J Chin Med Assoc

ORIGINAL ARTICLE

Risk factors and predictive markers for early and late-onset neonatal bacteremic sepsis in preterm and term infants

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Abstract

Background: The early detection and prediction of bacteremic sepsis in preterm and term neonates remains a challenging task because of their nonspecific clinical presentations. We aimed to investigate the risk factors associated with bacteremia and find the cutoff values of predictive markers to achieve accurate diagnosis of neonatal bacteremic sepsis.

Methods: Not-doing-well preterm and term neonates with suspected sepsis were retrospectively enrolled between January 2015 and December 2017 in Taipei Veterans General Hospital. Blood culture, hemogram, serum procalcitonin (PCT), and C-reactive protein (CRP) were drawn at the onset of clinical signs and symptoms. All cases were divided to either early-onset or late-onset groups according to postpartum age. Nonparametric statistic, logistic regression, and receiver operating characteristic analysis were performed to evaluate the risk factors and cutoff values for predicting bacteremia.

Results: A total of 169 suspected sepsis episodes were analyzed, 68.0% of which had cardiopulmonary dysfunction and 19.5% had perinatal stress. The early-onset group had 123 (72.8%) patients, 4 of which had bacteremia and 119 had nonbacteremia conditions. The late-onset group had 46 (27.2%) patients, 8 of which had bacteremia and 38 had nonbacteremia conditions. Gestational age, birth body weight, Apgar score at 5 minutes, serum PCT, CRP, and platelet (PLT) count in the early-onset group and white blood cell (WBC) count in the late-onset group were substantially different between the patients with bacteremia and nonbacteremia conditions. PCT greater than 27 μg/L (adjusted odd ratio [aOR], 21.6; 95% CI, 1.1–435.1) and thrombocytopenia less than 100 × 10^9/L (aOR, 38.6; 95% CI, 1.4–1030.3) were predictive markers for bacteremia in the early-onset group.

Conclusion: Early- and late-onset neonatal sepsis had different risk factors and predictive markers of bacteremia. PCT and PLT count in the early-onset group and WBC count in the late-onset group were accurate diagnostic serum markers for neonatal bacteremic sepsis.

Keywords: Bacteremia; C-reactive protein; Neonatal sepsis; Procalcitonin; Thrombocytopenia

1. INTRODUCTION

Bacteremic sepsis in preterm and term neonates is one of the main causes of mortality and morbidity in the neonatal intensive care unit (NICU) and intermediate care nursery (ICN).[1,2] The estimated incidence of neonatal bacteremic sepsis is about 0.77 to 1 per 1000 live births.[1,3] Given that neonates are immunocompromised, bacteremic sepsis may result in severe complications and even life-threatening sequelae or death if unrecognized and untreated.[2] The mortality rate of neonatal sepsis with bacteremia is high and varies about 23.5% to 41.4%.[1,4]

The age at onset time of neonatal sepsis must be defined because different bacterial pathogens are involved according to postpartum age.[5] Moreover, this uncertainty forces physicians to choose different empirical antibiotics at the beginning and prescribe the duration of antibiotic therapy.[6] According to the age at onset on time of sepsis, neonatal sepsis can be divided into two groups: early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS). EONS, which is defined as postpartum age less than seven days, is associated with intrapartum bacterial transmission, and the common pathogens involved group B *Streptococcus* and *Escherichia coli*.[5] LONS, which is defined as postpartum age within 7 to 28 days, is associated with hospital-acquired infection, especially invasive procedures that disrupt the mucosa, and the common pathogens involved coagulase-negative staphylococci and Gram-negative bacilli.[4,7]

Neonatal bacteremic sepsis must be promptly diagnosed because of its poor outcome and prognosis.[1,2] However,

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Conflicts of interest: Dr. Mei-Jy Jeng, an editorial board member at the Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 507-513.

Received September 1, 2021; accepted October 14, 2021.

doi: 10.1097/JCMA.0000000000000681.

recognizing neonatal bacteremic sepsis during initial presentations is challenging because of their nonspecific not-doing-well signs and symptoms, such as fever, hypothermia, irritable crying, apnea, feeding difficulty, lethargy, mottled skin, distend abdomen, cyanosis, or shock.[8] Blood culture is the standard diagnosis of bacteremic sepsis, but it is time-consuming and its sensitivity is affected by the manner of drawing blood, use of antibiotics, bacterial loading amount, maternal use of antibiotics, or skin microbiome contamination.[9] Therefore, multiple tools are applied to detect neonatal bacteremic sepsis early.

Many clinical characteristics are risk factors of neonatal bacteremic sepsis, such as maternal chorioamnionitis, gestational age (GA) less than 37 weeks, and prolonged rupture of membranes greater than 18 hours.[5] Furthermore, hematopoietic changes (leukocytosis, leukopenia, thrombocytosis, or thrombocytopenia) and many serum acute-phase reactants, such as C-reactive protein (CRP), procalcitonin (PCT), interleukin-6, ferritin, fibrinogen, or complement factors, are used to evaluate neonatal bacteremic sepsis.[10–12] Hemogram and serum CRP values are common blood tests used to detect neonatal bacteremic sepsis in NICU and ICN.[13,14] Serum PCT is a specific serum marker of bacterial infection. Serum PCT is known to increase early and rapidly compared with serum CRP in sepsis.[9,15] Serum PCT elevates within 2 to 4 hours after bacterial infection, whereas serum CRP increases within 6 to 12 hours. However, physiologically elevated periods occur in serum PCT and CRP in preterm and term neonates from birth to 96 hours after delivery.[16] Therefore, the cutoff values of PCT and CRP vary in neonatal bacteremic sepsis.

Given that the association between serum markers and bacteremic sepsis in preterm and term neonates remains unclear, our study aimed to clarify the cutoff values of serum markers to the accurate diagnosis of bacteremia in both EONS and LONS. The risk factors were also determined to detect bacteremic sepsis early in preterm and term neonates and improve treatment outcome.

2. METHODS

2.1. Study population and patient selection

The medical charts of patients with episodes of not-doing-well signs and symptoms admitted in the NICU and ICN of the Taipei Veterans General Hospital between January 2015 and December 2017 were retrospectively reviewed. These not-doing-well signs and symptoms were defined either by our clinical practice evaluation or the results of biochemistry tests. Fever and hypothermia were defined as body temperature over 38°C or less than 35.5°C, respectively. Bradycardia was heart rate less than 80 beats per minute as recorded by physiologic monitoring. Tachypnea was respiratory rate over 60 times per minute with or without nasal flaring and accessory muscle retraction. Apnea was an unexplained episode of cessation of breathing for 20 seconds.[17,18] Cyanosis was blue discoloration of the skin and mucus membranes, and shock was hypotension (below the 10th percentile for age) and acute failure of the circulatory system to maintain adequate tissue perfusion.[19,20] Jaundice was serum total bilirubin level over 15 mg/dL, or over the 95th percentile in an age-specific nomogram by hour.[21] Others index such as irritable crying, vomiting, feeding difficulty, lethargy, mottled skin, and distended abdomen were included herein.[22] Blood samples at initial clinical presentations were collected for complete blood count (CBC), serum PCT and CRP examination, and blood bacterial culture. The exclusion criteria were not-doing-well episodes at chronological age over 28 days, patients with complex congenital cardiac and thoracic anomaly, and episodes within 3 days after cardiothoracic surgery.[23] This retrospective study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan (IRB approval number 2021-09-010BC).

2.2. Data collection

Demographic characteristics, laboratory serum markers, pathogens of blood cultures, and initial clinical presentations were collected. Demographic characteristics were gender, GA, postpartum age, birth body weight (BBW), delivery mode, Apgar score at 1 and 5 minutes, and mortality. Serum markers included PCT, CRP, white blood cell (WBC) count, neutrophil percentage, hemoglobin (Hgb), and platelet (PLT) count. Each episode was at least 14 days apart from the other on the same patient.

2.3. Study design and end outcome

All cases were divided into two groups according to postpartum age to either EONS or LONS. Our end outcome was bacteremia or nonbacteremia. The characteristics and serum markers between patients with bacteremia and nonbacteremia conditions were analyzed to identify the risk factors of bacteremia. Cutoff values of serum markers were determined to assess their predictive values for bacteremia.

2.4. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were represented as median (interquartile range [IQR], 25%–75%), and categorical variables were reported as counts (percentage; n [%]). Chi-square or Fisher's exact test was used to analyze differences in categorical variables, whereas the Mann-Whitney *U* test was applied for comparison of continuous variables. Receiver operating characteristic (ROC) curve analysis was conducted to assess the cutoff values of significantly different serum markers for bacteremia prediction. Continuous variables were categorized into two groups according to the cutoff values, and then they were analyzed by a cross-tabulation and ROC curve analysis. The results were reported as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve with 95% CI. The odds ratios (ORs) and adjusted ORs (aORs) of serum markers were calculated via univariate and multivariate logistic regression analyses. A p value less than 0.05 was considered statistically different.

3. RESULTS

From January 2015 to December 2017, a total of 216 sick or not-doing-well patients were admitted in our NICU and ICN. A total of 235 blood samples including blood culture, serum CBC, PCT, and CRP were collected during episodes of not-doing-well signs and symptoms. The excluded episodes and the sample stratification are described in Fig. 1. A total of 169 episodes were analyzed. The most common signs and symptoms were cardiopulmonary dysfunction (68.0%), including tachypnea, apnea, bradycardia, cyanosis, or shock (Table 1).

Clinical demographic characteristics and serum markers are summarized in Table 2. One hundred and twenty-three cases were in EONS, of which 4 (3.3%) of the blood cultures had bacteremia and 119 (96.7%) had nonbacteremia conditions. The demographic characteristic of the patients in the bacteremia group of EONS were predominantly males (75%) with a median age of 1 day; a median GA of 29 weeks; a median BBW of 1287 gm; median Apgar scores 4 and 6 at 1 and 5 minutes, respectively; 75% cesarean section; and mortality rate of 25.0%. Significant differences were observed between the bacteremia and the nonbacteremia groups in EONS in terms of GA, BBW,

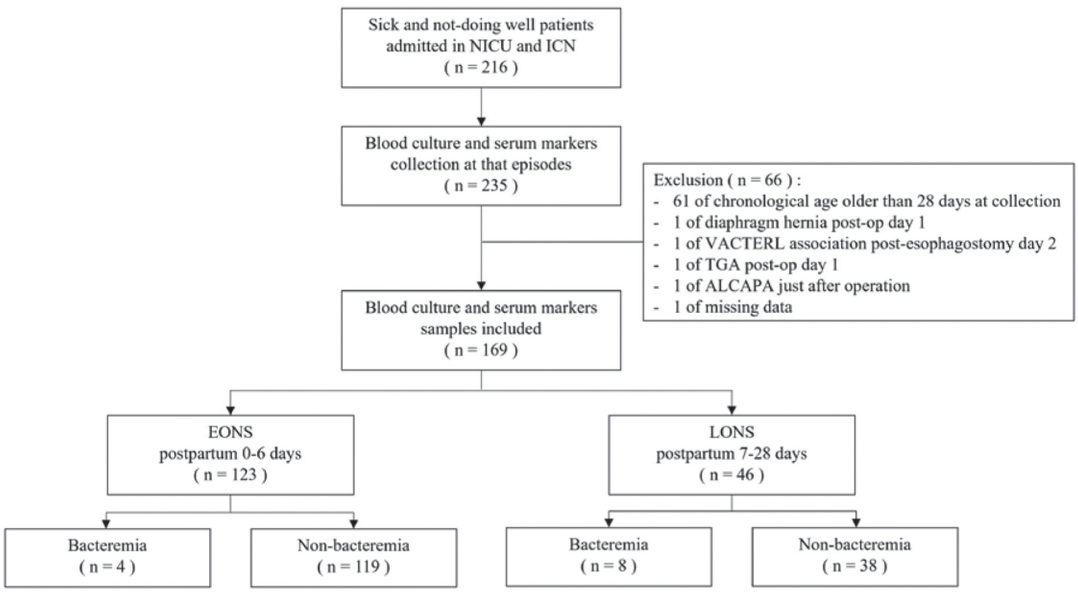

Fig. 1 Schematic flowchart for patient inclusion and stratification. ALCAPA = anomalous origin of the left coronary artery arising from the pulmonary artery; EONS = early-onset neonatal sepsis; ICN = intermediate care nursery; LONS = late-onset neonatal sepsis; NICU = neonatal intensive care unit; and TGA = transposition of the great arteries; VACTERL = V = vertebral abnormalities; A = anal atresia; C = cardiac defects; TE = tracheal-esophageal abnormalities; R = renal and radial abnormalities; L = limb abnormalities.

and Apgar score at 5 minutes, but no significant differences were found in terms of gender, postpartum age, delivery mode, and mortality rate. In ENOS, the bacteremia group had higher serum levels of PCT (42.9 [IQR, 7.4–85.9] vs 1.5 [IQR, 0.5–4.9] μg/L; $p < 0.05$), CRP (25.3 [IQR, 7.7–40] vs 1.6 mg/L [IQR, 0.5–8.2]; $p < 0.05$), and lower PLT counts (95×10^9/L [IQR, 43–115] vs 212×10^9/L [IQR, 158–285]; $p < 0.05$) than the nonbacteremia group. WBC, neutrophil percentage, and Hgb levels were not different between the bacteremia and the nonbacteremia groups. However, in LONS, the bacteremia group had a lower WBC count (8.6×10^9/L [IQR, 6.9–11.6] vs 13.4×10^9/L [IQR, 9.6–15.9]; $p < 0.05$) than the nonbacteremia group. PCT, CRP, PLT, Hgb, and neutrophil percentage were not significantly different between the bacteremia and the nonbacteremia groups in LONS.

Analyses of the ROC curves and cutoff values of PCT, CRP, and PLT in EONS and WBC in LONS were graphed and optimally estimated by ROC curves (Fig. 2). The cutoff values for bacteremia prediction were 27 μg/L for PCT, 15 mg/L for CRP, and 100×10^9/L for PLT in EONS and 12.1×10^9/L for WBC in LONS. The diagnostic accuracy of the serum markers for bacteremia prediction is given in Table 3. ORs analyzed by univariate and multivariate logistic regression models are presented in Table 4.

All 169 blood cultures were further stratified into two subgroups by GA of 34 weeks. The OR of bacteremia prediction by GA <34 weeks was 3.9 (95% CI, 1.1–15.1; $p < 0.05$). The other stratified subgroups by other GA, eg, <28 weeks or <37 weeks, were not significantly different between the bacteremia and the nonbacteremia groups.

The four pathogens in EONS were two (50%) Gram-positive bacteremia with one of *Streptococcus agalactiae* and one of *Staphylococcus epidermidis* and two (50%) Gram-negative bacteremia with two of *Escherichia coli*. The eight pathogens in LONS were six (75%) Gram-positive bacteremia with three of *Staphylococcus epidermidis* and three of *Staphylococcus capitis* and two (25%) Gram-negative bacteremia with one of *Escherichia coli* and one of *Klebsiella oxytoca*.

The cause of one mortality in the EONS bacteremia group was septic shock combined with pneumonia with *Escherichia coli* cultured in blood and sputum. Her GA was 31 weeks with BBW of 1556 gm, and serum markers revealed that PCT was 28.2 μg/L, CRP was 5.1 mg/L, WBC was 6.4×10^9/L, and PLT was 98×10^9/L. In the EONS without bacteremia, three died of birth asphyxia and one died of pulmonary hemorrhage with extreme low-body-weight prematurity (GA = 26 weeks). In the LONS without bacteremia group, two died of suspected septic shock, one died of pulmonary hemorrhage with congenital heart disease, and one died of methicillin-resistant *Staphylococcus aureus* pneumonia. No mortality was recorded among the patients in the LONS with bacteremia group.

Table 1

Initial clinical presentations

Signs and symptoms	n (%)
Cardiopulmonary dysfunction	115 (68.0)
Tachypnea/apnea	85 (50.3)
Bradycardia	9 (5.3)
Cyanosis	8 (4.7)
Shock	8 (4.7)
Apnea + bradycardia + cyanosis	5 (3.0)
Perinatal stress	33 (19.5)
PPROM/PROM	20 (11.8)
Birth asphyxia	13 (7.7)
Gastrointestinal abnormality	11 (6.5)
Abdominal dullness	6 (3.5)
Tarry stool	3 (1.8)
Jaundice	2 (1.2)
Fever >38 °C	11 (6.5)
Irritable	9 (5.3)
Seizure	3 (1.8)
Lethargy	1 (0.6)
Others[a]	5 (3.0)

[a]Two of wound discharge, one of umbilical cord bleeding, one of thrombocytopenia, and one of vesicles over soft palate.

PPROM = preterm premature rupture of membrane; PROM = premature rupture of membrane.

Table 2

Demographic characteristics and serum markers in EONS and LONS between the bacteremia and the nonbacteremia groups

	EONS (123)			LONS (46)		
Blood culture (n)	**Bacteremia (4)**	**Nonbacteremia (119)**	***p***	**Bacteremia (8)**	**Nonbacteremia (38)**	***p***
Demographic characteristics						
Male	3 (75)	62 (52)	0.621	5 (63)	23 (61)	0.918
PPA (d)	1 (0–4)	1 (1–3)	0.224	17 (12–25)	15 (11–21)	0.611
GA (wk)	29 (24–31)	36 (30–39)	0.02*	29 (27–38)	30 (27–37)	0.977
BBW (g)	1287 (742–1660)	2500 (1394–3130)	0.033*	1393 (768–2850)	1571 (1010–2533)	0.674
C/S	3 (75)	66 (56)	0.63	6 (75)	22 (58)	0.373
Apgar score#1	4 (1–5)	6 (4–8)	0.05	5 (3–7)	5 (4–7)	0.446
Apgar score#5	6 (4–7)	8 (7–9)	0.024*	7 (5–8)	8 (7–8)	0.591
Mortality rate	1 (25.0)	4 (3.4)	0.155	0 (0)	4 (10.5)	0.342
Serum markers						
PCT (μg/L)	42.9 (7.4–85.9)	1.5 (0.5–4.9)	0.042*	0.9 (0.2–1.8)	0.4 (0.2–1.0)	0.29
CRP (mg/L)	25.3 (7.7–40.0)	1.6 (0.5–8.2)	0.01*	1.9 (0.4–6.1)	1.0 (0.4–12.0)	0.965
WBC (10^9/L)	6.0 (4.9–43.9)	12.2 (8.0–19.2)	0.232	8.6 (6.9–11.6)	13.4 (9.6–15.9)	0.049*
Segment (%)	29 (7–77)	62 (51–72)	0.139	52 (43–59)	51 (34–65)	0.75
Hgb (g/L)	125 (96–170)	157 (135–181)	0.152	138 (105–145)	134 (11.8–147)	0.908
PLT (10^9/L)	95 (43–115)	212 (158–285)	0.001*	212 (121–467)	245 (180–448)	0.602

All values are shown as n (%) or median (interquartile range, 25%–75%).

Apgar score#1 = Apgar score at 1 min; Apgar score#5 = Apgar score at 5 min; BBW = birth body weight; C/S = Cesarean section; CRP = C-reactive protein; EONS = early-onset neonatal sepsis; GA = gestational age; Hgb = hemoglobin; LONS = late-onset neonatal sepsis; PCT = procalcitonin; PLT = platelet; PPA = Postpartum age; WBC = white blood count.

* $p < 0.05$.

4. DISCUSSION

Bacteremic sepsis in preterm and term neonates is known as a poor prognostic factor associated with a high mortality and increased risks of adverse outcomes in NICU and ICN.[24,25] The prognosis of bacteremic sepsis among preterm and term infants must be improved via early detection and early intervention with empirical antibiotics therapy.[11,26] Multiple serum markers are applied to diagnose neonatal bacteremic sepsis and adjust the prescription of antibiotics therapy. Hemogram, including WBC count, PLT count, and serum CRP level, is commonly used to evaluate the severity of bacterial infection among preterm and term infants.[27] Serum PCT level is one of the serum markers of preterm and term neonatal bacterial infection. Nevertheless, consensuses on the cutoff value of serum PCT level on bacterial infection is lacking because of postpartum age-specific, GA-related, and neonatal physiological changes in the early postpartum periods.[16,28] In this retrospective study of clinically suspected neonatal sepsis, we found that preterm labor with GA less than 34 weeks was a risk factor of bacteremia. This result could probably be attributed to the immature immune system of neonates and their poor skin defense barrier against bacterial invasion.[27] We also found that combined serum PCT level elevation and thrombocytopenia could predict bacteremia among suspected EONS with non–doing-well signs and symptoms. These findings will be helpful in the clinical practice of treatment of neonatal sepsis with bacteremia. Early prediction of bacteremia by serum markers can promote early and prompt antibiotic treatment, prognosis prediction, and resistant pathogen prevention.

PCT encoded by the *CALC-1* gene is physiologically produced in response to neuroendocrine tissues.[29,30] Respiratory distress after birth may stimulate the *CALC-1* gene, resulting in nonbacterial infectious PCT level elevation in the early postpartum period.[16,31,32] After bacterial infection, *CALC-1* gene expression widely and systemically increases in different organs and tissues, especially in the lungs and also in peripheral blood mononuclear cells.[27] PCT has recently become a promising diagnostic marker of both early-onset and late-onset preterm and term neonatal sepsis with bacteremia.[22,27,33,34] The accurate cutoff values vary and remain controversial.[35,36] Naramura et al[27] reported that the cutoff values of PCT with early bacterial infection are 15.25 and 7.77 μg/L at 7 to 18 hours and 19 to 36 hours after birth, respectively. In the present study, the cutoff value of PCT in EONS with bacteremia was 27 μg/L with a sensitivity of 75%, specificity of 95%, PPV of 33%, NPV of 99%, and aOR of 21.6 (1.1–435.1; $p < 0.05$). The present work noted lesser GA, lower BBW, and lesser APGAR score at 5 minutes in the cases of EONS with bacteremia than those reported by other studies.[37] This discrepancy would indicate that the underlying conditions were considerably more severe and complicated and would make the cutoff value of PCT in EONS with bacteremia obtained herein higher than that stated by other studies. Unlike other studies, no significant difference in serum PCT levels was observed between the bacteremia and the nonbacteremia groups in LONS in this study. Therefore, further research should focus on detecting serial changes in serum PCT level in LONS.

Serum CRP is an acute-phase reactant for infection, inflammation, and tissue injury/ischemia, and it is widely used in pediatric and neonatal bacteremic sepsis.[23,27,38,39] CRP is produced from hepatocytes stimulated by interleukin-6 and interleukin-1.[40] In preterm babies, serum CRP level has a lower and a slower physiological or infectious response than term neonates because of their immature liver function and insufficient materials of protein production.[10,14,39] To date, CRP is the standard serum marker used to determine neonatal bacteremic sepsis, but distinguishing physiological elevation after delivery within 24 hours from bacterial infection is sometimes bothersome.[16] The cutoff value of preterm neonatal sepsis remains uncertain.[10,13,26] In the present study, the cutoff value of CRP in EONS with bacteremia was 15 mg/L with a sensitivity of 75%, specificity of 84%, PPV of 14%, NPV of 99% ($p < 0.05$), and aOR of 12.3 (95% CI, 0.5–325.1). Given than lower preterm GA (29 weeks) and lower BBW (1287 g) were noted in the EONS bacteremia group, less CRP production was expected because of their immature liver function.[10,39] However, the lower Apgar score at 5 minutes in the bacteremia group (6 points) than that in the nonbacteremia group (8 points) of EONS indicated that more complicated delivery status and more cardiopulmonary stress induced high CRP

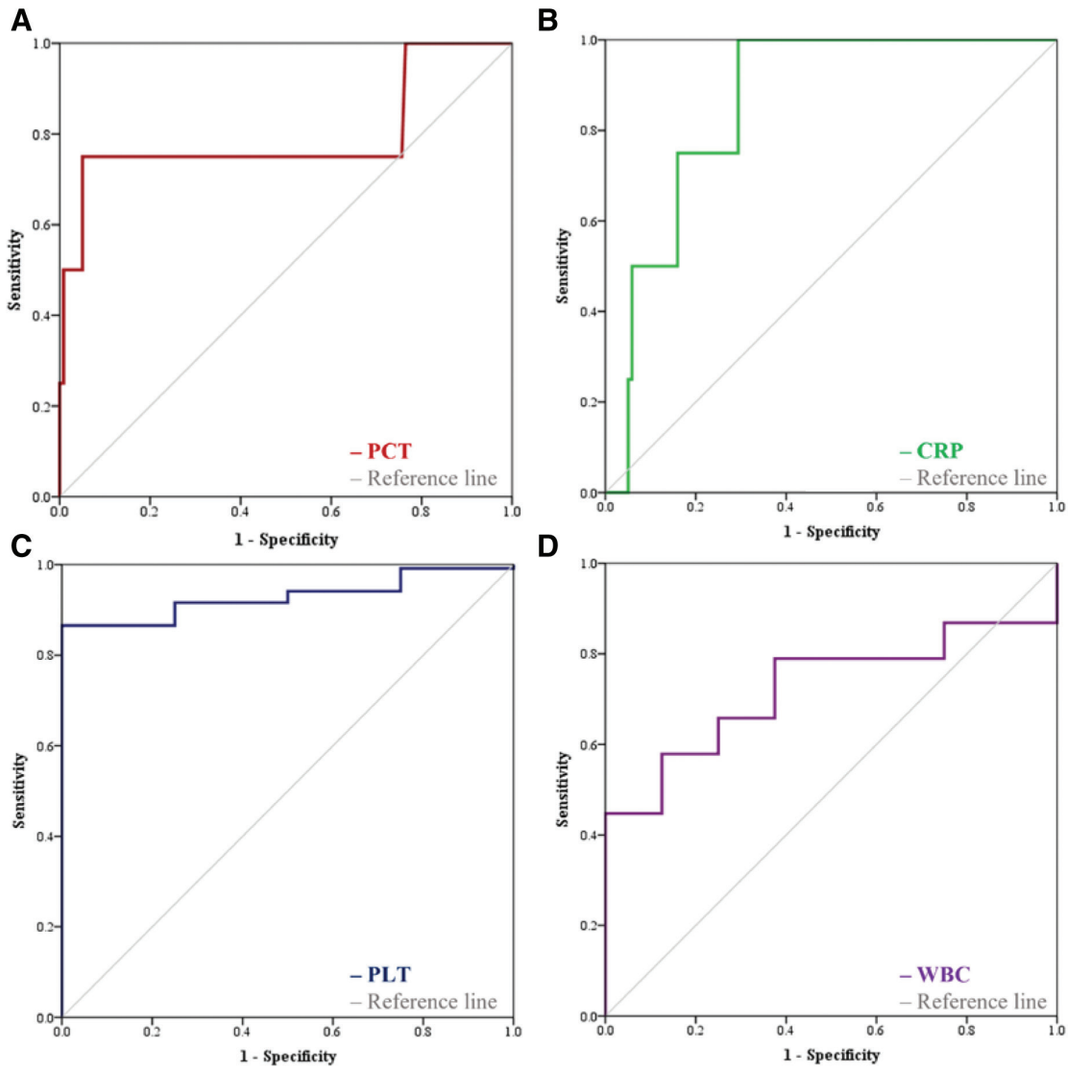

Fig. 2 Receiver operating characteristic (ROC) curve analysis of serum markers in early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS). A, ROC curve of procalcitonin (PCT) in EONS group with area under curve (AUC) = 0.80 (95% CI: 0.48-1.00). B, ROC curve of C-reactive protein (CRP) in EONS group with AUC = 0.86 (95% CI: 0.75-0.97). C, ROC curve of platelet count (PLT) in EONS group with AUC = 0.93 (95% CI: 0.87-0.99). D, ROC curve of white blood cell count (WBC) in LONS group with AUC = 0.72 (95% CI: 0.57-0.87). All *p* values of the above AUC were less than 0.05.

Table 3

Diagnostic accuracy of serum markers in EONS and LONS

Serum markers	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)	*p*
EONS						
PCT[a]	75	95	33	99	0.85 (0.6–1.0)	0.018*
CRP[b]	75	84	14	99	0.80 (0.55–1.0)	0.045*
PLT[c]	75	91	21	99	0.83 (0.58–1.0)	0.026*
PCT[a] + PLT[c]	75	100	100	99	0.88 (0.62–1.0)	0.011*
PCT[a] + CRP[b]	50	98	40	98	0.74 (0.42–1.0)	0.107
CRP[b] +PLT[c]	50	99	67	98	0.75 (0.43–1.0)	0.095
PCT[a] + CRP[b] + PLT[c]	50	100	100	98	0.75 (0.43–1.0)	0.090
LONS						
WBC[d]	88	58	30	96	0.73 (0.55–0.9)	0.049*

[a]PCT level more than 27 μg/L.
[b]CRP level more than 15 mg/L.
[c]PLT counts less than 100×10^9/L.
[d]WBC counts less than 12.1×10^9/L.
AUC = area under curve; CRP = C-reactive protein; EONS = early-onset neonatal sepsis; LONS = late-onset neonatal sepsis; NPV = negative predict value; PCT = procalcitonin; PLT = platelet; PPV = positive predict value; WBC = white blood cell.
* $p < 0.05$.

Table 4

OR for significantly different serum markers in EONS and LONS

Serum markers	OR (95% CI)	aOR (95% CI)
EONS		
PCT >27 μg/L	56.5 (5.1–627.5)*	21.6 (1.1–435.1)*
CRP >15 mg/L	15.8 (1.6–160.0)*	12.3 (0.5–325.1)
PLT <100 × 10^9/L	29.5 (2.8–307.8)*	38.6 (1.4–1030.3)*
LONS		
WBC <12.1 × 10^9/L	9.6 (1.1–86.2)*	

aOR = adjusted odds ratio; CRP = C-reactive protein; EONS = early-onset neonatal sepsis; LONS = late-onset neonatal sepsis; OR = odds ratio; PCT = procalcitonin; PLT = platelet; WBC = white blood cell.
*$p < 0.05$.

production.[27,39] Hence, the elevated CRP level in EONS was one of the risk factors of bacteremia established in this study. CRP levels were not considerably different between the bacteremia and the nonbacteremia groups in LONS. The risk factors of underlying conditions, including GA, BBW, and Apgar scores at 1 and 5 min, were also not statistically different between the LONS groups. Therefore, the serum CRP level at initial bacteremia of LONS is not an accurate diagnostic marker. Serial CRP assessment after 6 to 12 hours would be suggested for further bacterial infection evaluation because of the delayed response of serum CRP production.[36,38,40–42]

Thrombocytopenia is known as an early and nonspecific serum marker for bacterial sepsis, and it is also a poor prognostic factor for mortality and morbidity.[22,43] In this study, thrombocytopenia with a cutoff value of 100 × 10^9/L could be a diagnostic marker for bacteremia prediction in EONS. Few studies have attempted to determine the cutoff values of thrombocytopenia, PCT, and CRP levels for bacteremia prediction in neonatal sepsis. No statistically significant effects were observed after combining PCT, CRP, and PLT for bacteremia prediction in EONS. However, PCT level with a cutoff value of 27 μg/L combined with thrombocytopenia with a cutoff value of 100 × 10^9/L showed statistically significant difference for bacteremia prediction in EONS. The aORs were 21.6 (95% CI, 1.1–435.1) and 38.6 (95% CI, 1.4–1030.3) in PCT >27 μg/L and thrombocytopenia <100 × 10^9/L, respectively ($p < 0.05$). In the LONS group, PCT, CRP, and PLT counts were not different between the bacteremia and the nonbacteremia groups, and only WBC count with a cutoff value of 12.1 × 10^9/L could be used as a predictive marker for bacteremia. Further research on LONS that will establish a more delicate blood assessment protocol is warranted to evaluate the relationship between WBC count and other serum markers.

The limitation of this study was the small sample size that probably influenced our data interpretation. Moreover, the retrospective single-center cross-sectional design of this study possibly increased selective bias. Furthermore, patients with bacteremia without serum PCT data who were not included in the analysis possibly affected our measurements.

In conclusion, the risk factors and predictive markers of bacteremia in EONS and LONS are different. Our study clarified that the cutoff values of serum PCT combined with PLT count in EONS and serum WBC count in LONS might be accurate predictive markers for bacteremia. Recognizing the risk factors and early predictive serum markers of bacteremic sepsis in neonates may possibly promote early intervention and decrease the mortality and associated morbidity. Further research may adopt a prospective and observational study to evaluate the relationship between serial changes in serum markers and prognosis of neonatal sepsis.

ACKNOWLEDGMENTS

This work was supported, in part, by a grant from the Taipei Veterans General Hospital (grant number: V110C-170) and a grant from the Ministry of Science and Technology (grant number: MOST 110-2635-B-A49A-501), Taipei, Taiwan, ROC. The authors are grateful to the KGSupport Academic Submission Services for assisting with English editing.

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