Decrease in lipid metabolic indexes in infants with neonatal respiratory distress syndrome

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Abstract. Incomplete pulmonary function and insufficient production of pulmonary surfactant in premature infants may affect alveolar relaxation, inducing neonatal respiratory distress syndrome (NRDS). The present study was a retrospective comparison of lipid metabolism indexes and clinic information between NRDS and non-NRDS infants. Data on general information, pregnancy, clinical symptoms, family history as well as plasma biochemical and lipid metabolic indexes were retrospectively collected and statistically analyzed from 79 patients with NRDS and 44 non-NRDS infants. Infants in the NRDS group showed lower body weight (2,055 vs. 3,225 g) and gestation age (33.39 vs. 38.53 weeks) than those in the non-NRDS group (P<0.05). Baseline information was corrected by the inverse probability of treatment weighting (IPTW) analysis. The weighted adjusted median age was the same in both groups and there was no significant difference between two groups in birth weight. The IPTW analysis revealed that the levels of plasma triglyceride (TG), total cholesterol, low-density lipoprotein, free triiodothyronine, free thyroxine, glucose, calcium (Ca^{2+}) and phosphorus in the NRDS infants were significantly lower compared with those in the non-NRDS infants. Additionally, NRDS infants had significantly higher incidence rates of pneumonia, sepsis, brain injury infection, preterm birth, patent foramen ovale, patent ductus arteriosus and premature rupture of membranes compared with the non-NRDS infants (P<0.05). Multivariate logistic analysis showed that TG and Ca^{2+} were risk factors associated with NRDS (P<0.05). Infants with NRDS have significantly lower levels of plasma lipid indexes. The results of the present study provide data to guide the clinical management of NRDS.

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Introduction

Neonatal respiratory distress syndrome (NRDS) is one of the most common respiratory diseases in neonates, with ~1% prevalence in all deliveries worldwide (1,2) Moreover, NRDS is the major cause of infant death in the first 30 days of life, comprising ~30% of all neonatal deaths (3). Epidemiological studies have shown that there are nearly 60,000 to 80,000 cases of NRDS in the USA annually, among whom 6,000-12,000 infants succumb to the condition (3,4). Long-term studies indicated that 20% of surviving infants with NRDS suffer from chronic pulmonary disease in later life (5).

Clinic investigations have stated that gestational age and birth weight are inversely proportional to the risk of NRDS (6). The respiratory process comprises alveolar relaxation and contraction, which leads to the flow of air in the alveoli and exchange in blood oxygen. Alveolar contraction and relaxation are also dynamic balance processes. If a thoracic cavity loses its airtightness, the lung tissues would be in a state of natural atrophy. The relaxation process depends on the expansion of the thoracic cavity caused by the contraction of intercostal muscles, leading to negative pressure, resulting in the expansion of pulmonary alveoli. During the relaxation process, pulmonary surfactant plays an important role in relieving the tension of alveolar contraction (7). In premature infants, especially newborns under 34 weeks of gestational age, immature lung tissue, hypoxemia and insufficient production of pulmonary surfactant leads to increased alveolar diastolic resistance and insufficiency, which may be the major pathological mechanism of NRDS.

The characteristics of lipid metabolism in the early stage of preterm infants are not completely understood. However, it is generally considered that the lipid metabolism in preterm infants is immature compared to term infants. The role of lipids in the development and maturation of fetal lungs is still being investigated (8). The level of pulmonary maturity is closely related to the occurrence of NRDS in newborns (9). The secretion of pulmonary surfactant is an important index to evaluate pulmonary maturity (10). Lipids account for 85-90% of pulmonary surfactant components. Hass and Longmore (11) reported

that cholesterol occupies >50% of the neutral lipid of both the total surfactant and the lamellar body fractions. Lecithin, the major component of alveolar surfactant, is secreted through the stimulation of alveolar type II epithelial cells by high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) (12). In addition, fatty acids derived from triglyceride (TG) are important components in synthesizing alveolar surfactant (13).

The present clinical retrospective study was designed to investigate whether the abnormal lipid metabolism of infants is related to the pathogenesis of NRDS. Briefly, the characteristics of early neonatal blood lipid metabolism and its correlation with NRDS were explored by comparing and analyzing the blood lipid metabolism indexes and clinical data between infants with NRDS and non-NRDS infants. The results of the present study may provide clinical evidence for a deeper understanding of the pathological mechanism of NRDS.

Materials and methods

Patients and grouping. The data of newborns with NRDS (79 cases) admitted to the Neonatal Department of The First Hospital of Putian between January 1, 2019 and December 1, 2021, were retrospectively collected and classified as the NRDS group. In addition, 44 newborns without NRDS admitted to the Neonatal Department of our hospital were randomly selected as the non-NRDS group according to the random digital table method based on the medical record numbers during the same period. The present study was approved by the Ethics Committee of The First Hospital of Putian (approval no. 2022-010).

Inclusion criteria. Inclusion criteria included: i) The patients were in accord with the diagnosis criteria of NRDS. The diagnosis criteria was established as follows: Physical examination notable for obvious contraction of chest wall and cyanosis, compatible X-ray showing diffuse alveolitis and atelectasis, metabolic acidosis, hypoxemia and hypercapnia (14); ii) all included patients had no congenital abnormalities; iii) their mother was free of diabetes and dyslipidemia.

Exclusion criteria. Exclusion criteria included: Patients suffering from i) early developmental malformations (such as tracheoesophageal fistula, bronchopulmonary sequestration and bronchial cyst); ii) pulmonary parenchymal malformations (including congenital cystic adenomatoid malformation or congenital diaphragmatic hernia or pulmonary dysplasia caused by severe oligohydramnios); iii) diseases affecting respiration such as bronchopulmonary dysplasia, respiratory obstruction, abnormal chest wall, cardiovascular disease or neuromuscular disease, hypoglycemia and hypomagnesemia and pulmonary hypertension.

Clinical data collection. Clinical data were collected, including basic and clinical information, such as age, sex, gestational age, birth weight, Apgar score, jaundice, pneumonia, sepsis, brain injury, infection, premature infant, patent foramen ovale and patent ductus arteriosus. Maternal disease history during pregnancy was also obtained, including pregnancy-induced hypertension, premature rupture of membranes, placental abruption, hypoproteinemia and birth canal infection and information on the incidence of paternal diseases and family genetic diseases. Preterm baby was defined as newborns with a gestational age <37 weeks. The diagnostic criteria of neonatal jaundice, pneumonia, sepsis, brain injury, infection, patent foramen ovale and patent ductus arteriosus were from Pediatrics, 9th Edition (15).

Plasma biochemical analysis. Plasma biochemical indicators were measured once time at admission in both groups. Specifically, 2 ml of venous blood was collected and centrifuged (3,000 x g for 10 min at 4°C) to isolate serum. Serum total cholesterol (TC), TG, HDL, LDL, apolipoprotein (apo) A, apoB, calcium (Ca^{2+}), potassium (K), sodium (Na), chloride (Cl) and phosphorus (P^{3-}) were measured with the TBA-2000FR Automatic Biochemical Analyzer (Canon Medical Systems Corporation); serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) were detected with the ADVIA CENTAUR XP Automatic Chemiluminescence Immunoanalyzer (Siemens AG). In addition, another 2 ml of venous blood was collected and the whole blood plasma was separated and the level of serum C-reactive protein (CRP) was measured with the FS-301 Immunofluorescence analyzer (Guangzhou Wondfo Biotech Co., Ltd.).

Statistical analysis. *SPSS* version 26.0 software (IBM Corp.) and R language 4.1.1 (R core team; http://www.R-project.org/) were used for data analysis. The quantitative data of gestational age, plasma glucose, Ca^{2+}, K, Na, chlorine and P^{3-} were normally distributed and described by means ± standard deviation (SD). These data between the NRDS and non-NRDS groups were compared by two independent sample t-test. Since quantitative data, such as age, birth weight, plasma TG, TC, HDL, LDL, apoA, apoB, TSH, FT3 and FT4, had a skewed distribution, they were presented as median and interquartile spacing. The comparison of these data between the two groups was conducted by the Mann-Whitney U test. Qualitative data, such as sex and CRP, were described as frequency and proportion and the χ^2 test was used to compare these data between the two groups. All comparisons between the two groups were made using the inverse probability of treatment weighting (IPTW) method. Briefly, IPTW method utilized baseline features (including age, sex, birth weight, gestational age) to estimate the probability of the experimental groups and took the inverse probability weight to make the consistent distribution of propensity scores in all groups to eliminate the influence of confounding factors. $P<0.05$ was considered to indicate a statistically significant difference.

Results

General information. Following IPTW analysis, the sex ratio in the NRDS group was 36.5/87.3 cases (41.8%) for women and 50.8/87.3 cases (58.2%) for men; in the non-NRDS group it was 39.1/76.9 cases (50.8%) for women and 37.8/76.9 cases (49.2%) for men. Statistical analysis did not show any significant difference in sex distribution between the two groups (P=0.602) and the weighted adjusted median age was same

Table I. Comparison of the general information.

	Raw data			Inverse probability of treatment weighting		
Variable	NRDS (n=79)	Non-NRDS (n=44)	P-value	NRDS (n=87)	Non-NRDS (n=77)	Adjusted P-value
Age (days)[a]	1 (1,1)	5 (4,8)	<0.001	1 (1,1)	1 (1,5)	0.0031
Male sex, n (%)	49 (62.0)	25 (56.8)	0.572	50.8 (58.2)	37.8 (49.2)	0.602
Birth weight (g)[a]	2,055 (1,655, 2,335)	3,225 (3,000, 3,425)	<0.001	2,069 (1,675, 2,415)	3,000 (1,777, 3,227)	0.112
Gestational age, weeks	33.39±2.64	38.53±1.74	<0.001	33.37±2.96	36.16±2.56	0.005
1 min Apgar score	7.48±2.21	9.00±0.22	<0.001	7.57±2.28	8.97±0.24	<0.001
5 min Apgar score	8.48±1.16	9.77±0.42	<0.001	8.61±1.18	9.65±0.48	<0.001
10 min Apgar score	8.76±0.91	9.91±0.29	<0.001	8.87 ±0.93	9.55±0.50	0.002

[a]Since quantitative data on age and birth weight had a skewed distribution, they are presented as the median (interquartile spacing). NRDS, neonatal respiratory distress syndrome.

in both groups. The medium birth weights were 2,069 and 3,000 g in the NRDS and non-NRDS groups (P=0.112), respectively. The average gestational age of the NRDS group was significantly lower than that of the non-NRDS group (33.37 vs. 36.16 weeks; P=0.005) as the population of preterm ratio was higher in the NRDS group (Table I).

Clinical signs, symptoms and complications. The results of IPTW analysis revealed that the proportion of premature infants in the NRDS group was significantly higher than that in the non-NRDS group [76.9/87 cases (88.1%) vs. 42.4/77 cases (55.2%); P=0.024]. There were 47.3/87 cases (54.2%) of patients diagnosed as jaundice in the NRDS group, while in the non-NRDS group there were 68.3/77 cases (88.8%; P=0.006). Additionally, the diagnosis rates of pneumonia [61.9/87 cases (70.9%)], sepsis [39.7/87 cases (45.4%)], brain injury [60.7/87 cases (69.9%)], infection [12.8/87 cases (14.7%)], patent foramen ovale [48.5/87 cases (55.6%)] and patent ductus arteriosus [10.9/87 cases (12.5%)] of the NRDS group were significantly higher than those of the non-NRDS group [0/77 cases (0.0%), 0/77 cases (0.0%), 3.4/77 cases (4.5%), 0/77 cases (0.0%), 2.8/77 cases (3.6%) and 0/44 cases (0.0%), respectively; P<0.05; Table II].

Maternal pregnancy diseases, paternal diseases and family genetic diseases. The diagnosis rates of premature rupture of membranes [21/87.3 cases (24.0%)], placental abruption [7.2/87.3 cases (8.3%)], hypoproteinemia [5.1/87.3 (5.9%)] and birth canal infection [6.2/87.3 cases (7.1%)] in the NRDS group were significantly higher than those in the non-NRDS group [0/76.9 cases (0.0%); P<0.05]. There was no significant difference in the diagnosis proportion of maternal pregnancy-induced hypertension, paternal diseases and family genetic diseases between the NRDS and the non-NRDS groups (P>0.05; Table III).

Plasma lipid metabolism and biochemical indexes. Plasma lipid metabolic indexes were further analyzed in the plasma samples of patients in the two groups. The analysis outcomes showed that the levels of plasma TG (0.26 vs. 0.46 mmol/l), TC (2.17 vs. 2.49 mmol/l) and LDL (0.86 vs. 1.12 mmol/l) in the NRDS group were much lower than those in the non-NRDS group (P<0.05). However, no significant differences in plasma HDL, apoA and apoB were observed between the NRDS and non-NRDS groups (P>0.05; Table IV).

Blood biochemical indexes were detected in the plasma samples of patients in the two groups. The detection results indicated that the ratio of the plasma CRP ≥5 mg/l in the NRDS group was significantly higher than that in the non-NRDS group [34.53% (30.2/87.3 cases) vs. 0.0% (0/76.9 cases); P<0.001]. Notably, the plasma levels of FT3 (4.31 vs. 5.98 pmol/l), FT4 (16.91 vs. 21.90 pmol/l), glucose (2.49 vs. 3.87 mmol/l), Ca^{2+} (2.19 vs. 2.40 mmol/l), Cl^{-} (105.17 vs. 107.27 mmol/l) and P^{3-} (1.88 vs. 2.10 mmol/l) in the NRDS group were much lower than those in the non-NRDS group (P<0.05). However, the plasma levels of TSH, K^{+} and Na^{+} were not statistically different between the two groups (P>0.05; Table IV).

Risk factors affecting NRDS. Univariate logistic analysis showed that TG [Odds ratio (OR): 0.001, 95% confidence interval (CI): 0.000-0.016, P<0.001], TC (OR: 0.424, 95% CI: 0.253-0.711, P<0.001), LDL (OR: 0.170, 95% CI: 0.075-0.382, P<0.001), glucose (OR: 0.502, 95% CI: 0.379-0.665, P<0.001), FT4 (OR: 0.835, 95% CI: 0.754-0.925, P=0.001), Ca^{2+} (OR: 0.001, 95% CI: 0.000-0.009, P<0.001) and P^{3-} (OR: 0.015, 95% CI: 0.002-0.090, P<0.001) were risk factors associated with NRDS, whereas FT3 was not associated with NRDS (OR: 1.003, 95% CI: 0.990-1.015, P=0.676). Multivariate logistic analysis showed that TG (OR: 0.001, 95% CI: 0.000-0.559, P=0.033) and Ca^{2+} (OR: 0.000, 95% CI: 0.000-0.082, P<0.008) were risk factors associated with NRDS (Table V).

Discussion

In the present study, the comparison results of the general conditions between the NRDS and non-NRDS groups revealed that, except for sex distribution, all other variables, including age, gestational age and birth weight in the NRDS group

Table II. Comparison of clinical signs, symptoms and complications.

	Raw data				Inverse probability of treatment weighting			
Variable	n	NRDS (n=79)	Non-NRDS (n=44)	P-value	n	NRDS (n=87)	Non-NRDS (n=77)	Adjusted P-value
Preterm, n (%)				<0.001				0.024
No	43	5 (6.3)	38 (86.4)		44.9	10.4 (11.9)	34.5 (44.8)	
Yes	80	74 (93.7)	6 (13.6)		119.3	76.9 (88.1)	42.4 (55.2)	
Jaundice, n (%)				<0.001				0.006
No	42	39 (49.4)	3 (6.8)		48.6	40.0 (45.8)	8.6 (11.2)	
Yes	81	40 (50.6)	41 (93.2)		115.6	47.3 (54.2)	68.3 (88.8)	
Pneumonia, n (%)				<0.001				<0.001
No	68	24 (30.4)	44 (100.0)		102.3	25.4 (29.1)	76.9 (100.0)	
Yes	55	55 (69.6)	0 (0.0)		61.9	61.9 (70.9)	0.0 (0.0)	
Sepsis, n (%)				<0.001				<0.001
No	89	45 (57.0)	44 (100.0)		124.5	47.6 (54.6)	76.9 (100.0)	
Yes	34	34 (43.0)	0 (0.0)		39.7	39.7 (45.4)	0.0 (0.0)	
Brain injury, n (%)				<0.001				<0.001
No	63	20 (25.3)	43 (97.7)		100	26.6 (30.4)	73.4 (95.5)	
Yes	60	59 (74.7)	1 (2.3)		64.1	60.7 (69.6)	3.4 (4.5)	
Infection, n (%)				<0.05				0.003
No	111	67 (84.8)	44 (100.0)		151.4	74.5 (85.3)	76.9 (100.0)	
Yes	12	12 (15.2)	0 (0.0)		12.8	12.8 (14.7)	0.0 (0.0)	
PFO, n (%)				<0.001				<0.001
No	75	32 (40.5)	43 (97.7)		112.9	38.8 (44.4)	74.1 (96.4)	
Yes	48	47 (59.5)	1 (2.3)		51.3	48.5 (55.6)	2.8 (3.6)	
PDA, n (%)				<0.05				0.007
No	113	69 (87.3)	44 (100.0)		153.3	76.4 (87.5)	76.9 (100.0)	
Yes	10	10 (12.7)	0 (0.0)		10.9	10.9 (12.5)	0.0 (0.0)	

NRDS, neonatal respiratory distress syndrome; PFO, patent foramen ovale; PDA, patent ductus arteriosus.

were significantly lower than those in the non-NRDS. These differences were to be expected since most of the preterm infants had NRDS and other defects. It is quite challenging to organize a gestational age-comparable non-NRDS group. Therefore, to make the comparison between the two groups more significant, IPTW analysis was performed on all data to eliminate confounding factors. The analysis results revealed that there were no significant differences in sex, birth weight and median age between the two groups of infants after adjustment. In a recent comparison study of serum TG and TC in infants with or without NRDS, Kelishadi *et al* (16) reported that sex and mean gestational ages between the two groups were not significantly different. A comparison of clinical signs, symptoms and complications between the two groups suggested that the incidence rates of premature infants, pneumonia, sepsis, infection, brain injury, patent foramen ovale and patent ductus arteriosus in the NRDS group were significantly higher than those in the non-NRDS.

By contrast, the jaundice incidence rate in the non-NRDS group was much higher than in the NRDS group. Comparison of maternal pregnancy diseases between the two groups showed that the incidence rate of premature rupture of membranes in the NRDS group was significantly higher than in the non-NRDS group. Premature rupture of membranes is an important cause of preterm birth and fetal infection (17), which was consistent with the result that there were more premature infants and higher proportions of abnormal CRP in the NRDS group.

It is known that delayed lung development and insufficient pulmonary surfactant secretion of newborns are closely related to the occurrence of NRDS (18). Several experiments have confirmed the effectiveness of exogenous surfactant in reducing the mortality and incidence rate of NRDS (19-22). It is reported that pulmonary surfactant secretion is related to lipid metabolism (23,24). An imbalance of TG, TC and apo in the pulmonary surfactant seriously hinders the important function of surfactant in reducing surface tension (11). In addition, an *in vitro* study revealed that HDL-C and LDL-C stimulate alveolar type II cells to produce lecithin (the main component of pulmonary surfactant), indicating that lipids are involved in forming pulmonary surfactant (12). Lane *et al* (8) proposed that compared with the control group, NRDS infants with birth

Table III. Comparison of maternal pregnancy diseases, paternal diseases and family genetic diseases.

	Raw data				Inverse probability of treatment weighting			
Variable	N	NRDS (n=79)	Non-NRDS n=44)	P-value	N	NRDS (n=87)	Non-NRDS (n=77)	Adjusted P-value
MPH, n (%)				0.146				0.585
No	111	69 (87.3)	42 (95.5)		148.1	77.1 (88.3)	71.0 (92.4)	
Yes	12	10 (12.7)	2 (4.5)		16	10.2 (11.7)	5.8 (7.6)	
PRM, n (%)				<0.001				<0.001
No	103	59 (74.7)	44 (100.0)		143.2	66.3 (76.0)	76.9 (100.0)	
Yes	20	20 (25.3)	0 (0.0)		21	21.0 (24.0)	0.0 (0.0)	
PA, n (%)				0.104				0.021
No	116	72 (91.1)	44 (100.0)		157	80.1 (91.7)	76.9 (100.0)	
Yes	7	7 (8.9)	0 (0.0)		7.2	7.2 (8.3)	0.0 (0.0)	
Hypoproteinemia, n (%)				0.220				0.048
No	118	74 (93.7)	44 (100.0)		159.1	82.2 (94.1)	76.9 (100.0)	
Yes	5	5 (6.3)	0 (0.0)		5.1	5.1 (5.9)	0.0 (0.0)	
BCI, n (%)				0.151				0.031
No	117	73 (92.7)	44 (100.0)		158	81.1 (92.9)	76.9 (100.0)	
Yes	6	6 (7.6)	0 (0.0)		6.2	6.2 (7.1)	0.0 (0.0)	
Paternal diseases, n (%)				>0.999				>0.999
No	118	76 (96.2)	42 (95.5)		159	83.1 (95.2)	75.9 (98.7)	
Yes	5	3 (3.8)	2 (4.5)		5.2	4.2 (4.8)	1.0 (1.3)	
FGD, n (%)				>0.999				>0.999
No	123	79 (100.0)	44 (100.0)		164.2	87.3 (100.0)	76.9(100.0)	
Yes	0	0 (0.0)	0 (0.0)		0	0 (0.0)	0 (0.0)	

NRDS, neonatal respiratory distress syndrome; MPH, maternal pregnancy-induced hypertension; PRM, premature rupture of membranes; PA, placental abruption; BCI, birth canal infection; FGD, family genetic diseases.

weight of 1,000-1,999 g had lower levels of lipids and apo. It is also claimed that low TG level may be one of the reasons for NRDS in preterm infants with gestational age of 28-30 weeks and weight ≤1,499 g (24). The study by Hopiavuori *et al* (21) showed that the level of TC in the amniotic fluid of NRDS mothers was lower than in non-NRDS mothers. In addition, Gunes *et al* (25) reported that NRDS infants had lower HDL and LDL levels. These data indirectly confirm that low lipid levels may be one of inducing factors for NRDS. The data from the present study revealed a significant decrease in TG, TC and LDL levels in NRDS infants, although the levels of HDL, apoA and apoB did not change; and univariate logistic analysis also showed that TG, TC and LDL were risk factors associated with NRDS.

Dhanireddy *et al* (26) and Hadeed *et al* (27) studied the alteration of thyroxine levels in infants with NRDS and found that the cord thyroxine level in NRDS infants was significantly lower than that in healthy infants. Such hypothyroxinemia could be recovered by thyrotropin-releasing hormone administration, reverting to normal and becoming stable at 6-7 weeks postnatal age. Comparison of the plasma thyroid hormones showed that the plasma FT3 and FT4 levels were significantly decreased in the NRDS group compared with the non-NRDS group, even though plasma TSH was similar between the two groups. Such abnormality in thyroxine metabolism reflected the immature development of infants with NRDS. Further univariate logistic regression analysis indicated that FT4 was a risk factor for NRDS. The present study also showed that the plasma glucose levels were significantly lower in the NRDS group than in the non-NRDS group. This finding is similar to the report by Keret *et al* (28). They observed the alteration in the plasma blood insulin and glucose of the premature infants (with 26-34 weeks' gestation age) for two months after birth. Their results showed that the plasma glucose level almost doubled in premature infants from birth to two months; in addition, the plasma glucose levels were positively correlated with the plasma insulin levels. These data suggest that a decrease in plasma glucose levels in patients with NRDS may result in lower plasma insulin levels. Moreover, univariate logistic regression analysis showed that glucose was a risk factor leading to NRDS. In addition, premature infants may suffer from hypokalemia in the first few days after birth because of low activity of Na-K-ATPase, low transmembrane potential, reduced K permeability of cell membrane and low urinary

Table IV. Comparison of plasma lipid metabolism and biochemical indexes.

	Raw data			Inverse probability of treatment weighting		
Variables	NRDS (n=79)	Adjusted P-value	P-value	Non-NRDS (n=77)	NRDS (n=87)	Adjusted P-value
CRP			<0.001			<0.001
<5 (mg/l)	53 (67.1)	43 (97.7)		76.87 (100.00)	57.15 (65.47)	
≥5 (mg/l)	26 (32.9)	1 (2.3)		0.00 (0.00)	30.15 (34.53)	
TG (mmol/l)[a]	0.26 (0.19, 0.37)	0.57 (0.45, 0.93)	<0.001	0.46 (0.32, 0.81)	0.26 (0.19, 0.38)	0.001
TC (mmol/l)[a]	2.25 (1.83, 2.77)	2.71 (2.32, 3.32)	<0.001	2.49 (2.26, 2.94)	2.17 (1.84, 2.72)	0.0103
HDL (mmol/l)[a]	1.17 (0.95, 1.40)	1.09 (0.82, 1.37)	0.203	1.09 (1.00, 1.13)	1.17 (0.96, 1.37)	0.0937
LDL (mmol/l)[a]	0.93 (0.68, 1.25)	1.51 (1.26, 1.94)	<0.001	1.12 (0.95, 1.55)	0.86 (0.66, 1.20)	0.0025
apoA (g/l)[a]	0.85 (0.77, 0.94)	1.05 (0.90, 1.22)	<0.001	0.80 (0.73, 1.09)	0.83 (0.77, 0.95)	0.732
apoB (g/l)[a]	0.34 (0.28, 0.44)	0.52 (0.46, 0.63)	<0.001	0.39 (0.29, 0.55)	0.32 (0.26, 0.44)	0.1564
TSH (uIU/ml)[a]	3.99 (2.47, 6.16)	4.71 (2.85, 6.04)	0.612	2.82 (2.21, 4.75)	3.93 (2.50, 6.01)	0.5119
FT3 (pmol/l)[a]	4.26 (3.56, 5.07)	6.00 (5.33, 6.77)	<0.001	5.98 (5.34, 6.64)	4.31 (3.58, 5.04)	<0.001
FT4 (pmol/l)[a]	17.30 (15.10, 20.70)	21.85 (19.65, 24.15)	<0.001	21.90 (19.56, 25.02)	16.91 (15.04, 20.38)	<0.001
Glucose (mmol/l)	2.41±1.78	4.37±1.43	<0.001	3.87±1.34	2.49±1.78	<0.001
Ca^{2+} (mmol/l)	2.18±0.17	2.41±0.17	<0.001	2.40 (0.14)	2.19 (0.16)	<0.001
K^+ (mmol/l)	4.84±0.53	5.09±0.56	0.014	4.80 (0.64)	4.86 (0.52)	0.738
Na^+ (mmol/l)	139.24±3.09	140.30±3.91	0.102	139.24±4.44	139.16±3.05	0.958
Cl^- (mmol/l)	105.28±2.58	105.32±2.66	0.932	107.27 (3.01)	105.17 (2.56)	0.019
P^{3-} (mmol/l)	1.86±0.27	2.14±0.24	<0.001	2.10±0.24	1.88±0.27	0.002

[a]Since quantitative data, such as plasma TG, TC, HDL, LDL, apoA, apoB, TSH, FT3 and FT4, had a skewed distribution, they are presented as the median (interquartile spacing). NRDS, Neonatal respiratory distress syndrome; CRP, plasma C-reactive protein; TG, triglyceride; TC, total cholesterol; HDL, High-density lipoprotein; LDL, low-density lipoprotein; apoA, apolipoprotein A; apoB, apolipoprotein B; TSH, thyroid stimulating hormone; FT3, free thyroxine 3; FT4, free thyroxine 4; Ca^{2+}, calcium; K^+, potassium; Na^+, sodium; Cl^-, chloride; P^{3-}, phosphorus.

flow of the kidneys. It is worth noting that respiratory failure can exacerbate hypokalemia. However, the level of K would not be lower than 4 mmol/l (29). The results of the present study showed that the average K level of plasma in NRDS infants was 4.84 mmol/l, which is consistent with the above. Notably, the plasma Na levels between the two groups were not significantly different, but the plasma P^{3-} and Cl levels of the NRDS infants were significantly lower compared with those of the non-NRDS infants.

The present study showed that TG (OR: 0.001; 95% CI: 0.000-0.559; P=0.033) and Ca^{2+} (OR: 0.000; 95% CI: 0.000-0.082; P<0.008) were risk factors associated with NRDS. TG is an important source of fatty acid and an essential component of pulmonary surfactant synthesis, which is decomposed into fatty acids and glycerol under the action of lipoprotein lipase (11). The result that TG was a risk factor associated with NRDS further illustrated a close relationship between NRDS and lipid metabolism. However, not all infants with NRDS showed a significant decline in TG since data from Kelishadi *et al* (16) did not exhibit an obvious difference of TG between the infants with and without NRDS. Moreover, Wang *et al* (24) reported no statistical differences in TC, HDL and LDL levels between infants with and without NRDS. Therefore, more clinical studies concerning lipid metabolism and NRDS are needed to provide more reference data. Ca^{2+} was also a risk factor associated with NRDS. Mature infants usually receive most of their Ca^{2+} from their mothers to maintain fetal development. However, Ca^{2+} obtained from the mother in premature infants is limited and the Ca^{2+} in the exchange pool is insufficient. Although there is

Table V. Logistic regression analysis of risk factors leading to NRDS.

	Univariate logistic analysis			Multivariate logistic analysis		
Risk factor	OR	95% CI	P-value	OR	95% CI	P-value
CRP	21.094	2.750-161.808	0.003	4.390	0.309-62.426	0.275
TG	0.001	0.000-0.016	<0.001	0.001	0.000-0.559	0.033
TC	0.424	0.253-0.711	0.001	21.524	0.105-4406.261	0.258
LDL	0.170	0.075-0.382	<0.001	0.005	0.000-2.429	0.093
Glucose (mmol/l)	0.502	0.379-0.665	<0.001	0.876	0.533-1.437	0.599
FT3 (pmol/l)	1.003	0.990-1.015	0.676	1.006	0.979-1.034	0.648
FT4 (pmol/l)	0.835	0.754-0.925	0.001	1.019	0.815-1.273	0.871
Ca^{2+} (mmol/l)	0.001	0.000-0.009	<0.001	0.000	0.000-0.082	0.008
P^{3-} (mmol/l)	0.015	0.002-0.090	<0.001	0.131	0.005-3.483	0.225

OR, odds ratio; CI, confidence interval; CRP, plasma C-reactive protein; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; FT3, free thyroxine 3; FT4, free thyroxine 4; Ca^{2+}, calcium; P^{3-}, phosphorus.

normal parathyroid hormone and/or 1,25(OH) vitamin D, it is difficult to obtain Ca^{2+} from the exchange pool to supplement maternal supply (30,31). Hence, premature infants are prone to hypocalcemia and, also, most of NRDS occurs in premature infants. Hypocalcemia is a confounding factor and whether hypocalcemia is a risk factor needs to be further demonstrated in the population of premature infants.

Taken together, lipid metabolism not only plays an important role in maintaining the normal physiological function of the human body but also acts as an important factor in maintaining the normal development of a fetus (29). Experimental and clinical evidence showed that the lipid nutrition and lipid metabolism of fetus and newborn could significantly affect the growth, development and function of the lungs, as well as long-term pulmonary health and disease risk (32-34). Pediatricians consider that abnormal lipid metabolism caused by unknown reasons is closely related to NRDS. The Institute of Medicine guidelines for gestational weight gain recommend the highest gestational weight gain for underweight women, intermediate gestational weight gain for normal weight women and lowest gestational weight gain for obese women as an attempt to optimize birth weight (35). Additionally, it was reported that high body mass index and environmental factors such as weight gain and dietary and alcohol habits might influence lipid metabolism during pregnancy (36). Therefore, appropriate maternal weight gain during pregnancy may prevent lipid disturbances, decrease the risk of NRDS and reduce morbidity during the neonatal period.

There are some limitations to the present study. First, the gestational age of the non-NRDS group was not comparable to the NRDS group. It might be unrealistic to establish a gestational age-comparable non-NRDS group. Confounding factor is a common limitation that all retrospective studies face. Indeed, an IPTW analysis was performed on the baseline data of patients in the present study. The weighted adjusted median age was the same in both groups and there was no significant difference between the two groups in birth weight. All corresponding data were subsequently analyzed by IPTW and there was no change in the final conclusions. This may partly solve the problems arising from the uneven baseline information and confounding factors. However, preterm birth affects changes of numerous indicators such as Ca^{2+}, which is a large confounding factor. Hence, further experiments will be conducted in only preterm infants or only term infants to eliminate confounding factors from gestational age. Additionally, since the number of observed NRDS cases was limited, a more detailed analysis of the effects of weight or gestational age on the incidence rate of NRDS could not be conducted. Therefore, the findings still need to be validated by improved study design, large sample size and prospective multi-center settings.

The present study showed that the plasma levels of TG, TC, LDL FT3, FT4, glucose, Ca^{2+}, Cl and P^{3-} were significantly decreased in the NRDS infants with lower body weight and gestation age compared with non-NRDS infants who matured. Multivariate logistic analysis showed that TG and Ca^{2+} were risk factors associated with NRDS. Collectively, the present study has provided further data support for the clinical instruction of NRDS therapy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GZ and TZ designed the present study. GZ and XH collected clinical and experimental data. JZ performed the statistical analyses. GZ, JZ, XH and TZ analyzed the results. GZ and

TZ wrote the manuscript. GZ and TZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The First Hospital of Putian (approval no. 2022-010).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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