developing countries. Some surviving infants even suffer from adverse neurological outcomes^[1-2], making NPM one of the major causes of poor prognosis and even death in neonates, especially preterm infants. Early diagnosis and timely anti-infective treatment are crucial for improving patient prognosis and reducing mortality and can also reduce the irrational use of antibiotics.

The clinical symptoms of NPM are highly atypical and nonspecific. The gold standard for diagnosing NPM is a positive CSF microbial culture, but its positive rate is extremely low^[3]. At present, diagnosis is still based on classic CSF parameters, which are affected by factors such as antibiotic use, traumatic puncture, intraventricular hemorrhage and the time of specimen submission^[4-5]. In addition, most preterm infants with EOS are in critical condition in the early postnatal period and cannot tolerate lumbar puncture, leading to a delay in CSF detection, thus making early diagnosis difficult. Therefore, exploring effective indicators for the early prediction of EOS complicated with NPM in preterm infants is highly important for reducing the incidence and improving the prognosis of NPM. This study aimed to investigate the diagnostic value of inflammatory markers derived from CBC in umbilical cord blood for EOS complicated with NPM in preterm infants.

1 Materials and methods

1.1 Data sources and grouping

A prospective nested case–control study was adopted. A total of 119 preterm infants with EOS admitted to the Department of Neonatology of our hospital from January 2022 to December 2025 were initially enrolled, and 7 cases were excluded (2 cases of methylmalonic acidemia, 1 case of congenital hyperinsulinaemia, and 4 cases of specimen haemolysis), with 112 cases ultimately included in the study. The infants were divided into a meningitis group (31 patients) and a nonmeningitis group (81 patients) according to whether the meningitis was complicated with purulent meningitis. Inflammatory markers derived from CBC in umbilical cord blood were recorded for both groups. There were no significant differences in the general data between the two groups ($P > 0.05$), indicating good comparability (Table 1).

Table 1
Comparison of the general data between the two groups

Group	n	Gender (n, male/female)	Gestational age (± s, weeks)	Birth weight [M(P25, P75), g]	Delivery mode (n, cesarean section/vaginal delivery)
Meningitis	31	20/11	31.43 ± 2.20	1450(1170, 2050)	29/2
Nonmeningitis	81	59/22	32.19 ± 2.67	1575(1300, 2040)	73/8
χ ² /t value		0.075	1.352	-	1.247
P value		0.787	0.179	0.713	0.681

1.2 Diagnostic criteria

1.2.1 Neonatal early-onset sepsis

According to the *Expert Consensus on the Diagnosis and Treatment of Neonatal Sepsis (2019 Edition)* [6], the diagnosis was made in the presence of abnormal clinical manifestations plus a positive blood or CSF culture or clinical symptoms combined with at least one of the following conditions: (1) ≥ 2 nonspecific blood indicators abnormal; (2) purulent meningitis confirmed by CSF examination; or (3) pathogenic bacterial DNA detected in blood.

1.2.2 Neonatal Purulent Meningitis [7]

Preterm infants with clinical manifestations of infection met at least one of the following indicators: $\square$ pathogens grown in CSF culture or gram-positive/gram-negative bacteria found in CSF smears; $\square$ CSF white blood cell count $\geq 20 \times 10^6/L$, polymorphonuclear cell ratio $> 0.57 \sim 0.61$, protein > 1.70 g/L, and glucose concentration < 2.2 mmol/L or lower than 40% of the blood glucose at that time.

1.3 Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) preterm infants with a definite diagnosis of EOS and (2) sufficient umbilical cord blood successfully collected with the informed consent of guardians. **The exclusion criteria were as follows:** (1) complicated with central nervous system malformations, grade III ~ IV intracranial hemorrhage, viral meningitis or genetic metabolic diseases; (2) normal routine and biochemical CSF examinations with suspected contaminating bacteria in CSF culture; and (3) unreliable test results due to specimen hemolysis.

1.4 Research methods

For specimen collection, 1.5 ~ 2 ml of umbilical cord blood was collected with a 5 ml syringe during umbilical cord processing, stored at 4°C in a refrigerator, and sent for inspection within 1 hour after collection. The WBC count, neutrophil count, lymphocyte count, monocyte count, neutrophil percentage and PLT were measured. Inflammatory markers derived from CBC were calculated according to relevant formulas: the NLR, dNLR, MLR, NMLR, SIRI and SII. Moreover, the infant's sex, gestational age at birth, birth weight and delivery mode were recorded.

1.5 Observation indicators

(1) Comparison of the WBC count, NLR, dNLR, MLR, NMLR, SIRI, SII, PLT and neutrophil percentage in umbilical cord blood between the two groups; (2) analysis of the predictive value of the WBC count, PLT count, neutrophil percentage and WBC-derived inflammatory markers in umbilical cord blood for EOS complicated with NPM in preterm infants via ROC curves.

1.6 Statistical analysis

SPSS 27.0 software was used for data analysis. Normally or approximately normally distributed data are expressed as the means $\pm$ standard deviations ($\pm s$), and t tests were used for intergroup comparisons. The normally distributed data are expressed as medians (interquartile ranges) [M(P25, P75)], and the Mann–Whitney U test was used for intergroup comparisons. Count data are expressed as n values, and the chi-square test or Fisher's exact test was used for intergroup comparisons, P value < 0.05 indicated a statistically significant difference.

1.7 Ethics

This study was approved by the Medical Ethics Committee of Zunyi Medical University (Approval No. Zunyilunshen [2025–2–002]). The studies were conducted in accordance with local legislation and institutional requirements.

2 Results

2.1 Comparison of WBC, PLT and CBC-Derived Inflammatory Markers in Umbilical Cord Blood between the Two Groups

A total of 112 infants were included in this study. The WBC count, NLR, dNLR, MLR, NMLR, SIRI and neutrophil percentage in the meningitis group were significantly greater than those in the nonmeningitis group ($P < 0.05$), indicating that these indicators in umbilical cord blood have certain predictive value for EOS complicated with purulent meningitis in preterm infants, but the specific diagnostic efficiency remains to be further analysed. There were no significant differences in the SII or PLT between the two groups ($P > 0.05$), suggesting that the PLT or the SII alone cannot be used for the early prediction of EOS complicated with purulent meningitis in preterm infants, and further research can be conducted in combination with other indicators in the future (Table 2).

Table 2

Comparison of WBC, PLT and CBC-derived inflammatory markers in umbilical cord blood between the two groups

Group	n	WBC	NLR	PLT	dNLR	
		[M(P25, P75), $\times 10^9/L$]	[M(P25, P75)]	[M(P25, P75), $\times 10^9/L$]	[M(P25, P75)]	
Meningitis	31	10.40 (5.25, 20.40)	1.85 (1.03, 4.19)	243.00 (200.00, 280.00)	0.85 (0.78, 0.88)	
Nonmeningitis	81	6.40 (4.70, 10.40)	1.25 (0.69, 1.68)	240.00 (197.00, 277.00)	0.81 (0.77, 0.85)	
Z value		-2.09	-2.64	-0.68	-2.51	
P value		0.037	0.008	0.495	0.012	
Group	n	MLR	NMLR	SIRI	SII	N
		[M(P25, P75)]	[M(P25, P75)]	[M(P25, P75)]	[M(P25, P75)]	[M(P25, P75),%]
Meningitis	31	0.30 (0.20, 0.69)	2.58 (1.18, 6.38)	2.14 (0.43, 7.57)	255.56 (128.35, 782.97)	4.80 (2.40, 19.20)
Nonmeningitis	81	0.20 (0.13, 0.28)	1.33 (0.85, 1.94)	0.62 (0.30, 1.09)	247.50 (156.34, 369.60)	3.20 (1.80, 5.30)
Z value		-3.62	-3.00	-2.64	-1.09	-2.06
P value		< 0.001	0.003	0.008	0.275	0.040

2.2 Predictive Value of WBC, PLT and CBC-Derived Inflammatory Markers for EOS Complicated with NPM in Preterm Infants

ROC curves were plotted on the basis of the WBC count, NLR, dNLR, MLR, NMLR, SIRI, SII, PLT and neutrophil percentage in the umbilical cord blood of the two groups. ROC curve analysis revealed that the WBC count, NLR, dNLR, MLR, NMLR, SIRI and neutrophil percentage in umbilical cord blood had certain diagnostic values for EOS complicated with NPM in preterm infants. According to the AUC, the order of diagnostic value was as follows: MLR > NMLR > NLR/SIRI > dNLR > WBC/neutrophil percentage > SII > PLT (Table 3 and Fig. 1).

Table 3

ROC curve analysis of the PLT, WBC count and derived inflammatory markers for predicting EOS complicated with NPM in preterm infants

Variables	AUC (95%CI)	Accuracy(95%CI)	Sensitivity (95%CI)	Specificity(95%CI)	PPV (95%CI)	NPV (95%CI)	Cut-off
WBC	0.63	0.68	0.74	0.52	0.80	0.43	1.015
NLR	0.66	0.74	0.84	0.48	0.81	0.54	0.33
PLT	0.54	0.41	0.21	0.94	0.89	0.31	2.244
dNLR	0.65	0.69	0.74	0.55	0.81	0.45	-0.073
MLR	0.72	0.73	0.79	0.58	0.83	0.51	-0.535
NMLR	0.68	0.78	0.89	0.48	0.82	0.62	0.442
SIRI	0.66	0.77	0.88	0.480.	0.81	0.60	0.519
SII	0.57	0.79	0.95	0.35	0.79	0.73	2.776
N(%)	0.63	0.76	0.89	0.42	0.080	0.59	0.995

3 Discussion

Neonatal purulent meningitis is a common central nervous system infectious disease that occurs during the neonatal period and seriously threatens the life and health of neonates, especially preterm infants. Owing to the immature development of humoral immunity, cellular immunity and phagocyte function in neonates and the low level of maternally derived immunoglobulin received by preterm infants, the risk of meningitis in preterm infants is much greater than that in children of other age groups and is 10 ~ 15 times greater than that in full-term infants.

Clinical manifestations may include systemic infectious-toxic symptoms and neurological symptoms such as poor responsiveness, abnormal body temperature, respiratory distress, convulsions, increased intracranial pressure and altered mental status, which are usually accompanied by typical CSF changes. NPM has a high incidence, mortality and disability rate. The overall incidence of NPM is 0.2 ~ 0.3% in developed countries and as high as 0.8 ~ 6.1% in developing countries, showing a slight decline compared with that reported in the past ^[8-9]; the mortality rate is 10 ~ 15% in developed countries and still as high as 40 ~ 60% in developing countries. It is estimated that up to 190,000 neonates die of meningitis worldwide every year, with no significant annual decline ^[10-12]. Moreover, a meta-analysis on the global incidence and mortality of neonatal sepsis ^[13] revealed that from 1989–2018, the incidence of sepsis in neonates was 2824 cases per 100,000 live births, and approximately 25% of neonates with sepsis developed complicated purulent meningitis. Even some surviving infants suffer from adverse neurodevelopmental outcomes, such as cerebral palsy and cognitive dysfunction. Therefore, early diagnosis and timely anti-infective treatment are crucial for improving patient prognosis and reducing mortality and can also shorten the duration of empirical antibiotic use.

At present, the gold standard for diagnosing NPM is still positive CSF microbial culture, but CSF culture is time-consuming and has a high false negative rate and extremely low positive rate. In addition, the clinical manifestations of NPM are highly atypical and nonspecific. Moreover, most preterm infants with EOS are in critical condition in the early postnatal period and cannot tolerate lumbar puncture, leading to a delay in CSF detection,

thus making early diagnosis difficult. Clinically, classic CSF parameters are still used for auxiliary diagnosis, but these parameters are affected by factors such as antibiotic use, traumatic puncture, intraventricular hemorrhage and the time of specimen submission ^[4–5]. The value of these CSF parameters in the early diagnosis of neonatal NPM is still controversial and is prone to missed diagnosis and misdiagnosis. Therefore, the search for specific biomarkers for early diagnosis has always been the focus of research.

The cellular composition of umbilical cord blood is similar to that of fetal peripheral blood in the third trimester of pregnancy, so umbilical cord blood can be used as a feasible and reliable blood sample for evaluating postnatal hematological parameters ^[14–15]. Moreover, the collection of umbilical cord blood is simple, painless and noninvasive and neither affects the hemodynamics of neonates nor causes iatrogenic anemia and pain induced by puncture ^[16]. In recent years, noninvasive umbilical cord blood biomarkers have attracted much attention.

Inflammation causes changes in the total number and differential count of white blood cells in the body. Neutrophils are a type of myeloid white blood cell and one of the main immune cells involved in acute inflammation. In humans, neutrophils account for 50%~70% of all circulating white blood cells. Elevated levels of chemokines, neutrophils and other proinflammatory molecules have been observed in mouse models and humans with severe sepsis ^[17]. Moreover, lymphocyte homeostasis is severely disrupted, leading to lymphopenia, which in turn affects CD4 + T lymphocytes, CD8 + T lymphocytes, B cells and natural killer cells, ultimately impairing the coordinated response of the body's immune system to infection ^[18]. In addition, the detection technology for total white blood cell count and differential count is mature and can be carried out in hospitals at all levels with short time consumption and low cost; thus, it is widely used in the clinical diagnosis of infectious diseases ^[19]. However, there are few studies on the use of the WBC count and its derived immune-inflammatory markers to predict EOS complicated with NPM in preterm infants, and its clinical value needs further research.

The results of this study revealed that the WBC count, NLR, dNLR, MLR, NMLR, SIRI and neutrophil percentage in the meningitis group were significantly greater than those in the nonmeningitis group, indicating that the above indicators alone have certain diagnostic value for EOS complicated with NPM in preterm infants. Among them, the MLR had the highest diagnostic efficiency, with an AUC of 0.72, a sensitivity of 79% and a specificity of 58%, and can serve as a useful supplement for the early diagnostic indicators of EOS complicated with NPM in preterm infants. Therefore, the detection of the MLR in umbilical cord blood has good clinical value for the early diagnosis of EOS complicated with NPM in preterm infants.

This study has certain limitations. Due to the decline in the neonatal birth rate in recent years, the sample size of this single-center study is relatively small, which may lead to selection bias. Multicenter and large-sample clinical studies should be conducted in the future.

In conclusion, the MLR in umbilical cord blood is highly expressed in preterm infants with EOS complicated with NPM and has a relatively high predictive value for this complication. The collection of umbilical cord blood is noninvasive and painless, which can largely compensate for the diagnostic delay of CSF detection. Moreover, WBC detection features mature technology, low cost and short time consumption and is expected to serve as a useful supplement for early diagnostic indicators of EOS complicated with NPM in preterm infants.

Abbreviations

NPM Neonatal Purulent Meningitis

CSF Cerebrospinal Fluid

EOS Early-onset Sepsis

CBC Complete Blood Count

WBC White Blood Cell Count

NLR Neutrophil-to-lymphocyte Ratio

PLT Platelet Count

DNLR Derived Neutrophil-to-lymphocyte Ratio

MLR Monocyte-to-lymphocyte Ratio

NMLR Monocyte count + Neutrophil count/Lymphocyte count Ratio

SIRI Systemic Inflammatory Response Index

SII Systemic Immune-inflammation Index

ROC Receiver Operating Characteristic

AUC Area Under the Curve

Declarations

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Authors' Contributions

Zongli Chen: Literature review, drafting and revision of the manuscript, Data verification, statistical analysis and manuscript revision. Keyong Luo: Specimen collection and data statistics, Participation in the review and revision of the initial manuscript.

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Data availability

The data are available from the authors upon reasonable request.

Ethics approval

This study was approved by the Medical Ethics Committee of Zunyi Medical University (Approval No. Zunyilunshen [2025–2-002]). It conforms to the provisions of the Declaration of Helsinki and Ethical Review Measures for Human Life Sciences and Medical Research. All written informed consent was obtained from all participants' legal guardians.

Competing Interests

All the authors declare that they have no competing interests.

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Figures

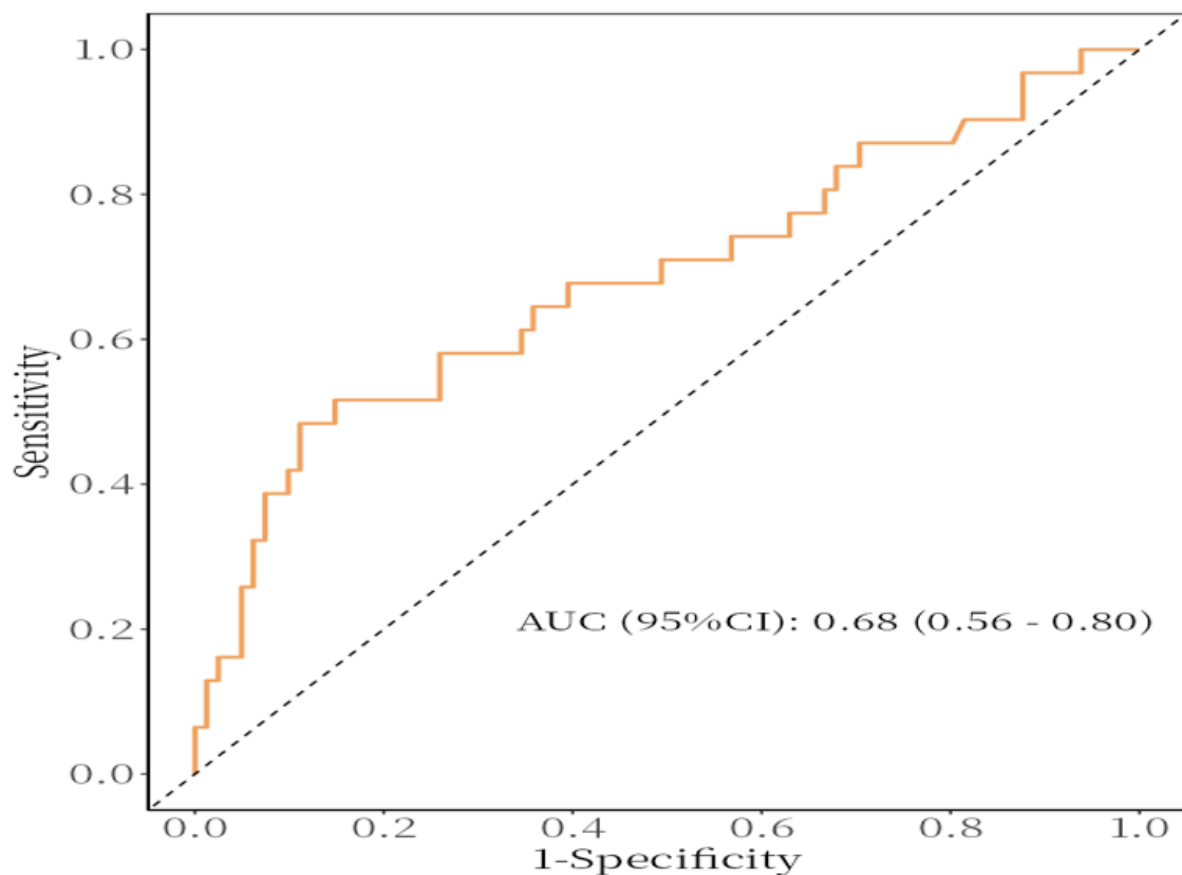


Figure 1

ROC curve analysis of the umbilical cord blood MLR for diagnosing EOS complicated with NPM in preterm infants