ORIGINAL RESEARCH

Low Prognostic Nutritional Index (PNI) Level is Associated with an Increased Risk of Neonatal Respiratory Distress Syndrome in Preterm Infants with Different Gestational Ages: A Retrospective Study

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Background: Neonatal respiratory distress syndrome (NRDS) is common in preterm infants. Prognostic nutritional index (PNI) ((albumin (g/L)+(5×total lymphocyte count (10^9/L)) is a comprehensive indicator of nutritional and immune levels, and associated with several diseases. The relationship between PNI and the risk of NRDS in newborns of different gestational ages remains unclear.
Methods: A total of 2722 preterm infants were included in this retrospective study. PNI level and clinical records of these neonates (adverse pregnancy and birth history, amniotic fluid contamination, nuchal cord, placental abnormality, mode of delivery, gender and birth weight of neonates, Apgar scores) were collected. The clinical features of the infants with and without NRDS were compared. Logistic regression analysis was used to evaluate the relationship between PNI and NRDS in newborns with different gestational ages.
Results: There were 1226 neonates with NRDS and 1496 without NRDS. The differences in the proportions of placenta abnormality, cesarean section, and small for gestational age (SGA) among infants with 34–37 weeks, 28^{+1}-33^{+6} weeks, and ≤28 weeks gestational age were statistically significant. Logistic analysis showed that cesarean section (odds ratio (OR): 1.550, 95% confidence interval (CI): 1.197–2.007, p=0.001), and low PNI (OR: 1.417, 95% CI: 1.110–1.808, p=0.005) were associated with NRDS in infants born at 34–37 weeks gestational. Adverse pregnancy and birth history (OR: 1.507, 95% CI: 1.124–2.019, p=0.006), SGA (OR: 1.994, 95% CI: 1.455–2.733, p<0.001), and low PNI (OR: 1.626, 95% CI: 1.230–2.149, p=0.001) were associated with NRDS in infants with 28^{+1}-33^{+6} weeks gestational age. Low PNI (OR: 5.512, 95% CI: 1.555–19.536, p=0.008) was associated with NRDS in infants with ≤28 weeks gestational age.
Conclusion: The risk factors for NRDS in preterm infants with different gestational ages were different. But the low PNI level is associated with an increased risk of NRDS in preterm infants with all different gestational ages.
Keywords: neonatal respiratory distress syndrome, preterm infants, risk factors, prognostic nutritional index

Introduction

Preterm birth refers to births that occur at a gestational age <37 weeks according to the American College of Obstetricians and Gynecologists (ACOG).[1] Preterm infant is a live birth neonate less than 37 weeks of gestational age.[2] Pulmonary surfactant can reduce the surface tension of the alveoli, so that the alveoli open, thereby maintaining the stability of the alveoli, so as to ensure normal breathing.[3,4] Due to the immature development of preterm infants, the alveolar epithelial cells that synthesize pulmonary surfactants are lacking.[5–7] When the pulmonary surfactant is insufficient, the alveolar surface tension increases, the alveolar collapse is easy, and progressive atelectasis occurs, leading to the occurrence of neonatal respiratory distress syndrome (NRDS).[8]

NRDS is a serious respiratory disease in which immature lung development or alveolar dysfunction after birth leads to lack of lung surface active substances on the lung surface and alveolar atrophy in newborns.[9] NRDS is characterized by progressive dyspnea and respiratory failure shortly after birth.[10,11] Premature infants with NRDS are prone to pulmonary infection, pulmonary hypertension, pulmonary hemorrhage and other complications, which can lead to respiratory failure.[12–14] The incidence of NRDS has an increasing trend.[15,16] NRDS has a high social burden globally, especially in low-income countries.[17,18]

The lower the gestational age, the higher the incidence of NRDS, the incidence of ≤25 weeks of gestational age is approximately 91%, the incidence of 26–28 weeks of gestational age is approximately 58%, the incidence of 29–31 weeks of gestational age is about 52%.[19] However, in recent years, the incidence of late preterm infants and full-term infants with gestational age >34 weeks has also increased significantly.[20] The physiological characteristics of newborns of different gestational ages are different, and the clinical characteristics of NRDS may also different among children of different gestational ages.[21] It is of great significance to explore the relationship between the occurrence of NRDS in newborns with different gestational ages and the situation of newborn and pregnant women.

The prognostic nutritional index (PNI) was initially used to evaluate the overall status of the patients undergoing surgery and the risk of postoperative complications.[22,23] The PNI mainly reflects the characteristics of serum albumin concentration and total number of lymphocytes in peripheral blood, and is a comprehensive index of body nutrition and immune level.[24] Previous studies have shown that PNI is associated with malignant tumors,[25,26] heart failure,[27] stroke,[28] and respiratory diseases.[29,30] But the relationship between PNI and the risk of NRDS in newborns of different gestational ages remains unclear. This study mainly analyzed the relationship of PNI and the risk of NRDS in preterm infants of different gestational ages, and provided reference data for the prevention of NRDS in newborns of different gestational ages.

Materials and Methods
Subjects
Data of 2722 preterm infants who were hospitalized at Meizhou People's Hospital from October 2018 to March 2024 were collected in this retrospective observational study. In this study, premature birth is defined as delivery ≤37 weeks according to gestational weeks at birth. The inclusion criteria for NRDS patients were as follows: (1) newborns who met the diagnostic criteria of the Montreux Criteria for NRDS;[14,31] (2) preterm infants with gestational age ≤37 weeks; and (3) complete clinical data. Preterm infants without NRDS who were born at our hospital during the same period were selected as non-NRDS group. The inclusion criteria for non-NRDS were as follows: (1) preterm infants with a gestational age of ≤37 weeks; (2) newborns without NRDS; and (3) clinical data were complete. Exclusion criteria of NRDS patients: (1) newborns with other respiratory diseases causing respiratory distress; (2) newborns with autoimmune diseases or serious infectious diseases; and (3) newborns with congenital diseases. This study was supported by the Ethics Committee of the Meizhou People's Hospital.

Clinical Data Collected
Clinical data of the neonates and their mothers were collected from the medical records system of our hospital, including: (1) data of neonates' mothers: adverse pregnancy and birth history, scarred uterus, pregnancy conditions (amniotic fluid contamination, nuchal cord, placental abnormality, and mode of delivery); (2) data of neonates: gender, birth weight, 1-minute Apgar score, 5-minute Apgar score, respiratory distress, serum albumin level, and total lymphocyte count. The PNI was calculated as follows: albumin (g/L) + (5×total lymphocyte count (10^9/L). According to the gestational age at the time of delivery, the newborns in this study were divided into infants with 34–37 weeks gestational age, infants with 28^{+1}-33^{+6} weeks gestational age, and infants with ≤28 weeks gestational age. The birth weight of newborns in each gestational age group was referred to the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) standard.[32] The diagnostic criteria for infants with large for gestational age (LGA) is that their birth weight is above the 90th percentile of average weight for the same gestational age.[33] Small for gestational age

(SGA) is diagnosed as having a birth weight below the 10th percentile of the average weight for the same gestational age.[34]

Statistical Analysis

The data analysis was performed using SPSS 26.0 (IBM Inc., USA). The measurement data are expressed as mean ±standard deviation (SD), and the distributions of continuous variables were evaluated using Student's t-test or the Mann–Whitney U-test. Categorical variables were compared using χ^2 test and Fisher's exact test. When NRDS was regarded as the end point, receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of the PNI. Adverse pregnancy and birth history of pregnant women, amniotic fluid contamination, nuchal cord, placental abnormality, mode of delivery, gender and birth weight of neonates, 1-minute and 5-minute Apgar scores were selected as covariates in the multivariate logistic regression analysis for the association between the related factors and NRDS, based on estimating the odds ratios (OR) and their 95% confidence intervals (CIs) in preterm infants with different gestational ages. $p<0.05$ was considered statistically significant.

Result

The Clinical Features of the Preterm Neonates and Comparison of Clinical Features Among NRDS Patients and Controls

There were 1567 (57.6%) male preterm infants and 1155 (42.4%) female preterm infants. There were 1038 (38.1%) newborns born to women with a history of adverse pregnancy, and 109 (4.0%) preterm infants born to mothers with a scarred uterus. During the perinatal period, 63 (2.3%), 6 (0.2%), and 264 (9.7%) neonates showed amniotic fluid contamination, nuchal cord, and placental abnormality, respectively. There were 1163 (42.7%) and 1559 (57.3%) newborns who delivered via spontaneous and caesarean section, respectively. There were 667 (24.5%), 1969 (72.3%), and 86 (3.2%) preterm infants with SGA, normal, and LGA, respectively (Table 1).

Table 1 The Clinical Features of the Preterm Neonates and Comparison of Clinical Features Among NRDS Patients and Non-NRDS Neonates

Variables	Preterm neonates (n=2722)	Non-NRDS (n=1496)	NRDS (n=1226)	p values
Gender of neonates				
Male, n(%)	1567 (57.6%)	847 (56.6%)	720 (58.7%)	0.275
Female, n(%)	1155 (42.4%)	649 (43.4%)	506 (41.3%)	
Adverse pregnancy and birth history of pregnant women				
No, n(%)	1684 (61.9%)	937 (62.6%)	747 (60.9%)	0.383
Yes, n(%)	1038 (38.1%)	559 (37.4%)	479 (39.1%)	
Scarred uterus				
No, n(%)	2613 (96.0%)	1423 (95.1%)	1190 (97.1%)	0.011
Yes, n(%)	109 (4.0%)	73 (4.9%)	36 (2.9%)	
Perinatal conditions				
Amniotic fluid contamination				
No, n(%)	2659 (97.7%)	1452 (97.1%)	1207 (98.5%)	0.020
Yes, n(%)	63 (2.3%)	44 (2.9%)	19 (1.5%)	
Nuchal cord				
No, n(%)	2716 (99.8%)	1492 (99.7%)	1224 (99.8%)	0.696
Yes, n(%)	6 (0.2%)	4 (0.3%)	2 (0.2%)	
Placenta abnormality				
No, n(%)	2458 (90.3%)	1354 (90.5%)	1104 (90.0%)	0.697
Yes, n(%)	264 (9.7%)	142 (9.5%)	122 (10.0%)	

(*Continued*)

Table 1 (Continued).

Variables	Preterm neonates (n=2722)	Non-NRDS (n=1496)	NRDS (n=1226)	p values
Mode of delivery				
Spontaneous, n(%)	1163 (42.7%)	619 (41.4%)	544 (44.4%)	0.119
Cesarean section, n(%)	1559 (57.3%)	877 (58.6%)	682 (55.6%)	
Birth weight (kg)				
SGA, n(%)	667 (24.5%)	236 (15.8%)	431 (35.2%)	<0.001
Normal, n(%)	1969 (72.3%)	1202 (80.3%)	767 (62.6%)	
LGA, n(%)	86 (3.2%)	58 (3.9%)	28 (2.3%)	
1-minute Apgar score				
7–10, n(%)	2356 (86.6%)	1284 (85.8%)	1072 (87.4%)	<0.001
4–6, n(%)	125 (4.6%)	43 (2.9%)	82 (6.7%)	
<4, n(%)	46 (1.7%)	15 (1.0%)	31 (2.5%)	
Unknown	195 (7.2%)			
5-minute Apgar score				
7–10, n(%)	2483 (91.2%)	1322 (88.4%)	1161 (94.7%)	0.021
4–6, n(%)	41 (1.5%)	13 (0.9%)	28 (2.3%)	
<4, n(%)	7 (0.3%)	4 (0.3%)	3 (0.2%)	
Unknown	191 (7.0%)			
Prognostic nutritional index, mean±standard deviation	50.18±9.48	51.62±8.90	48.42±9.86	<0.001

Abbreviations: NRDS, neonatal respiratory distress syndrome; SGA, small for gestational age; LGA, large for gestational age.

This study included 1226 NRDS patients and 1496 neonates without RDS. The proportions of mothers with scarred uterus (2.9% vs 4.9%, p=0.011) and amniotic fluid contamination in the perinatal period (1.5% vs 2.9%, p=0.020) in NRDS group were significantly lower than those in non-NRDS group. The proportions of SGA (35.2% vs 15.8%), 1-minute Apgar score <7 (9.2% vs 3.9%), and 5-minute Apgar score <7 (2.5% vs 1.2%) in the NRDS group was higher than those in non-NRDS infants (all p<0.05). The level of PNI (48.42±9.86 vs 51.62±8.90, p<0.001) in NRDS patients was significantly higher than that in non-NRDS infants. The differences of gender of neonates, adverse pregnancy and birth history of pregnant women, nuchal cord, placenta abnormality, and mode of delivery between the two groups were not statistically significant (Table 1).

Comparison of Clinical Features Among Preterm Neonates with Different PNI Levels

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value of the PNI to distinguish NRDS from non-NRDS. The critical value of PNI was 46.875 (sensitivity 48.4%, specificity 69.5%, area under the ROC curve (AUC)=0.613) (Figure 1). There were 1050 preterm neonates with PNI<46.875 and 1672 with PNI≥46.875. The proportion of male (62.1% vs 54.7%, p<0.001), and SGA (36.0% vs 17.3%, p<0.001) in preterm neonates with PNI<46.875 were significantly higher than those in preterm neonates with PNI≥46.875. And the proportion of adverse pregnancy and birth history of pregnant women (35.3% vs 39.9%, p=0.019), mothers with scarred uterus (8.4% vs 12.9%, p<0.001), and placenta abnormality (6.9% vs 11.5%, p<0.001) in preterm neonates with PNI<46.875 were significantly lower than those in preterm neonates with PNI≥46.875. The differences of amniotic fluid contamination, nuchal cord, and 5-minute Apgar score between the two groups were not statistically significant (Table 2).

Comparison of Clinical Features of NRDS Patients with Different Gestational Weeks at Birth

The difference in the proportion of placental abnormality among infants with 34–37 weeks gestational age, 28^{+1}-33^{+6} weeks, and infants with ≤28 weeks gestational age was statistically significant (p=0.016). With an increase in gestational age at birth, the proportion of caesarean sections showed an increasing trend (p<0.001). With the decrease of gestational age at birth, the
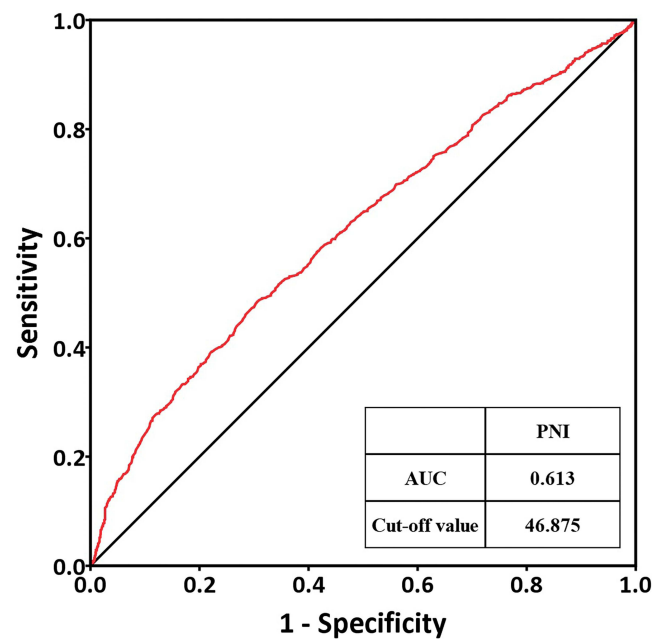
	PNI
AUC	0.613
Cut-off value	46.875

Figure 1 ROC curves of PNI for NRDS.
Abbreviation: ROC, receiver operating characteristic; PNI, prognostic nutritional index; NRDS, neonatal respiratory distress syndrome.

proportion of SGA, and low 1-minute Apgar score showed an increasing trend (all $p<0.001$). The differences of gender of neonates, adverse pregnancy and birth history of pregnant women, scarred uterus, amniotic fluid contamination, nuchal cord, mode of delivery, and 5-minute Apgar score between the three groups were not statistically significant. With the increase of the gestational age at birth, the PNI level showed an increasing trend (Table 3).

Table 2 Comparison of Clinical Features Among Preterm Neonates with Different PNI Levels

Variables	PNI<46.875 (n=1050)	PNI≥46.875 (n=1672)	p values
Gender of neonates			
Male, n(%)	652 (62.1%)	915 (54.7%)	<0.001
Female, n(%)	398 (37.9%)	757 (45.3%)	
Adverse pregnancy and birth history of pregnant women			
No, n(%)	679 (64.7%)	1005 (60.1%)	0.019
Yes, n(%)	371 (35.3%)	667 (39.9%)	
Scarred uterus			
No, n(%)	962 (91.6%)	1456 (87.1%)	<0.001
Yes, n(%)	88 (8.4%)	216 (12.9%)	
Perinatal conditions			
Amniotic fluid contamination			
No, n(%)	1028 (97.9%)	1631 (97.5%)	0.602
Yes, n(%)	22 (2.1%)	41 (2.5%)	
Nuchal cord			
No, n(%)	1047 (99.7%)	1669 (99.8%)	0.682
Yes, n(%)	3 (0.3%)	3 (0.2%)	
Placenta abnormality			
No, n(%)	978 (93.1%)	1480 (88.5%)	<0.001
Yes, n(%)	72 (6.9%)	192 (11.5%)	

(Continued)

Table 2 (Continued).

Variables	PNI<46.875 (n=1050)	PNI≥46.875 (n=1672)	*p* values
Mode of delivery			
Spontaneous, n(%)	478 (45.5%)	685 (41.0%)	0.021
Cesarean section, n(%)	572 (54.5%)	987 (59.0%)	
Birth weight (kg)			
SGA, n(%)	378 (36.0%)	289 (17.3%)	<0.001
Normal, n(%)	644 (61.3%)	1325 (79.2%)	
LGA, n(%)	28 (2.7%)	58 (3.5%)	
1-minute Apgar score			
7–10, n(%)	892 (85.0%)	1464 (87.6%)	0.001
4–6, n(%)	67 (6.4%)	58 (3.5%)	
<4, n(%)	22 (2.1%)	24 (1.4%)	
5-minute Apgar score			
7–10, n(%)	954 (90.9%)	1529 (91.4%)	0.230
4–6, n(%)	21 (2.0%)	20 (1.2%)	
<4, n(%)	2 (0.2%)	5 (0.3%)	

Abbreviations: PNI, prognostic nutritional index; SGA, small for gestational age; LGA, large for gestational age.

Table 3 Comparison of Clinical Features of NRDS Patients with Different Gestational Weeks at Birth

Variables	34–37 weeks (n=418)	28+1-33+6 weeks (n=709)	≤28 weeks (n=99)	*p* values
Gender of neonates				
Male, n(%)	234 (56.0%)	425 (59.9%)	61 (61.6%)	0.362
Female, n(%)	184 (44.0%)	284 (40.1%)	38 (38.4%)	
Adverse pregnancy and birth history of pregnant women				
No, n(%)	260 (62.2%)	428 (60.4%)	59 (59.6%)	0.799
Yes, n(%)	158 (37.8%)	281 (39.6%)	40 (40.4%)	
Scarred uterus				
No, n(%)	402 (96.2%)	690 (97.3%)	98 (99.0%)	0.299
Yes, n(%)	16 (3.8%)	19 (2.7%)	1 (1.0%)	
Perinatal conditions				
Amniotic fluid contamination				
No, n(%)	408 (97.6%)	702 (99.0%)	97 (98.0%)	0.140
Yes, n(%)	10 (2.4%)	7 (1.0%)	2 (2.0%)	
Nuchal cord				
No, n(%)	416 (99.5%)	709 (100.0%)	99 (100.0%)	0.271
Yes, n(%)	2 (0.5%)	0 (0)	0 (0)	
Placenta abnormality				
No, n(%)	362 (86.6%)	652 (92.0%)	90 (90.9%)	0.016
Yes, n(%)	56 (13.4%)	57 (8.0%)	9 (9.1%)	
Mode of delivery				
Spontaneous, n(%)	119 (28.5%)	341 (48.1%)	84 (84.8%)	<0.001
Cesarean section, n(%)	299 (71.5%)	368 (51.9%)	15 (15.2%)	
Birth weight (kg)				
SGA, n(%)	65 (15.6%)	267 (37.7%)	99 (100.0%)	<0.001
Normal, n(%)	334 (79.9%)	433 (61.1%)	0 (0)	
LGA, n(%)	19 (4.5%)	9 (1.3%)	0 (0)	

(*Continued*)

Table 3 (Continued).

Variables	34–37 weeks (n=418)	28^{+1}-33^{+6} weeks (n=709)	≤28 weeks (n=99)	p values
1-minute Apgar score				
7–10, n(%)	384 (91.9%)	617 (87.0%)	71 (71.7%)	<0.001
4–6, n(%)	15 (3.6%)	56 (7.9%)	11 (11.1%)	
<4, n(%)	7 (1.7%)	16 (2.3%)	8 (8.1%)	
5-minute Apgar score				
7–10, n(%)	401 (95.9%)	676 (95.3%)	84 (84.8%)	0.053
4–6, n(%)	5 (1.2%)	19 (2.7%)	4 (4.0%)	
<4, n(%)	0 (0)	2 (0.3%)	1 (1.0%)	
PNI, mean±standard deviation	50.70±9.72	47.71±9.47	43.90±10.99	<0.001

Abbreviations: NRDS, neonatal respiratory distress syndrome; SGA, small for gestational age; LGA, large for gestational age; PNI, prognostic nutritional index.

Logistic Regression Analysis of Predictor Factors of NRDS in Different Gestational Ages at Birth

The results of univariate analysis showed that cesarean section (cesarean section vs spontaneous, odds ratio (OR): 1.503, 95% confidence interval (CI): 1.179–1.918, p=0.001), and low PNI level (<46.875 vs ≥46.875, OR: 1.420, 95% CI: 1.121–1.799, p=0.004) were significantly associated with NRDS in infants with 34–37 weeks gestational age. Adverse pregnancy and birth history of pregnant women (yes vs no, OR: 1.459, 95% CI: 1.102–1.932, p=0.008), SGA (SGA vs normal, OR: 2.145, 95% CI: 1.576–2.919, p<0.001), and low PNI level (<46.875 vs ≥46.875, OR: 1.750, 95% CI: 1.335–2.292, p<0.001) were significantly associated with NRDS in infants with 28^{+1}-33^{+6} weeks of gestational age. A low PNI level (<46.875 vs ≥46.875, OR: 5.571, 95% CI: 1.782–17.418, p=0.003) was significantly associated with NRDS in infants with gestational age ≤28 weeks (Table 4).

Multivariate logistic regression analysis showed that cesarean section (cesarean section vs spontaneous, OR: 1.550, 95% CI: 1.197–2.007, p=0.001), and low PNI level (<46.875 vs ≥46.875, OR: 1.417, 95% CI: 1.110–1.808, p=0.005) were significantly associated with NRDS in infants with 34–37 weeks gestational age. Adverse pregnancy and birth history of pregnant women (yes vs no, OR: 1.507, 95% CI: 1.124–2.019, p=0.006), SGA (SGA vs normal, OR: 1.994, 95% CI: 1.455–2.733, p<0.001), and low PNI level (<46.875 vs ≥46.875, OR: 1.626, 95% CI: 1.230–2.149, p=0.001) were significantly associated with NRDS in infants with 28^{+1}-33^{+6} weeks gestational age. And low PNI level (<46.875 vs ≥46.875, OR: 5.512, 95% CI: 1.555–19.536, p=0.008) was significantly associated with NRDS in infants with gestational age ≤28 weeks. In other words, newborns with low PNI level were more than 1.4, 1.6, and 5.5 times more likely to develop NRDS than those with high PNI among preterm infants with 34–37 weeks, 28^{+1}-33^{+6} weeks, and ≤28 weeks gestational age, respectively (Table 5).

Discussion

NRDS has long been one of the most common respiratory diseases in newborns, especially in preterm infants.[7,35] The lower the gestational age at birth, the higher the incidence of NRDS.[36,37] Studies have found that the incidence of NRDS in preterm infants increases with the decrease of gestational age.[19] There may be differences in the risk factors for NRDS among preterm infants with different gestational ages. It is of great significance to explore the relationship between the occurrence of NRDS in preterm infants of different gestational ages and the situation of newborns and pregnant women, and to analyze its clinical characteristics and related risk factors.

Lymphocytes are an important components of the immune system and play a key role in some lung diseases.[38,39] Several studies have shown that lymphocyte count is associated with the development and prognosis of respiratory distress.[40–42] Albumin is a multifunctional plasma protein, that has important physiological functions in material transport and transportation, maintenance of colloid osmotic pressure, elimination of free radicals, anticoagulation and

Table 4 Associated Factors of NRDS in Different Gestational Ages at Birth by Univariate Logistic Regression Analysis

Variables	34–37 weeks		28⁺¹-33⁺⁶ weeks		≤28 weeks	
	OR (95% CI)	p values	OR (95% CI)	p values	OR (95% CI)	p values
Gender of neonates (male vs female)	0.984 (0.786–1.233)	0.891	0.997 (0.761–1.306)	0.983	1.246 (0.396–3.925)	0.707
Adverse pregnancy and birth history of pregnant women (yes vs no)	0.934 (0.742–1.176)	0.561	1.459 (1.102–1.932)	0.008	4.407 (0.943–20.594)	0.059
Scarred uterus (yes vs no)	0.731 (0.416–1.284)	0.276	0.704 (0.338–1.469)	0.350	0.143 (0.008–2.415)	0.177
Amniotic fluid contamination (yes vs no)	0.789 (0.387–1.608)	0.515	0.343 (0.127–0.931)	0.036	-	0.999
Nuchal cord (yes vs no)	1.392 (0.254–7.627)	0.703	-	-	-	-
Placenta abnormality (yes vs no)	1.343 (0.957–1.885)	0.088	1.180 (0.708–1.967)	0.525	-	0.999
Mode of delivery (cesarean section vs spontaneous)	1.503 (1.179–1.918)	0.001	1.263 (0.969–1.646)	0.084	0.714 (0.180–2.837)	0.633
Birth weight						
Normal	1.000 (reference)		1.000 (reference)		1.000 (reference)	
SGA	1.232 (0.898–1.689)	0.196	2.145 (1.576–2.919)	<0.001	-	-
LGA	1.140 (0.661–1.967)	0.638	0.499 (0.200–1.245)	0.136	-	-
PNI (<46.875 vs ≥46.875)	1.420 (1.121–1.799)	0.004	1.750 (1.335–2.292)	<0.001	5.571 (1.782–17.418)	0.003

Abbreviations: NRDS, neonatal respiratory distress syndrome; OR, odds ratio; CI, confidence interval; SGA, small for gestational age; LGA, large for gestational age; PNI, prognostic nutritional index.

Table 5 Associated Factors of NRDS in Different Gestational Ages at Birth by Multivariate Logistic Regression Analysis

Variables	34–37 weeks		28^{+1}-33^{+6} weeks		≤28 weeks	
	OR (95% CI)	p values	OR (95% CI)	p values	OR (95% CI)	p values
Gender of neonates (male vs female)	1.002 (0.796–1.261)	0.986	0.974 (0.735–1.292)	0.856	1.376 (0.384–4.934)	0.624
Adverse pregnancy and birth history of pregnant women (yes vs no)	0.932 (0.737–1.179)	0.557	1.507 (1.124–2.019)	0.006	4.939 (0.848–28.754)	0.076
Scarred uterus (yes vs no)	0.703 (0.492–1.007)	0.054	0.624 (0.388–1.002)	0.051	2.028 (0.087–47.401)	0.660
Amniotic fluid contamination (yes vs no)	0.748 (0.364–1.535)	0.428	0.298 (0.107–0.834)	0.021	-	0.999
Nuchal cord (yes vs no)	1.785 (0.320–9.973)	0.509	-	-	-	-
Placenta abnormality (yes vs no)	1.269 (0.892–1.807)	0.186	1.127 (0.653–1.947)	0.668	-	0.999
Mode of delivery (cesarean section vs spontaneous)	1.550 (1.197–2.007)	0.001	1.273 (0.949–1.709)	0.107	0.160 (0.019–1.325)	0.089
Birth weight						
Normal	1.000 (reference)		1.000 (reference)		1.000 (reference)	
SGA	1.097 (0.790–1.523)	0.581	1.994 (1.455–2.733)	<0.001	-	-
LGA	1.139 (0.657–1.977)	0.643	0.499 (0.195–1.276)	0.147	-	-
PNI (<46.875 vs ≥46.875)	1.417 (1.110–1.808)	0.005	1.626 (1.230–2.149)	0.001	5.512 (1.555–19.536)	0.008

Abbreviations: NRDS, neonatal respiratory distress syndrome; OR, odds ratio; CI, confidence interval; SGA, small for gestational age; LGA, large for gestational age; PNI, prognostic nutritional index.

antithrombosis, and participation in capillary permeability.[43–46] The level of albumin level can also reflect the inflammation and nutrient levels of patients, hypoalbuminemia is associated with neonatal infection and poor prognosis.[47,48] Several studies have found that albumin level is associated with the onset and outcome of acute respiratory distress.[49–51] However, PNI, as a comprehensive index of albumin and lymphocyte levels, has not been reported in relation to respiratory distress. In this study, low PNI level (<46.875) was significantly associated with NRDS in preterm infants of different gestational ages.

There have been some reports on the relationship between PNI and respiratory diseases. Some studies have shown that patients with low PNI levels of non-small cell lung cancer (NSCLC),[24,52,53] and small-cell lung cancer (SCLC)[54,55] have a worse prognosis than those with high PNI. PNI also can serve as a prognostic biomarker for chronic obstructive pulmonary disease (COPD).[56–58] In addition, some studies suggest that PNI can be used as a prognostic indicator for COVID-19 patients.[59–61] Moreover, PNI was a prognostic biomarker for community acquired bacterial pneumonia,[62] and pulmonary embolism.[63]

In this study, cesarean section was significantly associated with NRDS in infants at 34–37 weeks gestational age, but not in infants with 28^{+1}-33^{+6} weeks, and ≤28 weeks gestational age. Some studies have found that cesarean section is an important reasons for NRDS.[64] Normal uterine contractions can increase the secretion of adrenaline and promote the secretion of pulmonary surfactant secretion. Compared to newborns born naturally, the role of corticosteroids related to delivery in promoting lung maturation is reduced in newborns born by cesarean section.[65] At the same time, newborns born via cesarean section do not undergo birth canal compression during delivery, resulting in delayed removal of lung fluid.[66] Therefore, in clinical practice, the relevant indications of cesarean section should be expanded to ensure the safety of children and the impact of cesarean section on children should be reduced.

Low weight infants are mainly seen as premature infants, and some full-term infants can also appear to have low weight for various reasons. Low birth weight may be related to a variety of factors, such as an abnormal umbilical cord, placenta, insufficient nutrition of the mother, backward respiratory system development, and the possibility of NRDS is high. This study also found that SGA was significantly associated with NRDS in infants with 28^{+1}-33^{+6} weeks gestational age. Some studies have suggested that low birth weight is the main risk factor for NRDS.[21,67] However, other studies have suggested that the risk of NRDS is not related to birth weight of preterm infants.[68] It may be related to the difference in the number of cases included in different studies.

Summary, cesarean section, and low PNI level (<46.875) were significantly associated with NRDS in infants with 34–37 weeks gestational age; adverse pregnancy and birth history of pregnant women, SGA, and low PNI level (<46.875) were significantly associated with NRDS in infants with 28^{+1}-33^{+6} weeks gestational age; low PNI level (<46.875) was significantly associated with NRDS in infants with ≤28 weeks gestational age. This study has some limitations that are worth noting. First, because this was a retrospective study, other possible factors influencing NRDS were not included in the analysis. Second, there were fewer patients with amniotic fluid contamination and nuchal cord, and the assessment results for these factors and NRDS may have been biased. Third, this single-center study lacked external data for verification. Further expansion of clinical sample sizes and multi-center prospective studies are needed to confirm the risk factors for NRDS in preterm infants of different gestational ages.

Conclusions

In conclusion, the risk factors for NRDS in preterm infants of different gestational ages are different. Low PNI level is associated with an increased risk of neonatal respiratory distress syndrome in preterm infants with all different gestational ages. In addition, cesarean section was associated with NRDS in infants born at 34–37 weeks gestational; adverse pregnancy and birth history of pregnant women, and SGA were associated with NRDS in infants with 28^{+1}-33^{+6} weeks gestational age. The above factors should be considered in clinical studies to achieve early detection and prevention to reduce the incidence of NRDS.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital, Meizhou Academy of Medical Sciences (Clearance No.: 2024-C-60). The parents or legal guardians of all neonates signed informed consent forms.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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