Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2024**; 51(10): 216
https://doi.org/10.31083/j.ceog5110216

Original Research

Platelet-Related Indicators: Potential Role in Early Prediction of Bronchopulmonary Dysplasia

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Academic Editor: Andrea Tinelli
Submitted: 29 April 2024 Revised: 14 July 2024 Accepted: 1 August 2024 Published: 29 September 2024

Abstract

Background: Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory disease in extreme preterm infants, and inflammation is the main contributor that initiates this lung injury. As platelet-related indicators such as platelet-to-lymphocyte ratio (PLR) and platelet-to-neutrophil ratio (PNR) are potential systemic inflammatory biomarkers and it has been shown to be good predictors of lung diseases. The objective of this study was to assess the potential role of platelet-related indicators in early prediction for BPD. **Methods**: Neonates with gestational ages <32 weeks (w) from two tertiary neonatal intensive care units between January 2019 and April 2022 were included and the association between the platelet-related indicators and BPD were analyzed by logistic regression analysis and receiver operating characteristic curve. **Results**: 533 preterm infants were admitted, including 165 preterm infants with BPD and 368 preterm infants without BPD. The infants in the BPD group had higher PLR and PNR at birth, lower platelet (P) count at 2 w than those in the without BPD group. The high PLR at birth, high PNR at birth and low P at 2 w were independently associated with the risk of BPD. PLR at birth represented a predictive value for BPD with the area under the curve (AUC) being 0.589, sensitivity was 0.661, and specificity was 0.579 when the threshold was 135.33. PNR at birth represented a predictive value for BPD with the AUC being 0.576, sensitivity was 0.612, and specificity was 0.589 when the threshold was 129.12. P at 2 w represented a predictive value for BPD with the AUC being 0.668, sensitivity was 0.548, and specificity was 0.711 when the threshold was 285.5. The predictive value of the model was improved when including PLR at birth, PNR at birth, P at 2 w, and gestational age, with AUC being 0.798, sensitivity was 0.754, and specificity was 0.737. **Conclusions**: Combining PLR at birth, PNR at birth, P at 2 w, and gestational age improved the value in early prediction of BPD.

Keywords: platelet; platelet-to-lymphocyte ratio; platelet-to-neutrophil ratio; bronchopulmonary dysplasia; predict; preterm infants

1. Introduction

Bronchopulmonary dysplasia (BPD) is a severe chronic lung disease of extreme preterm infants. Recently, the advances in perinatal care have resulted in reductions in neonatal morbidity and mortality, but the incidence of BPD has not decreased [1,2]. BPD has been characterized by arrested alveoli and pulmonary vessel development [3]. Infants with BPD may lead to respiratory dysfunction, cardiopulmonary dysfunction, nervous system development retardation and potential death [4,5]. The therapeutic approaches for BPD, such as non-aggressive ventilator measures, glucocorticoids, diuretics, caffeine and vitamins, are only partly satisfactory [6].

Inflammation is a major contributor to the pathogenesis of BPD [7]. In BPD patients, the increase of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, monocyte chemo-attractant proteins, and the decrease of anti-inflammatory cytokines IL-10 in the lung, tracheal aspirate and peripheral blood induced imbalance of pro-inflammatory and anti-inflammatory cytokines has been demonstrated [8]. Recently, neutrophil-to-lymphocyte ratio (NLR) [9], eosinophil-to-basophil ratio (EBR) [10], platelet-related indicators, such as platelet-to-lymphocyte ratio (PLR) [11] and platelet-to-neutrophil ratio (PNR) [12] calculated from parameters in peripheral blood, can be used to evaluate the prognosis of inflammatory diseases with increased sensitively, without increasing the cost. PLR and PNR can act as novel prognostic markers in various clinical conditions, such as cardiovascular disease [13,14], rheumatic disease [11], acute ischemic stroke [15], bacterial infection [12], cancer [16] and preterm necrotizing enterocolitis (NEC) [17]. PLR is associated with prognosis in patients with early-onset sepsis (EOS) in neonates [18]. PLR and PNR were associated with a variety of lung diseases. Qu *et al.* [19] found that PLR can be used as a parameter

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in predicting coronavirus disease-19, as the patients with significantly elevated platelets during treatment had longer average hospitalization days. Luo *et al*. [20] found that combination of the PLR and fibrinogen was an independent prognostic factor for 5-year overall survival in patients with non-small cell lung cancer. Serdar Karakaya *et al*. [21] demonstrated that PLR could be used as an independent predictive biomarker for the use of diffusing capacity of the lungs for carbon monoxide decline which is used to identify bleomycin-induced pulmonary toxicity. PLR also has significative diagnostic value in patients with solitary pulmonary nodules [22]. Meanwhile, PNR have good applied value in the diagnosis of neonatal pneumonia with high sensitivity and specificity [23].

In a previous study, we found that NLR at 72 h after birth can be considered as an important early indicator of BPD in preterm infants [24]. However, the relationship between the platelet-related indicators and BPD remains unknown. In this study, we aimed to assess the potential role of platelet-related indicators in early prediction for BPD.

2. Materials and Methods

2.1 Study Population

We conducted an observational, retrospective cohort study to evaluate newborns born at gestational age <32 weeks (w) admitted to neonatal intensive care units (NICU) of the First Affiliated Hospital of Wenzhou Medical University and Yiwu Maternity and Children Hospital between January 2019 and April 2022. The current definition of BPD utilized was according to NICHD in 2018, referring to the newborns born at gestational age <32 w who need supplemental oxygen treatment or oxygen plus respiratory support at 36 w post-menstrual age (PMA) [2]. We collected the clinical data of 543 preterm infants in this study. Exclusion criteria included genetic abnormalities, chromosomal abnormalities, complex congenital heart disease, congenital gastrointestinal malformation, congenital metabolic diseases and incomplete information. Finally, 533 preterm infants were enrolled, and 10 infants were excluded. The flowchart of the study is shown in Fig. 1. The infants who died from respiratory failure within 36 w PMA were considered as BPD patients. Consistent with the World Medical Association Declaration of Helsinki, this study was approved by the Institutional Ethics Committee. Informed consent was obtained from all the parents.

The data were collected from the hospital electronic medical record system database with the following information collected: sex, gestational age, birth weight, delivery pattern, Apgar score, neonatal respiratory distress syndrome (NRDS), antenatal steroid administration, sepsis, pneumonia, oxygen therapy, mechanical ventilation administration, BPD, retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), pulmonary hypertension, duration of NICU stay, comorbidities and maternal health status.

2.2 Laboratory Measurements

Peripheral blood specimen less than 0.3 mL were harvested from the radial artery or radial vein. Blood samples were placed in standardized tubes containing dipotassium ethylene dinitro tetraacetic acid (EDTA) for complete blood count (CBC). UniCel DxH 800 (Beckman Coulter Inc., Hialeah, FL, USA) was used for CBC analysis. The PLR was calculated as the absolute Platelet (P) count divided by the absolute Lymphocyte (L) count from the CBC. The PNR was calculated as the absolute P count divided by the absolute Neutrophil (N) count from the CBC. The PLR and PNR at birth, 72 h, 1 w, 2 w and 4 w after birth were collected. The standards for blood routine testing referred to our previous study [24].

2.3 Statistical Analysis

Statistical analyses were performed by the SPSS 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as the mean $\pm$ standard deviation (SD) when fit a normal distribution, continuous variables were presented as the median (quartile) when do not fit a normal distribution, and categorical variables were expressed as frequencies and percentages. The continuous variables were analyzed by independent sample *t*-test or Kruskal-Wallis test and the categorical variables were analyzed by Chi-square test. The applicability of test are as follows: when the sample size is $\geq$40 and the theoretical frequency T $\geq$5, the basic formula of Chi-square test was used; when the sample size is $\geq$40, but the theoretical frequency $1 \leq T < 5$, the corrected Chi-square test was used. Multivariate logistic regression analysis was used to identify independent risk factors. A *p*-value less than 0.05 was considered statistically significant. The performance of laboratory features in the diagnosis of BPD was calculated by using the receiver operating characteristic (ROC) curve.

3. Results

3.1 Patients Characteristics

Of the enrolled 533 preterm infants, there were 165 preterm infants with BPD (including 3 who died from respiratory failure within 36 w PMA) and 368 preterm infants without BPD. Baseline demographic and clinical characteristics of the neonates with BPD and without BPD are presented in Table 1. Neonates that were diagnosed with BPD had more unfavorable baseline characteristics compared to neonates without BPD. The gestational age and birth weight were significantly lower in BPD patients and the Apgar scores at 1 min and at 5 min were also significantly lower in BPD patients. The incidence of NRDS, congenital sepsis, and congenital pneumonia were higher in the BPD patients. Days with invasive mechanical ventilation, oxygen therapy, intravenous nutrition therapy and duration of NICU stay were significantly prolonged in the BPD patients.

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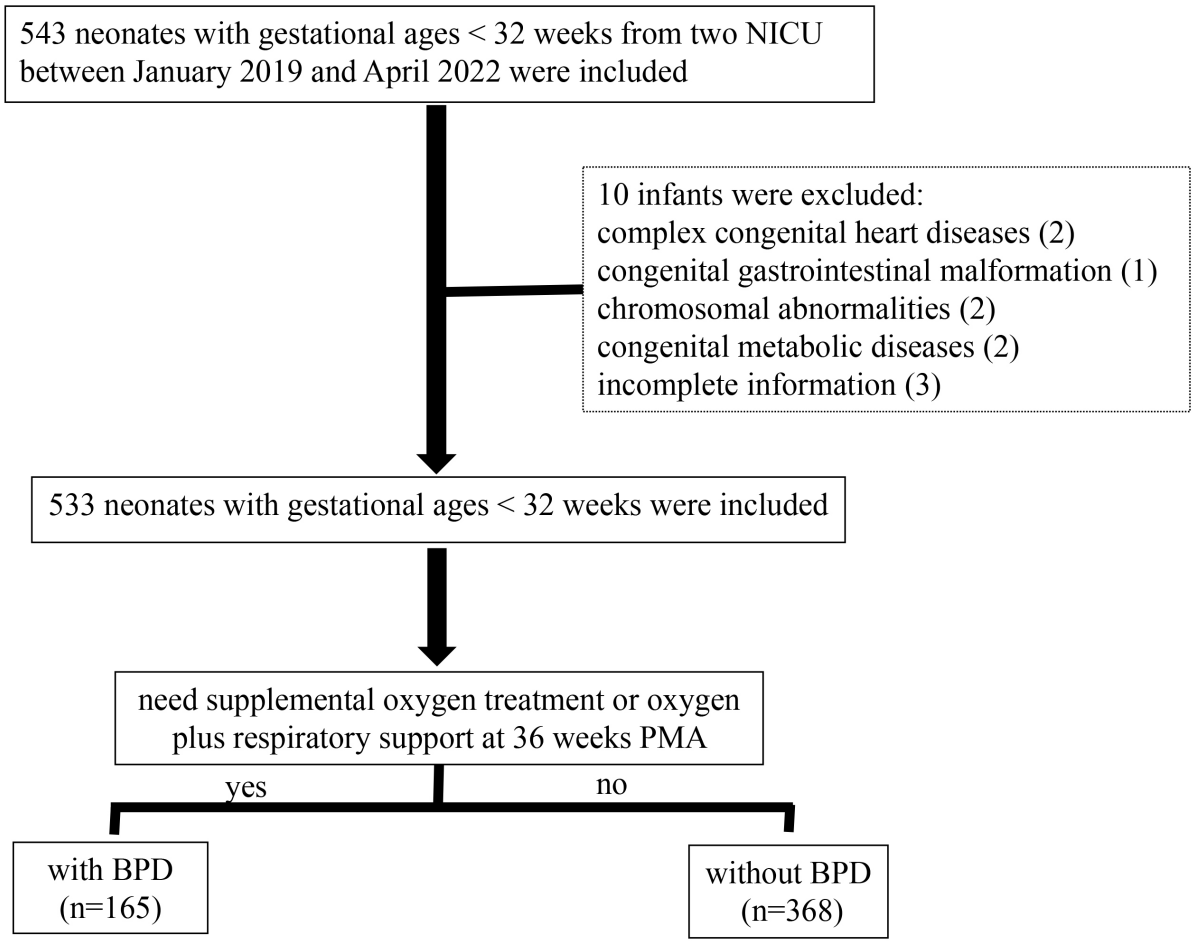

Fig. 1. The flowchart of the study. NICU, neonatal intensive care units; PMA, post-menstrual age; BPD, bronchopulmonary dysplasia.

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

	Without BPD (n = 368)	With BPD (n = 165)	χ^2 or T or Z	p
Male	207 (56.2%)	93 (56.3%)	0.001	0.98
Gestational age (weeks)	30.18 ± 1.41	28.77 ± 1.62	10.106	0.000**
Birth weight (grams)	1452.45 ± 303.95	1162.48 ± 266.98	10.546	0.000**
Antenatal steroid	304 (82.6%)	133 (80.6%)	0.921	0.631
Maternal age (years)	29.18 ± 4.37	30.97 ± 3.73	3.479	0.062
Gestational hypertension	70 (19.0%)	29 (17.5%)	10.478	0.581
Gestational diabetes mellitus	77 (20.9%)	39 (23.6%)	1.164	0.281
In vitro fertilization	125 (34.0%)	70 (42.4%)	3.512	0.061
Caesarean delivery	147 (39.9%)	53 (32.1%)	2.975	0.085
Apgar score at 1 min	7.23 ± 2.29	6.35 ± 2.60	3.924	0.000**
Apgar score at 5 min	9.19 ± 1.06	8.67 ± 1.38	4.699	0.000**
NRDS	231 (62.7%)	146 (88.4%)	36.453	0.000**
Congenital sepsis	108 (29.3%)	74 (44.8%)	12.173	0.001**
Congenital Pneumonia	93 (25.2%)	88 (53.3%)	40.000	0.000**
Invasive mechanical ventilation (h)	24 (0, 120)	0 (0, 0)	−7.318	0.000**
Oxygen therapy (d)	20.5 (7, 38)	58 (43, 68)	−14.088	0.000**
Intravenous nutrition therapy (d)	15 (10, 23)	28 (19, 36)	−10.121	0.000**
duration of NICU stay (d)	45 (35, 58)	71 (59, 86)	−12.557	0.000**

**$p < 0.01$; BPD, bronchopulmonary dysplasia; NRDS, neonatal respiratory distress syndrome; NICU, neonatal intensive care units.

Table 2. The platelet-related indicators of patients in preterm infants with or without BPD.

		Without BPD	With BPD	*T* or *Z*	*p*
at birth		n = 368	n = 165		
	P (10^9/L)	232.53 ± 64.54	225.33 ± 66.35	1.181	0.238
	PLR	105.61 (66.74, 524.27)	322.22 (90.60, 594.35)	−3.283	0.001**
	PNR	80.49 (41.82, 447.78)	300.00 (45.99, 544.73)	−2.798	0.005**
at 72 h		n = 257	n = 120		
	P (10^9/L)	222.73 ± 84.24	193.13 ± 89.53	3.114	0.002**
	PLR	94.59 (60.56, 395.39)	216.60 (70.61, 473.82)	−0.579	0.563
	PNR	82.46 (43.67, 370.62)	113.56 (41.42, 361.11)	−0.056	0.955
at 1 w		n = 120	n = 54		
	P (10^9/L)	226.27 ± 92.76	262.71 ± 116.71	3.944	0.013*
	PLR	231.27 (61.59, 729.66)	269.07 (62.18, 496.63)	−0.888	0.375
	PNR	258.97 (60.23, 687.33)	323.24 (63.37, 581.97)	−0.374	0.708
at 2 w		n = 334	n = 142		
	P (10^9/L)	300.58 ± 111.32	237.11 ± 93.92	5.951	0.000**
	PLR	85.53 (56.61, 559.50)	300.90 (59.33, 524.66)	−1.430	0.153
	PNR	146.00 (76.46, 647.21)	306.32 (60.95, 789.28)	1.312	0.189
at 4 w		n = 321	n = 150		
	P (10^9/L)	328.88 ± 118.05	289.75 ± 105.48	3.464	0.001**
	PLR	99.77 (65.50, 526.04)	306.32 (60.95, 789.28)	−2.432	0.015*
	PNR	244.89 (133.21, 526.05)	515.79 (125.84, 1021.13)	−0.829	0.407

*$p < 0.05$; **$p < 0.01$; P, platelet; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio.

3.2 Comparison of the Platelet-Related Indicators in Preterm Infants with or without BPD

The preterm infants in the BPD group had lower P count at 72 h (193.13 ± 89.53 *vs.* 222.73 ± 84.24, $p < 0.05$), at 2 w (237.11 ± 93.92 *vs.* 300.58 ± 111.32, $p < 0.05$) and at 4 w (289.75 ± 105.48 *vs.* 328.88 ± 118.05, $p < 0.05$), but had higher P count at 1 w (262.71 ± 116.71 *vs.* 226.27 ± 92.76, $p < 0.05$). The preterm infants in the BPD group had higher PLR at birth [322.22 (90.60, 594.35) *vs.* 105.61 (66.74, 524.27), $p < 0.05$] and at 4 w [306.32 (60.95, 789.28) *vs.* 99.77 (65.50, 526.04), $p < 0.05$], and had higher PNR at birth [300.00 (45.99, 544.73) *vs.* 80.49 (41.82, 447.78), $p < 0.05$] as compared to preterm infants without BPD (Table 2). Further multivariate logistic regression analysis demonstrated that gestational age (odds ratio (OR) = 0.627, [95% confidence interval (95% CI): 0.424–0.927], $p < 0.05$), PLR at birth (OR = 1.001, [95% CI: 1.000–1.002], $p < 0.05$), PNR at birth (OR = 1.001, [95% CI: 1.000–1.002], $p < 0.05$), and P at 2 w (OR = 0.992, [95% CI: 0.986–0.999], $p < 0.05$) were independent risk factors for BPD (Table 3).

3.3 Potential Role in Early Prediction of BPD by the Platelet-Related Indicators

The ROC curves of the PLR at birth, PNR at birth and gestational age for the prediction of BPD are shown in Fig. 2 and Table 4. PLR at birth represented a predictive value for BPD with the area under the curve (AUC) being 0.589, sensitivity was 0.661, and specificity was 0.579 when the threshold was 135.33. PNR at birth represented a predictive value for BPD with the AUC being 0.576, sensitivity was 0.612, and specificity was 0.589 when the threshold was 129.12. The most accurate discriminatory gestational age at birth threshold was 30.07 with AUC being 0.749, the sensitivity was 0.601, the specificity was 0.770 for BPD. When combining gestational age with PLR at birth, the AUC was 0.757, the sensitivity was 0.770, and the specificity was 0.628. When combining gestational age with PNR at birth, the AUC was 0.762, the sensitivity was 0.764, and the specificity was 0.629. The predictive value of the model was improved when including gestational age, PLR at birth and PNR at birth with AUC being 0.762, sensitivity was 0.642, and specificity was 0.776. When PLR at birth cutoff was 135.33, PNR at birth cut off was 129.12, gestational age cut off was 30.07, the positive predictive value of BPD was 56.2%.

Furthermore, P at 2 w represented a predictive value for BPD with the AUC being 0.668, sensitivity was 0.548, and specificity was 0.711 when the threshold was 285.5. When combining gestational age, PLR at birth, PNR at birth and P at 2 w, the AUC was 0.798, the sensitivity was 0.754, and the specificity was 0.737. When PLR at birth cutoff was 135.33, PNR at birth cut off was 129.12, P at 2 w cut off was 285.8, gestational age cut off was 30.07, the positive predictive value of BPD was 64.6%.

3.4 The Clinical Outcomes when Stratified by the PLR at Birth, PNR at Birth and P at 2 w

The clinical outcomes of this cohort stratified by the PLR at birth, PNR at birth and P at 2 w are presented in Table 5. Besides the effect on the occurrence of BPD, the

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Table 3. Multivariate logistic regression analysis of risk factors for peterm infants with BPD.

	With BPD					
	B	SE	Wald	p	OR	95% CI
Gestational age (weeks)	−0.467	0.200	5.474	0.019*	0.627	0.424−0.927
Birth weight (grams)	0.001	0.001	0.202	0.653	1.001	0.998−1.003
NRDS	0.633	0.715	0.783	0.376	1.883	0.463−7.652
Apgar score at 1 min	0.108	0.101	1.142	0.285	1.114	0.914–1.358
Apgar score at 5 min	−0.364	0.192	3.583	0.058	0.695	0.477−1.013
Congenital sepsis	0.034	0.465	0.005	0.942	1.035	0.416−2.572
Nosocomial sepsis	−0.362	0.481	0.567	0.451	0.696	0.271−1.787
Invasive mechanical ventilation (h)	0.000	0.001	0.079	0.779	1.000	0.998−1.002
PLR at birth	0.001	0.001	5.984	0.014*	1.001	1.000−1.002
PNR at birth	0.001	0.001	4.472	0.034*	1.001	1.000−1.002
P at 72 h (10^9/L)	0.000	0.003	0.001	0.976	1.000	0.994−1.006
P at 1 w (10^9/L)	0.000	0.004	0.000	0.998	1.000	0.993−1.007
P at 2 w (10^9/L)	−0.008	0.003	5.793	0.016*	0.992	0.986−0.999
P at 4 w (10^9/L)	0.001	0.001	0.329	0.566	1.001	0.997−1.005

*$p < 0.05$. SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval.

Table 4. The value of prediction of platelet-related indicators for BPD.

	AUC	Sensitivity	Specificity	Cut off Point	p
Gestational age (weeks)	0.749	0.601	0.770	30.07	0.000**
PLR at birth	0.589	0.661	0.579	135.33	0.001**
PNR at birth	0.576	0.612	0.589	129.12	0.005**
P at 2 w (10^9/L)	0.668	0.548	0.711	285.50	0.000**
Gestational age and PLR at birth	0.757	0.770	0.628	30.07 and 135.33	0.000**
Gestational age and PNR at birth	0.762	0.764	0.629	30.07 and 129.12	0.000**
Gestational age, PLR at birth and PNR at birth	0.762	0.642	0.776	30.07, 135.33 and 129.12	0.000**
Gestational age, PLR at birth, PNR at birth and P at 2 w	0.798	0.754	0.737	30.07, 135.33, 129.12 and 285.8	0.000**

**$p < 0.01$; AUC, area under the curve.

occurrences of NEC, pulmonary hypertension, IVH grade 3 or 4, retinopathy of prematurity (ROP) requiring intervention, and death of infants with PLR $\geq$135.33 at birth, PNR $\geq$129.12 at birth and P at 2 w $<$285.8 were higher than those of newborns without PLR $\geq$135.33, PNR $\geq$129.12 and P at 2 w $\geq$285.8. The hospital stay of infants with PLR $\geq$135.33, PNR $\geq$129.12 and P at 2 w $\geq$285.8 was also longer.

4. Discussion

BPD is a severe clinical syndrome of lung injury that impedes alveolarization and microvascular development in preterm infants. Inflammation, caused by hyperoxia, chorioamnionitis and postnatal infection, is the main factor that initiates lung injury and contributes to BPD in preterm infants. It is clear that inflammation-related signaling pathways, such as NF-kB, Toll-like receptor 4, interferon, and pro-inflammatory cytokines are associated with the development of BPD [25,26]. Platelets, small anucleate cellular fragments that are released by megakaryocytes, are critical for inflammatory and immune responses. Platelets have been shown to influence leukocyte recruitment and cytokine response [27], to limit bacterial growth and dissemination [28], to influence activation of the vascular endothelium and the coagulation system [29], and to shape immune responses to pathogens and tumor cells [30]. During the development of sepsis, platelets are one of the first cells to respond when the pro-inflammatory and pro-coagulant mechanisms are disrupted [28,29]. In an inflammatory model, researchers found that many interactions of platelets with the leading edge of adherent neutrophils, and recruited neutrophils searched for activated platelets to initiate inflammation in the early phase [31]. Looney *et al.* [32] reported that it is vital for the coordinated interactions between neutrophils and platelets in the lung microcirculation of acute lung injury and the elimination of platelets in the blood significantly reduced lung damage in a preclinical study.

Inflammation plays a key role in lung development in extremely preterm infants and is a major contributor to the pathogenesis of BPD. The lung has been confirmed to be a primary site of terminal platelet biogenesis with approximately 10 million platelets per hour [33]. Thrombocytopenia is associated with a more disturbed host response [34]. Therefore, we speculated that the platelet count may be related to the outcomes of BPD. In our study, we found that the significant decrease in P counts at 72 h, at 2 w and at 4

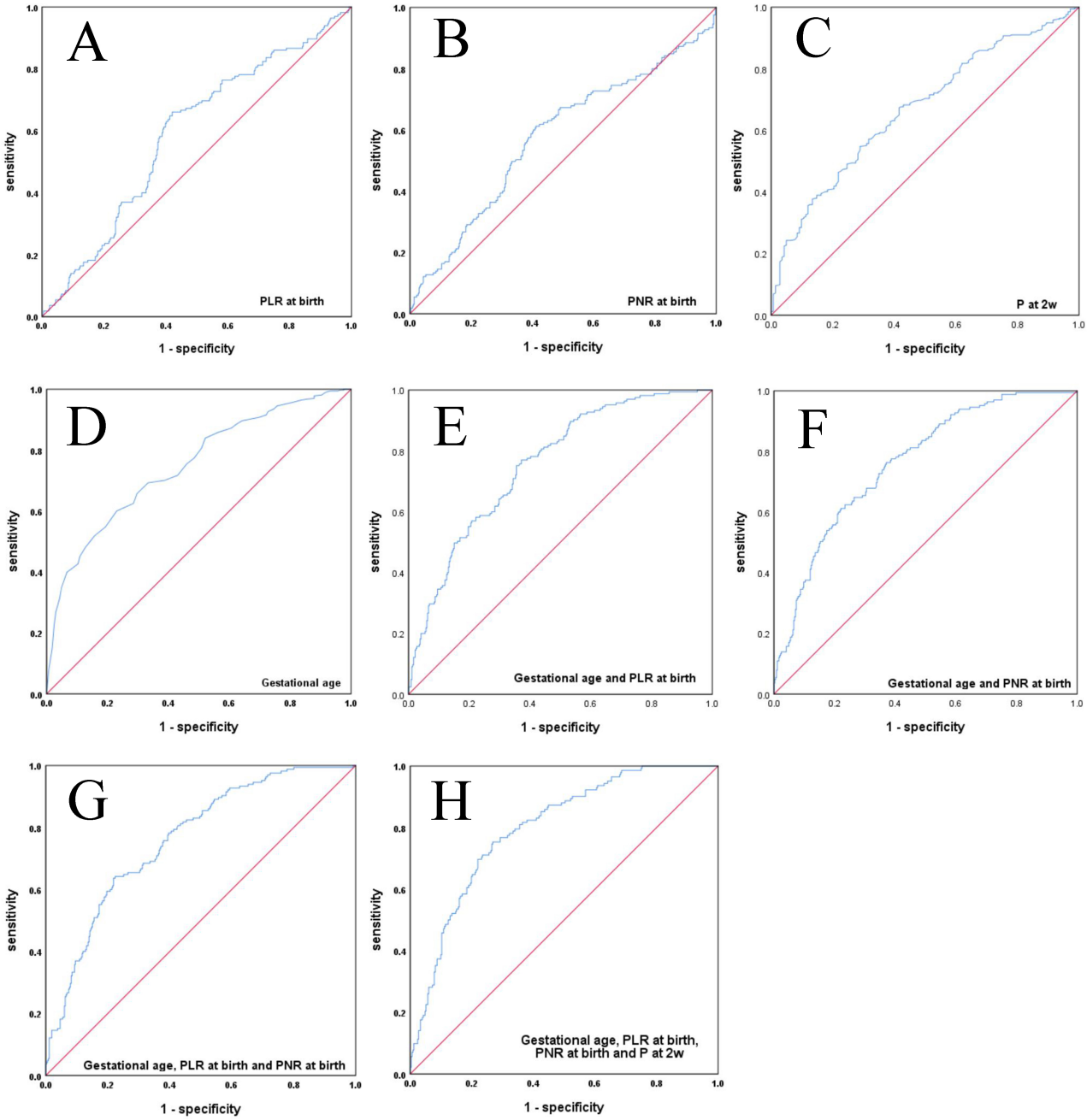

Fig. 2. The ROC curves of the platelet-related indicators and gestational age for the prediction of BPD. (A) The ROC curves of the PLR at birth for the prediction of BPD. (B) The ROC curves of the PNR at birth for the prediction of BPD. (C) The ROC curves of the P at 2 w for the prediction of BPD. (D) The ROC curves of gestational age for the prediction of BPD. (E) The ROC curves of combining gestational age and PLR at birth for the prediction of BPD. (F) The ROC curves of combining gestational age with PNR at birth for the prediction of BPD. (G) The ROC curves of combining gestational age, PLR at birth with PNR at birth for the prediction of BPD. (H) The ROC curves of combining gestational age, PLR at birth, PNR at birth with P at 2 w for the prediction of BPD. ROC, receiver operating characteristic; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio; BPD, bronchopulmonary dysplasia; P, platelet.

w and the significant increase in P counts at 1 w in infants with BPD, which associations may be due to inflammation in the pulmonary and peripheral blood. However, Chen *et al*. [35] found that the platelet counts at birth were higher in 115 preterm infants who were delivered at a gestational age ≤28 weeks or a birth weight ≤1000 g who developed BPD, but we found no difference in platelet counts at birth in the current study. This discrepancy may be owing to the different study populations including the different gestational age and birth weight, and further clarification is needed in future studies.

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Table 5. The clinical outcomes of the cohort by PLR at birth, PNR at birth and P at 2 w.

	PLR ≥135.33 at birth, PNR ≥129.12 at birth and P at 2 w <285.8 (n = 109)	Except PLR ≥135.33 at birth, PNR ≥129.12 at birth and P at 2 w ≥285.8 (n = 424)	χ^2 or T	p
BPD	58 (53.21%)	107 (25.23%)	31.794	0.000**
NEC	11 (10.09%)	3 (0.71%)	26.299[a]	0.000**
Pulmonary hypertension	11 (10.09%)	5 (1.17%)	23.654	0.000**
IVH grade 3 or 4	8 (7.34%)	2 (0.47%)	18.641[a]	0.000**
ROP requiring intervention	8 (7.34%)	3 (0.71%)	15.73[a]	0.000*
Hospital Stay	57.16 ± 2.40	55.61 ± 2.52	5.817	0.000**
Death	6 (5.50%)	2 (0.47%)	11.647[a]	0.001*

[a], corrected χ^2; *$p < 0.05$, **$p < 0.01$; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity.

Recently, a number of studies have shown that platelet-related indicators can be used as prognostic biomarkers for a variety of diseases [11–18]. Several studies demonstrated the significance of PLR and PNR in evaluating and predicting the severity of systemic inflammation, infections, immune and neoplastic diseases [19–23]. Studies also demonstrated that the PLR as an inflammatory marker along with NLR, which provides information about the disease activity and severity in early onset sepsis [36] and cancer [37]. Yun *et al*. [38] demonstrated that PNR and PLR as novel inflammatory biomarkers could predict the clinical outcome after aneurysmal subarachnoid hemorrhage. Liao *et al*. [23] clarified that peripheral blood parameter of NLR and PNR have good applied value in the diagnosis of neonatal pneumonia with high sensitivity and specificity. Similarly, inflammation and immune response depend on N, P and L counts in BPD patients. In our previous study, we confirmed that the higher NLR at 72 h after birth can be considered as an early indicator of BPD [24]. Accordingly, we speculated that the platelet-related indicators may be associated with BPD. In this study, we confirmed that the value of PLR at birth and PNR at birth were higher in preterm infants with BPD, while PLR at birth and PNR at birth were independently associated with the risk for BPD. When combining gestational age with PLR at birth and PNR at birth, the sensitivity and specificity for predicting BPD were improved. At the same time, we found that P at 2 w in infants with BPD was lower than that in infants without BPD, suggesting that it could be used as an independent predictor of BPD. When combined with PLR at birth, PNR at birth, P at 2 w, and gestational age, the sensitivity of the diagnosis of BPD was increased.

Severe complications such as NEC, pulmonary hypertension, IVH and ROP are often associated with premature infants, which can lead to poor prognosis. In this study, we observed a correlation between PLR and severe adverse complications. The occurrences were higher for adverse outcomes such as NEC, pulmonary hypertension, IVH grade 3 or 4, ROP requiring intervention, and death of infants with PLR ≥135.33 at birth, PNR ≥129.12 at birth and P at 2 w <285.8. Go *et al*. [39] found mean platelet volume ≥10.2 fL within 12 h of birth correlates with mortality among infants born <32 weeks' gestation. However, there are few studies on the prediction of adverse outcomes in premature infants by platelet-related indicators. We speculated that platelet-related indicators can be a meaningful indicator for complications of preterm infants and further relevant prospective studies are needed.

The main advantage of our research is that platelet-related indicators are easily accessible with no extra expense in the clinic practice. However, the present study has some limitations. The specificity and sensitivity of the indicators are not the strongest, and it is necessary to combine gestational age and other indicators to predict BPD. Meanwhile, the subjects were relatively few and the potential residual confounding could not be eliminated in the data from the regional two-centers. A larger number of subjects and multicenter studies are required to confirm the findings in the present study.

5. Conclusions

We confirmed that the platelet-related indicators PLR at birth, PNR at birth, and P at 2 w combined with gestational age, might be considered as a significant indicator of BPD. Furthermore, the occurrence rates were higher for adverse outcomes with PLR at birth ≥135.33, PNR at birth ≥129.12 and P at 2 w <285.8 in preterm infants.

Abbreviations

BPD, bronchopulmonary dysplasia; PLR, platelet-to-lymphocyte ratio; PNR, platelet-to-neutrophil ratio; NICU, neonatal intensive care units; AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; EBR, eosinophil-to-basophil ratio; NEC, necrotizing enterocolitis; PMA, postmenstrual age; EOS, early-onset sepsis; NRDS, newborn respiratory distress syndrome; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; EDTA, ethylene dinitro tetraacetic acid; CBC, complete blood count; N, neutrophil; L, lymphocyte; P, platelet; ROC, receiver operating characteristic; W, week;

SE, standard error; 95% CI, 95% confidence interval; OR, odds ratio; SD, standard deviation.

Availability of Data and Materials

The research data was uploaded as a file of supplementary materials. All data reported in this paper will also be shared by the corresponding author upon request.

Author Contributions

XZ and YS designed the research study. CuiC and JZ performed the research. ChaC analyzed the data. SC and NL collected data and drafted the work. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The research protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (Ethic Approval Number: No.2020-064) and Yiwu Maternity and Children Hospital (Ethic Approval Number: No.000021), and all of the participants provided signed informed consent.

Acknowledgment

Not applicable.

Funding

This research was funded by Taizhou Social Development Science and Technology Project (21ywb136), Zhejiang Medical Health Science and Technology Project, China (2023KY1293), Zhejiang Medical Association clinical research fund project, China (2024ZYC-B51) and Wenzhou Science and Technology Research Project, China (Y2023003).

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5110216.

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