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Characteristics of Respiratory Distress Syndrome in Infants of Different Gestational Ages

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Abstract
Background The purpose of this study was to compare the risk factors, clinical characteristics, and complications of respiratory distress syndrome (RDS) in infants delivered very preterm, late preterm, and term in order to help optimize the management of RDS in neonates.
Methods A retrospective study was conducted on neonates admitted to the NICU between January 2006 and December 2010. The enrolled infants with RDS were categorized as very preterm (<$32^{0/7}$ weeks gestation), moderately preterm ($32^{0/7}$–$33^{6/7}$ weeks), late preterm ($34^{0/7}$–$36^{6/7}$ weeks), and term ($37^{0/7}$–$42^{0/7}$ weeks). The rates, potential risk factors, clinical characteristics, and complications of RDS of these four groups were comparatively analyzed.
Results There was an increasing trend in incidence of RDS among the NICU admissions annually. Caesarean section without labor was significantly associated with RDS in term and late preterm infants ($P < 0.001$). Rates of requirements for ventilator and pulmonary surfactant were similar in very preterm and term infants but significantly lower in late preterm infants ($P < 0.001$). The oxygenation index value was not substantially lower in late preterm and term infants compared to very preterm infants, and the arterial oxygenation efficiency was improved slowly ($P < 0.001$). Incidence of pneumonia and occurrence of pneumothorax were significantly higher in term infants ($P < 0.001$).
Conclusions Term infants with RDS showed an association of RDS with caesarean section without labor and lung infection. These infants also showed slower improvement of oxygenation after surfactant administration and mechanical ventilation, and they experienced a high rate of pneumothorax complication, which was also noticed in late preterm neonates.

Keywords Respiratory distress syndrome · Preterm infants · Term infants · Caesarean section · Lung infection

Abbreviations

BPD	Bronchopulmonary dysplasia
CMV	Conventional mechanical ventilation
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
FIO_2	Fraction of inspiration oxygen
INSURE	Intubation-surfactant-extubation
IVH	Intraventricular hemorrhage
MAP	Mean airway pressure
MOSF	Multiple organ system failure
NEC	Necrotizing enterocolitis

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NICU	Neonatal intensive care unit
OI	Oxygenation index
PaO_2	Partial arterial oxygen pressure
PS	Pulmonary surfactant
RDS	Respiratory distress syndrome

Introduction

In China, the number of preterm infants with respiratory distress syndrome (RDS) has risen steadily every year over the past decade. While the reason for the increase in preterm births is not well understood, possible contributing factors include the increased use of reproductive technologies [1–3] and of some newer obstetric practices such as caesarean section [1–4]. Preterm infants, born before 37 weeks of gestation (259 days from the first day of the mother's last menstrual period) [1–3], are associated with a higher rate of respiratory morbidity. However, many of the obstetric management decisions use 34 weeks as an influential marker for assessing the potential for developing newborn complications because by 34 weeks of gestation, neonates have a lower risk for complications such as RDS [1–3]. The term "late preterm" was proposed to describe neonates born at $34^{0/7}$–$36^{6/7}$ weeks of gestation [5]. Most of the studies on morbidity and outcome of preterm infants to date have addressed either very preterm (<32 weeks of gestation) [1] or low-birth weight infants; very few studies have addressed problems in late preterm infants. Thus, the differences in risk, clinical characteristics, and complications of RDS among the late preterm, moderately preterm, very preterm, and term infants remains unclear.

The purpose of this study was to compare the risks, clinical characteristics, and complications between very preterm, moderately preterm, late preterm, and term infants with RDS. These data are expected to highlight areas where further intervention is needed and to identify preventive aspects, thereby decreasing the incidence of RDS and improving perinatal outcomes for all infants with RDS.

Materials and Methods

Patient Population

Newborn infants admitted to the neonatal intensive care unit (NICU) at either Zhengzhou Children's Hospital or the Third Affiliated Hospital of Zhengzhou University from January 2006 to December 2010 were retrospectively included in the study. The infants were categorized as very preterm (<$32^{0/7}$ weeks of gestation), moderately preterm ($32^{0/7}$–$33^{6/7}$ weeks of gestation), late preterm ($34^{0/7}$–$36^{6/7}$ weeks of gestation), and term ($37^{0/7}$–$42^{0/7}$ weeks of gestation) [5]. Infants were excluded from study enrollment if they had incomplete medical records, were admitted to the NICU at >72 h of age, or had a major congenital anomaly. The study was approved by the hospitals' ethical committees.

Definitions

Neonates were diagnosed with RDS if they presented with grunting, flaring, tachypnea, retractions, and/or supplemental oxygen requirement [6], and had imaging findings of homogeneous opaque infiltrates with air bronchograms, indicating contrast in airless lung tissue seen against air-filled bronchi or decreased lung volumes on chest radiography [7]. Perinatal variables included premature rupture of membranes, defined as rupture of membranes before the first stage of labor; and maternal diabetes, defined as women who had preexisting diabetes mellitus, gestational diabetes, or an abnormal glucose-tolerance test result. The chorioamnionitis was defined as either clinically diagnosed chorioamnionitis [presence of maternal fever ≥38 °C, elevated maternal C-reactive protein (CRP) >10 mg/L, fetal tachycardia, and prolonged (>24 h) rupture of membranes] or histologically diagnosed chorioamnionitis [8]. Primary emergency caesarean section was defined as caesarean section performed on an emergency basis for a mother who had not had a previous caesarean section [9]. Neonatal complications included bronchopulmonary dysplasia (BPD), defined as the need for supplemental oxygen on corrected age at 36 weeks of gestation [10, 11]; sepsis, defined as neonatal laboratory data obtained in the setting of suspected early-onset sepsis, with or without associated antibiotic treatment, and which was detected by one of three clinical approaches: (a) blood culture and complete blood count with differential count, (b) option (a) plus antibiotic treatment for 48 h, or (c) option (a) plus antibiotic therapy for at least 7 days [10, 11]; necrotizing enterocolitis (NEC), defined according to the modified Bell's staging criteria [12] and for which NEC "watch" was carried out to evaluate NEC over a brief period (48–72 h) without abdominal radiographs demonstrating the presence of pneumatosis; neonatal pneumonia [13], defined as a neonate with respiratory distress (indicated by rapid, noisy, or difficult breathing, respiratory rate >60/min, chest retractions, cough, or grunting) as well as a positive blood culture or any two or more of the following: (1) predisposing factors: maternal fever (38 °C), foul smelling liquor, prolonged rupture of membranes (>24 h); (2) clinical features of sepsis: poor feeding, lethargy, poor neonatal reflexes, hypothermia or hyperthermia, abdominal distension; (3) radiography findings suggestive of pneumonia that are not resolved within 48 h, i.e., nodular or coarse patchy infiltrate, diffuse haziness or granularity, air bronchogram, lobar or segmental consolidation; (4) sepsis screening positive results for leukocyte bands >20 %, leukocyte count out of reference range ($<4 \times 10^9$, $>12 \times 10^9$), elevated CRP (>10 mg/L), or elevated erythrocyte sedimentation rate (>10 mm/h).

Data Collection

Each patient's data were recorded on a standardized case report form. The data included demographic variables, perinatal history, maternal diseases, mode of delivery, problems at birth, neonatal morbidity, and complications. The annual rates of RDS in very preterm, moderately preterm, late preterm, and term infants were calculated and compared for the calendar years of 2006–2010. The differences in demographic variables, risk factors, clinical outcomes, and complications between the groups of the very preterm, moderately preterm, late preterm, and term infants with RDS were analyzed. For infants who received mechanical ventilation, the oxygenation index (OI = [mean arterial pressure (MAP) × fraction of inspiration oxygen (FiO_2) × 100]/partial arterial oxygen pressure (PaO_2)) and the PaO_2/FiO_2 ratio were calculated. To ensure quality, data collection was supervised by NICU directors of the respective hospitals.

Statistical Analyses

Statistical analyses were performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). Univariate analyses on continuous variables were compared by one-way ANOVA test, and categorical variables were compared by χ^2 test or Fisher's exact test as appropriate. Continuous variables are expressed as mean ± SD or as median with range, and categorical variables are expressed as counts or rates. The level of statistical significance was set at $P < 0.05$.

Results

A total of 26,634 infants less than 72 h of age were identified for the study's target period, which included 4,437 infants born in 2006; 4,288 infants born in 2007; 5,693 infants born in 2008; 5,581 infants born in 2009; and 6,635 infants born in 2010. The annual admission rate increased 49.5 % over the 5-year study period. A total of 174 infants (71 with incomplete medical records and 103 with a major congenital anomaly) were excluded from analysis. The remaining 26,460 infants used in analysis included 3,036 very preterm infants (1,922 with RDS and 1,114 without RDS), 1,851 moderately preterm infants (892 with RDS and 959 without RDS), 5,060 late preterm infants (657 with RDS and 4,403 without RDS), and 16,513 term infants (276 with RDS and 16,237 without RDS) (Fig. 1).

Demographic Characteristics of RDS

NICU admissions showed an increasing annual trend. There was no significant difference in the mean birth weight for each of the 5 years of the study period. The overall ratio of RDS among the NICU admissions increased yearly from 5.4 % in 2006 to 21.1 % in 2010 ($P < 0.001$). The incidence of RDS over the 5-year period in the very preterm, moderately preterm, late preterm, and term groups was 10, 9, 6.6, and 2.8 %, respectively. The incidence of RDS increased annually for all groups over the 5-year study period, with intergroup differences showing statistical significance (Table 1). Intriguingly, the increase was highest in the very preterm group and lowest in the term group. Moreover, the annual increases for the term group were significantly different from 2006 to 2009, and for late preterm infants in 2010 compared to 2009 (Table 1).

By birth weight category, the incidence of RDS over the 5-year period in the less than 1,500-g group was 22 %, and in the 1,500–2,000-g, 2,001–2,500-g, and more than 2,500-g groups it was 21.8, 10.6, and 7.4 %, respectively. The increase was highest in the less than 1,500-g group and lowest in the more than 2,500-g group. The annual increase in RDS incidence for the less than 1,500-g group was significantly different in 2008 compared to 2007 and in 2010 compared to 2009; for the 1,500–2,000-g group in 2009 compared to 2008 and in 2010 compared to 2009; for the 2,001–2,500-g group in 2008 compared to 2007; or for the more than 2,500-g group in 2008 compared to 2007 and in 2009 compared to 2008.

The ratio of males to females was 1,240/682 (64.5 %) in the very preterm group, 584/308 (65.5 %) in the moderately preterm group, 445/212 (67.7 %) in the late preterm group, and 234/42 (84.8 %) in the term group. Boys are more vulnerable to RDS than girls and it is even more pronounced in the term infants ($P < 0.001$). When age at admission and age at need for mechanical ventilation were considered, term infants were the oldest and late preterm infants were older than very preterm infants. Prenatal steroid use was highest in very preterm infants and lowest in term infants. Apgar score at 5 min was highest in term infants and lowest in very preterm infants. All of these characteristics were significantly different between the very preterm, moderately preterm, late preterm, and term groups ($P < 0.001$) (Table 2).

Risk Factors for RDS

As shown in Table 3, maternal age > 40 years, antenatal vaginal bleeding, oligohydramnios, premature rupture of membranes, and fetal growth restriction were significantly

Fig. 1 Overview of the studied neonates

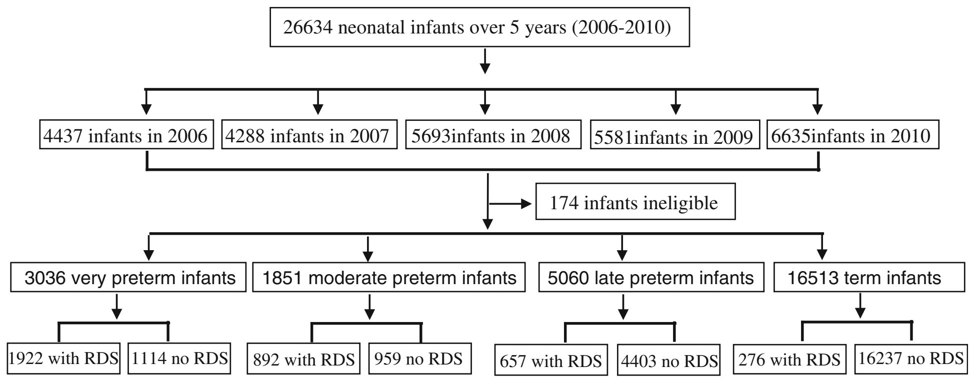

Table 1 RDS incidence in very preterm, moderately preterm, late preterm, and term infants over the 5-year study period

	2006	2007	2008	2009	2010	*P* value
Neonates with RDS [*n*/*N* (%)]	240/4,437 (5.4)	404/4,288 (9.4)*	707/5,693 (12.4)**	997/5,581(17.9)***	1,399/6,635 (21.1)****	<0.001
Gestational age						
Very preterm [*n*/*N* (%)]	141/235 (60.0)	216/337 (64.1)	392/622 (63.0)	498/753 (66.1)	675/961 (70.2)	0.006
Moderately preterm [*n*/*N* (%)]	66/218 (30.3)	94/311 (30.2)	153/493 (31.0)	228/645 (35.3)	351/897 (39.1)	0.004
Late preterm [*n*/*N* (%)]	24/126 (19.0)	74/334 (22.2)	113/566 (20.0)	187/890 (21.0)	259/1,010 (25.6)****	0.043
Term [*n*/*N* (%)]	9/3,858 (0.2)	20/3,306 (0.6)*	49/4,012 (1.2)**	84/3,293 (2.6)***	114/3,767 (3.0)	<0.001
Birth weight						
<1,500 g [*n*/*N* (%)]	86/157 (54.9)	181/317 (57.2)	271/401 (67.6)**	333/484 (69.0)	525/683 (77.0)****	<0.001
~2,000 g [*n*/*N* (%)]	66/392 (17.0)	101/453 (22.3)	152/593 (25.6)	195/594 (32.8)***	292/753 (38.8)****	<0.001
~2,500 g [*n*/*N* (%)]	59/440 (13.4)	97/634 (15.3)	148/711 (20.8) **	182/791 (23.0)	235/982 (24.0)	<0.001
>2,500 g [*n*/*N* (%)]	29/3,448 (0.8)	25/2,884 (0.9)	136/3,281 (4.1)**	287/3,712 (7.7)***	347/4,217 (8.2)	<0.001

* 2006 vs. 2007, $P < 0.05$; ** 2007 vs. 2008, $P < 0.05$; *** 2008 vs. 2009, $P < 0.05$; **** 2009 vs. 2010, $P < 0.05$

Table 2 Demographic data for very preterm, moderate preterm, late preterm, and term infants

	Very preterm ($n = 1{,}922$)	Moderately preterm ($n = 892$)	Late preterm ($n = 657$)	Term ($n = 276$)	*P* values
Overall RDS rate [*n*/total (%)]	1922/3,036 (63.3)	892/1,851 (48.2)	657/5,060 (13.0)	276/16,513 (1.7)	<0.001
Male/female	1240/682	584/308	445/212	234/276	<0.001
Age at admission (h) (mean ± SD)	2.70 ± 4.18*	5.21 ± 4.71**	9.50 ± 6.80***	11.01 ± 9.82****	<0.001
Prenatal steroid [*n* (%)]	947(49.3)	411(46.1)	235(35.8)	23(8.3)	<0.001
Apgar score at 5 min (mean ± SD)	7.29 ± 2.21†	7.31 ± 2.18††	8.07 ± 2.09†††	8.95 ± 1.67††††	<0.001
Mechanical ventilation age (h) (mean ± SD)	8.12 ± 9.35	12.23 ± 9.86	26.90 ± 19.71	29.13 ± 18.90	<0.0001
Maternal age in years[a] (mean ± SD)	30.31 ± 6.25	30.10 ± 5.97	29.34 ± 6.16	29.24 ± 4.90	<0.001

* range: 25, median: 2.70; **range: 28, median: 5.21; ***range: 40, median: 9.50; ****range: 59, median: 11.13

† range: 13, median: 7.29; †† range: 13, median: 7.31;††† range: 12, median: 8.07; †††† range: 10, median: 8.95

[a] Maternal age in years (mean ± SD): $F = 5.76$, $P < 0.001$

associated with RDS in preterm infants and especially in very preterm infants. Maternal hypertension, diabetes, chorioamnionitis, and reduced fetal movements were significantly higher in the late preterm group and significantly lower in the term group. Asphyxia risk was similar among the very preterm, moderately preterm, and term groups but significantly lower in the late preterm group. Caesarean section without labor was significantly associated with RDS in the term and late preterm groups. Maternal age > 40 years, maternal hypertension, anemia, antenatal vaginal bleeding, oligohydramnios, chorioamnionitis, premature rupture of membranes, caesarean section without labor, perinatal asphyxia, reduced fetal movements, and fetal growth restriction were all significantly associated with RDS in the very preterm group ($P < 0.05$) (Table 4). In the moderately preterm group, the occurrence of multiple birth (twins and triplets) in addition to above-mentioned factors were also significantly associated with RDS ($P < 0.05$). In the late preterm group, the occurrence of multiple birth (twins and triplets), maternal age > 40 years, maternal hypertension, diabetes, anemia, vaginal bleeding, oligohydramnios, chorioamnionitis, premature rupture of membranes, caesarean section without labor, and perinatal asphyxia were significantly associated with RDS ($P < 0.05$) (data not shown). In the term group, occurrence of multiple birth (twins and triplets), maternal age > 40 years, maternal hypertension, diabetes, oligohydramnios, chorioamnionitis, premature rupture of membranes, caesarean section without labor, and perinatal asphyxia were significantly associated with RDS ($P < 0.05$) (Table 5).

Comparison of Respiratory Morbidity

When age at NICU admission and age at surfactant administration were evaluated, both the term group and the late preterm group were significantly older than the very preterm group; the term infants were the oldest ($P < 0.001$). In addition, the association of pneumonia with RDS was significantly higher in the term group ($P < 0.001$) and otherwise similar among the other three groups. More term infants received continuous positive airway pressure (CPAP) than very preterm infants, and the use of CPAP was lowest in the late preterm group. The use of mechanical ventilation and administration of surfactant were similar in the very preterm group and the term group and were lowest in the late preterm group (all $P < 0.001$) (Table 6).

None of the groups showed significant differences in OI, PaO_2/FiO_2 ratio, and $PaCO_2$ measured before mechanical ventilation and after ventilation with surfactant use. The OI value was substantially lower in the very preterm and moderately preterm groups than in the late preterm and term groups, which accompanied improvements in the PaO_2/FiO_2 ratio. Significant difference in this ratio was observed 4 h after ventilation ($P < 0.05$) (Table 7).

Complications in Infants with RDS

The occurrence of pneumothorax was 9/1,922 (0.5 %) in the very preterm group, 5/892 (0.6 %) in the moderately preterm group, 11/657 (1.7 %) in the late preterm group, and 19/276 (6.9 %) in the term group; it was highest in the

Table 3 Risk factors for RDS in very preterm, moderately preterm, late preterm, and term infants

	Very preterm ($n = 1,922$)	Moderately preterm ($n = 892$)	Late preterm ($n = 657$)	Term infants ($n = 276$)	*P* value
Singletons [*n* (%)]	1,392 (72.4)	585 (65.6)	399 (60.7)	272 (98.6)	<0.001
Twins and triplets [*n* (%)]	530 (27.6)	307 (34.4)	258 (39.3)	4 (1.4)	<0.001
Maternal age [*n* (%)]					
18–40 years	1,480 (77.0)	702 (78.7)	526 (80.1)	232 (84.2)	0.04
>40 years	442 (23.0)	190 (21.3)	131 (19.9)	44 (15.8)	0.04
Maternal hypertension [*n* (%)]	559 (29.0)	269 (30.2)	207 (31.5)	22 (8.0)	<0.001
Diabetes [*n* (%)]	13 (0.7)	13 (1.5)	97 (14.8)	29 (10.5)	<0.001
Anemia [*n* (%)]	67 (3.5)	28 (3.1)	10 (1.5)	6 (2.2)	0.06
Vaginal bleeding [*n* (%)]	521 (27.1)	198 (22.2)	135 (20.5)	15 (5.4)	<0.001
Oligohydramnios [*n* (%)]	401 (20.9)	170 (19.1)	101 (15.4)	17 (6.2)	<0.001
Chorioamnionitis [*n* (%)]	288 (15.0)	127 (14.2)	131 (19.9)	52 (18.8)	0.005
PROM [*n* (%)]	596 (31.0)	251 (28.1)	139 (21.1)	15 (5.8)	<0.001
Delivery type [*n* (%)]					
Caesarean section	793 (41.3)	364 (40.8)	537 (81.7)	241 (87.3)	<0.001
Caesarean section without labor	220 (11.0)	99 (11.1)	101 (15.4)	136 (49.3)	<0.001
Perinatal asphyxia [*n* (%)]	323 (16.8)	136 (15.3)	73 (11.1)	45 (16.3)	0.006
Reduced fetal movements [*n* (%)]	462 (24.0)	218 (24.4)	199 (30.3)	53 (19.2)	<0.001
Fetal growth restriction [*n* (%)]	365 (19.0)	162 (18.2)	73 (11.1)	4 (1.4)	<0.001

PROM premature rupture of membrane

Table 4 Association of risk factors for RDS in very preterm infants

	Very preterm with RDS ($n = 1922$)	Very preterm without RDS ($n = 1{,}114$)	OR [95 % CI]	P value
Twins and triplets [n (%)]	530 (27.6)	245 (22.0)	0.98 [0.83–1.16]	0.83
Maternal age > 40 years [n (%)]	442 (23.0)	119 (10.7)	2.45 [2.01–3.11]	<0.001
Maternal hypertension [n (%)]	559 (29.0)	215 (19.3)	1.72 [1.44–2.05]	<0.001
Diabetes [n (%)]	13 (0.7)	14 (1.3)	0.54 [0.25–1.14]	0.11
Anemia [n (%)]	67 (3.5)	89 (8.0)	0.42 [0.3–0.58]	<0.001
Vaginal bleeding [n (%)]	521 (27.1)	257 (23.1)	1.24 [1.04–1.47]	0.01
Oligohydramnios [n (%)]	401 (20.9)	187 (16.8)	1.31 [1.08–1.58]	0.01
Chorioamnionitis [n (%)]	288 (15.0)	85 (7.6)	2.13 [1.66–2.75]	<0.001
PROM [n (%)]	596 (31.0)	183 (16.4)	2.29 [1.90–2.75]	<0.001
Caesarean section without labor [n (%)]	220 (11.4)	89 (8.0)	1.49 [1.15–1.93]	0.002
Perinatal asphyxia [n (%)]	323 (16.8)	20 (1.8)	11.05 [6.99–17.47]	<0.001
Reduced fetal movements [n (%)]	462 (24.0)	223 (20.0)	1.26 [1.06–1.51]	0.01
Fetal growth restriction [n (%)]	365 (19.0)	135 (12.1)	1.70 [1.37–2.10]	<0.001

PROM premature rupture of membrane

Table 5 Associations of risk factors for RDS in term infants

	Term infants with RDS ($n = 276$)	Term infants without RDS ($n = 16{,}237$)	OR [95 % CI]	P value
Twins and triplets [n (%)]	4 (1.4)	32 (0.2)	7.42 [2.61–21.13]	0.003
Maternal age > 40 years [n (%)]	44 (15.8)	160 (1.0)	19.06 [13.32–27.26]	<0.001
Maternal hypertension [n (%)]	22 (8.0)	747 (4.6)	1.80 [1.16–2.79]	0.01
Diabetes [n (%)]	29 (10.5)	97 (0.6)	19.54 [12.67–30.14]	<0.001
Anemia [n (%)]	6 (2.2)	162 (1.0)	2.21 [0.97–5.03]	0.06
Vaginal bleeding [n (%)]	15 (5.4)	1120 (6.9)	0.78 [0.46–1.31]	0.40
Oligohydramnios [n (%)]	17 (6.2)	373 (2.3)	2.89 [1.75–4.28]	<0.001
Chorioamnionitis [n (%)]	52 (18.8)	97 (0.6)	38.63 [26.90–55.46]	<0.001
PROM [n (%)]	15 (5.8)	161 (1.0)	5.74 [3.33–9.88]	<0.001
Caesarean section without labor [n (%)]	136 (49.3)	860 (5.3)	17.37.20 [13.59–22.21]	<0.001
Perinatal asphyxia [n (%)]	45 (16.3)	146 (0.9)	21.44 [14.98–30.69]	<0.001
Reduced fetal movements [n (%)]	53 (19.2)	3258 (20.1)	0.95 [0.70–1.28]	0.76
Fetal growth restriction [n (%)]	4 (1.4)	325 (2.0)	0.72 [0.27–1.94]	0.67

PROM premature rupture of membrane

term group and lowest in the very preterm group ($P < 0.001$). The occurrence of pulmonary hemorrhage was 142/1,922 (7.4 %) in the very preterm group, 61/892 (6.8 %) in the moderately preterm group, 20/657 (3.0 %) in the late preterm group, and 15/276 (5.4 %) in the term group; it was highest in the very preterm group, followed by the moderately preterm group ($P < 0.001$). The occurrence of intracranial hemorrhage was 135/1,922 (7.0 %) in the very preterm group, 47/892 (5.3 %) in the moderately preterm group, 13/657 (2.0 %) in the late preterm group, and 2/276 (0.7 %) in the term group. The very preterm group also had the highest occurrences of intracranial hemorrhage > grade II and BPD, while the rates of these two complications were lowest in the term group ($P <$ 0.001 and $P < 0.001$, respectively). There was no significant difference in the occurrence of sepsis among the different gestation age groups (Table 8).

The incidence of NEC was 39/1,922 (2.0 %) in the very preterm group, and 33 of those infants had medical NEC (10 with stage I, 11 with stage IIa, 7 with stage IIb, and 5 with stage IIIa) and 6 had surgical NEC. In the moderately preterm group, 11/892 (1.2 %) had NEC, including 9 with medical NEC (4 with stage I, 3 with stage IIa, 1 with stage IIb, and 1 with stage IIIa) and 2 had surgical NEC. In the late preterm group, 5/657 (0.8 %) had NEC and all of them were medical (2 with stage I, 2 with stage IIa, and 1 with stage IIb). In the term infants, only 1/276 (0.3 %) had NEC and the case was medical NEC (stage IIa). No cases of

Table 6 Age at admission, incidence of pneumonia, and respiratory support for RDS in the neonatal groups

	Very preterm ($n = 1{,}922$)	Moderately preterm ($n = 892$)	Late preterm ($n = 657$)	Term ($n = 276$)	P value
Age at NICU admission (h) (mean ± SD)*	3.41 ± 3.74	5.12 ± 4.27	10.65 ± 6.32	16.78 ± 8.39	<0.001
Infants with pneumonia [n (%)]**	766 (39.9)	348 (39.0)	263 (40.0)	182 (65.9)	<0.001
Respiratory support [n (%)]**					
CPAP	1209 (62.9)	536 (60.1)	383 (58.3)	199 (72.1)	<0.001
Ventilator	749 (39.0)	331 (37.1)	171 (26.0)	110 (39.9)	<0.001
Surfactant administration	1459 (75.9)	561 (62.9)	380 (57.8)	193 (70.0)	<0.001
Age at surfactant administration (h) (mean ± SD)	4.72 ± 4.53	5.38 ± 4.91	11.89 ± 11.73	17.73 ± 14.23	<0.001

* P values by one-way ANOVA test; ** P values by χ^2 test or Fisher's exact test, as appropriate

CPAP continuous positive airway pressure

Table 7 Respiratory outcomes for infants with RDS

	CMV					CMV + PS				
	Very preterm ($n = 181$)	Moderately preterm ($n = 134$)	Late preterm and term ($n = 106$)	F value	P value	Very preterm ($n = 568$)	Moderately preterm ($n = 197$)	Late preterm and term ($n = 175$)	F value	P value
OI										
0 h	24.2 ± 4.6	24.4 ± 4.8	24.6 ± 5.1	0.24	0.78	28.3 ± 5.2	28.2 ± 5.2	28.1 ± 4.9	0.09	0.91
4 h	20.2 ± 4.1	20.4 ± 4.1	21.8 ± 4.3	5.39	<0.001	21.4 ± 4.9	21.9 ± 5.0	23.5 ± 5.6	11.95	<0.001
8 h	18.1 ± 5.7	18.9 ± 4.9	21.0 ± 4.7	10.46	<0.001	16.5 ± 3.7	17.4 ± 4.0	24.9 ± 4.2	325.03	<0.001
12 h	15.9 ± 4.3	16.1 ± 4.2	20.2 ± 3.9	39.89	<0.001	13.1 ± 4.8	15.0 ± 4.4	23.1 ± 4.7	303.08	<0.001
24 h	13.6 ± 4.1	13.8 ± 4.2	19.8 ± 4.0	87.27	<0.001	9.9 ± 3.7	10.1 ± 4.0	20.1 ± 4.5	471.67	<0.001
PaO_2/FiO_2										
0 h	109.4 ± 62.1	104.6 ± 59.1	103.1 ± 40.5	0.50	0.61	93.7 ± 30.3	94.1 ± 30.2	94.9 ± 29.6	0.10	0.91
4 h	110.3 ± 13.2	111.3 ± 15.1	100.9 ± 30.3	10.17	<0.001	129.2 ± 30.2	129.0 ± 29.7	110.2 ± 28.4	28.81	<0.001
8 h	118.2 ± 17.3	116.5 ± 18.1	107.6 ± 25.7	9.97	<0.001	139.1 ± 26.3	138.4 ± 6.0	112.7 ± 25.3	71.90	<0.001
12 h	129.3 ± 13.2	128.3 ± 14.4	116.2 ± 29.8	17.48	<0.001	151.2 ± 27.1	149.7 ± 25.5	111.5 ± 24.8	158.45	<0.001
24 h	150.3 ± 14.7	149.9 ± 15.4	139.3 ± 20.1	17.16	<0.001	193.3 ± 31.3	190.3 ± 30.2	141.3 ± 25.2	208.30	<0.001

CMV conventional mechanical ventilation, *PS* pulmonary surfactant

Table 8 Complications among infants with RDS

	Very preterm ($n = 1{,}922$)	Moderately preterm ($n = 892$)	Late preterm ($n = 657$)	Term ($n = 276$)	P value
Pneumothorax [n (%)]	9 (0.5)	5 (0.6)	11 (1.7)	19 (6.9)	<0.001
Pulmonary hemorrhage [n (%)]	142 (7.4)	61 (6.8)	20 (3.0)	15 (5.4)	<0.001
Intracranial hemorrhage > grade II [n (%)]	135 (7.0)	47 (5.3)	13 (2.0)	2 (0.7)	<0.001
BPD [n (%)]	154 (8.0)	46 (5.2)	18 (2.7)	3 (1.1)	<0.001
NEC [n (%)]	39 (2.0)	11 (1.2)	5 (0.8)	1 (0.3)	<0.001
Sepsis [n (%)]	51 (2.7)	17 (1.9)	12 (1.8)	4 (1.4)	0.35
Mortality [n (%)]	97 (5.0)	25 (2.8)	13 (2.0)	3 (1.1)	<0.001

surgical NEC occurred in the late preterm and term groups. The mortality rate was 5.0 % (97/1,922) for very preterm infants, 2.8 % (25/892) for moderately preterm infants, 2 % (13/657) for late preterm infants, and 1.1 % (3/276) for term infants. Mortality decreased with increase in gestational age ($P < 0.001$) (Table 8).

Discussion

NICU admissions have continued to increase in China, as has the incidence rate of RDS in neonates. In the past, RDS has been studied mainly in very preterm infants and less so in late preterm and term infants [14]. In China, however, late preterm and term infants account for many of the NICU admissions for respiratory failure, including cases of RDS. The present study found that the incidence of RDS in late preterm infants was one-third of that in very preterm infants, and that the incidence in term infants was one-fifth of that in very preterm infants. Males accounted for 84.8 % of the term, 67.7 % of the late preterm, and 64.5 % of the very preterm infants with RDS. Preterm males have a greater risk of RDS than their female counterparts [15], and this difference was more significant for term infants. When the age at admission and age at mechanical ventilation were analyzed, the term infants and late preterm infants were found to be older than the moderately preterm and very preterm infants. This fact indicates that the clinical signs of RDS in late preterm infants and term infants appear later than in the moderately and very preterm infants.

Advanced age of the mother [16] and twin gestation [17] have been previously reported as associated with increased risk of preterm delivery, and the results from the current study agree with those findings. Hypertension and fetal growth restriction are the other major predisposing conditions for elective preterm delivery, but neither was investigated in the present study. Finally, the strong association of vaginal bleeding, oligohydramnios, and premature rupture of membranes in pregnancy with both spontaneous and elective preterm deliveries in the present study also agreed with a previous report [18].

Caesarean section without labor was found to be strongly associated with RDS in late preterm and term neonates in the present study. In recent decades, the rate of caesarean section in China has increased and may be related to the concomitant increase in RDS incidence in late preterm and/or term infants. Caesarean section without labor has already been reported as increasing the risk of respiratory morbidity in neonates [19, 20] due to delayed clearance of lung fluid [21]. Transient tachypnea of the newborn is one such morbid condition [22] and usually lasts for 2–5 days [7]. Neonates born by caesarean section have a larger residual volume of lung fluid and secrete less surfactant to the alveolar surface; thus, they are at higher risk of developing RDS. The process of labor is considered beneficial to the maturation of the surfactant system, by which the surfactant protein's maturation and secretion are triggered by β-adrenergic agents and prostaglandins. The lungs of neonates born by caesarean section prior to the onset of labor are significantly more immature (as evidenced by the lecithin–sphingomyelin ratio) than those born by caesarean section after the onset of labor. The concentration of surfactant protein-Ain cord blood has also been shown to be significantly lower in neonates who were delivered by elective caesarean section close to term than in those delivered after onset of labor [23].

The gestational age-related decline in both the incidence of RDS and the need for mechanical ventilation observed in the present study agrees with the results of a previous epidemiological study [24]. In addition, the term infants with RDS showed a higher pneumonia rate than the preterm infants. The term infants with RDS improved with CPAP more often than the very preterm infants or the late preterm infants, both of whom required more intubations. The need for ventilator and surfactant administration was similar among term infants and very preterm infants with RDS but was lower in late preterm infants.

In the present study, OI and PaO_2/FiO_2 ratio did not change dramatically after ventilation or surfactant administration in term or late preterm infants with RDS compared to very preterm infants. This finding may indicate a different pathogenesis of RDS in late preterm and term infants [23]. It is likely that the high rates of chorioamnionitis and pneumonia in late preterm infants and term infants may have contributed, at least partly, to the RDS. Infection can result in direct injury to the type II alveolar cells of the lung, decreasing synthesis, release, and processing of surfactant. Increased permeability of the alveolar capillary membrane to both fluid and solutes is known to result in entry of plasma proteins into the alveolar hypophase, further inhibiting the surface properties of surfactant [25]. In term neonates, early RDS development manifests as a more severe form of the condition and its pathogenesis evolves more rapidly; thus, it is more likely to lead to the development of persistent pulmonary hypertension of the newborn and multiple organ system failure (MOSF), especially involving myocardial injury and acute renal failure [5]. Most neonates with this condition require prolonged mechanical ventilation, ranging from 10 to 14 days, while a minority requires mechanical ventilation for only 7 days [6]. Regardless, the mortality rate remains relatively high for these infants, and mortality is most often related to severe infection complicated by MOSF [26]. Cheong et al. [27] identified adenosine triphosphate-binding cassette protein, member A_3 in term neonates with fatal RDS of unknown etiology.

The use of ventilation and CPAP was much higher in term infants than in late preterm infants [110/276 (39.9 %) vs. 171/657 (26.0 %)]; correspondingly, there was a higher incidence of pneumothorax in term infants than in late preterm infants. Management strategies for very preterm infants and moderately preterm infants with RDS include early surfactant administration, the intubation-surfactant-extubation sequence (known as INSURE) [28], and noninvasive ventilation [29]. However, the management strategies for late preterm infants and term infants with RDS are more complex. Perinatally acquired infection usually causes RDS in term neonates and broad spectrum antibiotics need to be administered as soon as possible, in addition to surfactant therapy and ventilation support. Meanwhile, attention should be given to identify and treat any cases of myocardial injury.

In summary, the rates of preterm births and of RDS are steadily on the rise in China. Surfactant deficiency is the most frequent etiology of RDS in very preterm and moderately preterm infants, while caesarean section and lung infection play major roles in RDS development in late preterm and term infants. Term infants with RDS need more respiratory support and have a higher incidence of pneumothorax. The different etiologies of neonatal RDS at different gestational ages necessitate tailored preventive and treatment strategies.

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