

Pregnancy risk factors and outcomes in the transition from respiratory distress syndrome (RDS) to RDS and acute respiratory distress syndrome (ARDS) in preterm infants: a retrospective cohort study

Long Chen

Chongqing Medical University Affiliated Children's Hospital

Jing Xiong

Children's Hospital of Chongqing Medical University

Jingyu Guo

Chongqing Medical University Affiliated Children's Hospital

Jie Li

Chongqing Medical University First Affiliated Hospital

Yuan Shi

Chongqing Medical University Affiliated Children's Hospital

Lei Bao (✉ 400702@hospital.cqmu.edu.cn)

Chongqing Medical University Affiliated Children's Hospital <https://orcid.org/0000-0001-5675-9014>

Research

Keywords: ARDS, RDS, risk factors, outcomes, neonate

Posted Date: January 23rd, 2020

DOI: <https://doi.org/10.21203/rs.2.21709/v1>

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Abstract

Background: Neonatal acute respiratory distress syndrome (ARDS) has been proposed in 2017. Growing evidence suggests that pregnancy risk factors (PRF) contribute to the deterioration of respiratory distress. The present study aims to clarify PRF and outcomes in the transition from respiratory distress syndrome (RDS) to RDS and ARDS in preterm infants.

Methods : A retrospective study was conducted at a tertiary neonatal intensive care unit from Jan-1, 2017 to July-30, 2018. Preterm neonates diagnosed with RDS were enrolled at baseline and followed up during hospitalization. The primary outcomes were to identify the relationships between PRF and transition from RDS to RDS and ARDS and the incidences of bronchopulmonary dysplasia (BPD).

Results: A total of 269 preterm infants were included. Of them, 168 were diagnosed with both RDS and ARDS, and 101 with RDS. Comparing with preterm neonates with both RDS and ARDS, that with RDS was related to the decreased incidence of BPD (22:79 vs 61:107, 95%CI:0.27-0.85, P =0.010), especially in the subgroup of severe BPD (3:98 vs 17:151, 95%CI:0.08-0.95, P =0.032) and two or more of surfactant (14:87 vs 43:125, 95%CI:0.24-0.91, P =0.023). PRF including intrahepatic cholestasis during pregnancy (ICP), pernicious placenta previa (PPP), hypertensive disorder complicating pregnancy (HDCP) and gestational diabetes mellitus (GDM) were not shown differences between the two groups.

Conclusion : Preterm infants with both RDS and ARDS were easier to convert to BPD as compared with that with RDS. Trial registration: Chinese Clinical Trial Registry, ChiCTR1900026980

Keywords: ARDS · RDS · risk factors · outcomes · neonate

Introduction

Neonatal respiratory distress related to bronchopulmonary dysplasia (BPD) is a major health problem affecting the increasing premature birth population [1]. It is of great importance to recognize and treat the preterm infants at the early stage of respiratory distress. Neonatal respiratory distress syndrome (RDS) is associated with an increased risk for progression to BPD, and its incidence has been confirmed to be gradually increased with the decreased gestational age [2]. Exogenous surfactant replacement is a key treatment to reduce the incidence of BPD [3]. In 2017, the international neonatal acute respiratory distress syndrome (ARDS) collaborative group provides the first consensus definition for neonatal ARDS [4]. To date, no studies have indicated beneficial effects of surfactant on adult and pediatric ARDS [5, 6], its action for neonatal ARDS is therefore needed to be further elucidated [7]. Otherwise, the impact of RDS and/or ARDS on BPD is also unclear.

Given RDS is a disease of respiratory distress that commences within 24 h after birth [3], and most ARDS also appears in the first three days [5]. The optimal active measures should be taken before birth. Pregnancy risk factors (PRF), including gestational diabetes mellitus (GDM), hypertensive disorder complicating pregnancy (HDCP), and intrahepatic cholestasis during pregnancy (ICP), are related to

increase the incidences of preterm birth and RDS [3, 8]. The identification and subsequent active management for PRF before neonates' birth should be more beneficial strategies for preventing deterioration of RDS. We have found that PRF is related to the deterioration of RDS in a Chinese cohort [9]. However, no studies report the relationships between PRF and the transition from RDS to RDS and ARDS in preterm infants, and it also remains unknown whether stayed in RDS is related to the decreased incidences of BPD, as well as other complications.

The aims of the present study are: 1) to report the effects of PRF on the transition from RDS to RDS and ARDS, and 2) to clarify whether stayed in RDS, as compared with transition to RDS and ARDS, is associated with the decreased incidence of BPD.

Methods

Study registrations and Ethics consideration

The study was approved by the Ethics Committee of Children's Hospital of Chongqing Medical University and registered at <http://www.chictr.org.cn>. (ID: ChiCTR1900026980) (registration time: Oct-27, 2019). The study was performed in accordance with the approved guidelines and regulations of the participating institutions.

Study Design and Participants.

This was a retrospective study conducted in the neonatal intensive care unit (NICU), Children's Hospital of Chongqing Medical University from Jan-1, 2017 to July-30, 2018.

Eligibility requirements for neonates were as follows: (1) The gestational age was less than 37 weeks and admitted to NICU in 24 h after birth; (2) These neonates were initially diagnosed with RDS. Exclusion criteria were: (1) major congenital anomalies; (2) chromosomal abnormalities; (3) neuromuscular diseases; (4) upper respiratory tract abnormalities.

Diagnosis of neonatal RDS

The diagnosis criteria of RDS was based on clinical manifestations and chest X-ray findings. The clinical signs and symptoms of RDS were respiratory distress, tachypnea, nasal flaring, groan, and cyanosis appear within 24 h after birth, as well as beneficial response to pulmonary surfactant and/or lung recruitment strategies. The other criteria include the typical X-ray picture of a grain shadow, air bronchogram or white lung [3].

Diagnosis of neonatal ARDS.

The diagnosis of ARDS was according to the criteria established by [pediatric acute lung injury consensus conference group](#) in 2015 [6] and Montreux conference in 2017 [4], which mainly included: (1) A known or suspected clinical insult-associated acute onset within one week; (2) Exclusion of transient tachypnea of newborn (TTN), RDS, or congenital anomalies as a primary current acute respiratory condition. (3) Chest imaging changes cannot be explained by local effusions, atelectasis, RDS, TTN, or congenital anomalies; (4) Exclusion: edema induced by acute heart failure, fluid overload; (5) Oxygen index (OI) ≥ 4 should be used to diagnose ARDS for patients receiving noninvasive and invasive ventilation.

Definition of the transition from RDS to RDS and ARDS

Definition of the transition from RDS to RDS and ARDS must fulfill both the following conditions: 1. The first diagnosis in the first 24 h after birth was RDS; 2. The preterm infants were diagnosed with both RDS and ARDS within one week after birth;

The administration of surfactant replacement and caffeine citrate.

When the neonate was admitted to the NICU and had fulfilled the entry criteria, pulmonary surfactant (Curosurf, Chiesi Pharmaceuticals, Parma, Italy) was administered with a dosage of 200 mg/kg as a rescue treatment using the INSURE (intubation-surfactant-extubation) technique of surfactant administration if an infant needed $FiO_2 > 0.40$ to maintain the targeted SpO_2 with 90%-95%. The intervals of surfactant administration were 6 to 12 hours without more than four doses allowed, and the second and later dose was 100 mg/kg.

Also, these preterm infants received a loading dose of 20 mg/kg caffeine citrate and a maintenance dose of 10 mg/kg/d until 34 weeks of GA. Other care was at the discretion of the attending neonatologist.

Definition of PRF.

Four individual PRF were analyzed in the present study, including ICP, HDCP, GDM, and pernicious placenta previa (PPP). Diagnosis of PRF were consistent with recommendations and guidelines from international consensus files [10] and Chinese Medical Association [11-14]. The preterm infants with RDS were considered to be with PRF as long as having one or more individual PRF. The diagnosis of BPD is consistent with definition of BPD [15].

Evaluation of primary and secondary outcomes.

The primary outcomes were: 1) to report the effects of PRF on the transition from RDS to RDS and ARDS in preterm infants, and 2) to clarify whether stayed in RDS, as compared with transition to RDS and ARDS, is associated with the decreased incidence of BPD. And the secondary outcomes is mortality and other complications.

Data Collection

The clinical data of all enrolled neonates were collected in standardized case report forms, including gender, gestational age, birth weight, Apgar score, administration of surfactant, respiratory mode, PRF, death, BPD, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and so on.

Sample Size Estimation.

The sample size estimation was calculated by PASS software (2008 v8.0.3). According to previous studies [16], the incidence of RDS in newborns from ICP was about 28%. Our previous study have indicated that the incidence of severe RDS in newborns from ICP was about 7% [9], the incidence of ARDS was therefore thought to no less than 7%, if the severe RDS was considered as ARDS. With 80% power and a 2-sided significance level of 0.05, 21 neonates would be needed at least in RDS and ARDS conversion group. According to the nature of cohort study, the number in the RDS group was usually not less than RDS and ARDS conversion group, so at least 42 neonates would be needed in preterm infants from ICP. In the present study, four PRF were included, the total number was therefore 168. Actually, during the study period, 269 preterm infants were enrolled. Therefore, the actual sample size was more than theoretical need.

Statistical analysis.

Continuous variables, expressed as mean \pm standard deviation, were compared using independent samples t test. Categorical variables were compared using the χ^2 test or the Fisher's test. The predefined BPD subgroups were: mild, moderate and severe BPD. To further assess the effects of surfactant administration on the rate of BPD between the two groups, use of surfactant were divided into three subgroups: zero, one and two of surfactant. Subgroup analyses were conducted for the primary outcome. All analyses were carried out using computer software (SPSS 16.0 for windows). A *p*-value less than 0.05 was regarded as statistically significant.

Results

From Jan-1, 2017 to July-30, 2018, 775 preterm neonates with respiratory distress were admitted to NICU of Children's Hospital of Chongqing Medical University, China. And 506 were excluded for the following causes: 274 were full term infants, 35 underwent surgery operation, 20 were diagnosed upper respiratory tract abnormalities, 85 were admitted after 24 h, 50 of ARDS were diagnosed after one week after birth and 42 were TTN. Finally, 269 preterm infants were included in the final analysis. 62.4% (168/269) converted to RDS and ARDS and 37.6% (101/269) stayed in RDS. And the prevalence of RDS in preterm neonates with respiratory disorders was 13.0% (101/775) and the conversion incidence from RDS to RDS and ARDS was 21.7% (168/775). (Fig 1)

Baseline characteristics for the included preterm neonates.

All the included neonates were born in other hospitals and transferred to the NICU due to respiratory distress within one week after birth. The baseline characteristics of neonates who stayed in RDS and who converted to RDS and ARDS are presented in table 1. There were also no significant differences in the main clinical characteristics of neonates, including gestational age, gender, birth weight, Apgar score, and invasive ventilation between two groups. The primary noninvasive modes were nasal continuous positive airway pressure (NCPAP) and nasal intermittent positive pressure ventilation (NIPPV). Compared with neonates who converted to RDS and ARDS, those who stayed in RDS had more primary mode of NCPAP (81:4 vs 103:24, 95%CI: 2.59-147.70, $P=0.000$).

All subjects with RDS were diagnosed within 3 days. Otherwise, among the neonates with both RDS and ARDS, 83.9% of them were diagnosed with ARDS (141/168) between 1-3 days, and 16.1% (27/168) were 4-7 days. Surfactant replacement was administrated within three days after birth to 86 and 106 preterm infants in the RDS and RDS combined with ARDS groups, respectively. No neonates received 4 of surfactant and no neonates received surfactant after three days after birth.

The primary and secondary outcomes.

Association between PRF and the conversion from RDS to RDS and ARDS are shown in table 1. Generally, PRF was not found to be related to the increased conversion rate from RDS to RDS and ARDS.

Comparing with preterm neonates with both RDS and ARDS, that with RDS was related to the decreased incidence of BPD (22:79 vs 61:107, 95%CI:0.27-0.85, $P=0.010$), especially in the subgroup of severe BPD (3:98 vs 17:151, 95%CI:0.08-0.95, $P=0.032$).

No difference was found in the administration of surfactant between the subjects with RDS and RDS combined with ARDS (86:15 vs 106:35, 95%CI: 0.97-3.69, $P=0.059$). In the preterm infants administrated with surfactant, less frequency of surfactant was needed in the RDS group as compared with RDS and ARDS group (1.2 ± 0.5 vs 1.6 ± 0.7 , 95%CI: (-0.56)-(-0.21), $P=0.000$). Otherwise, comparing with preterm neonates with both RDS and ARDS, less preterm infants with RDS were administrated with two or more surfactant (16:85 vs 50:91, 95%CI: 0.18-0.65, $P=0.001$). In contrast, when only one of surfactant was need, there were more preterm infants with RDS (70:31 vs 56:85, 95%CI: 2.00-5.89, $P=0.000$).

To further assess the effects of surfactant administration on the rate of BPD between the two groups, the subgroup analysis was also conducted. As far as two or more of surfactant was considered, there was still decreased incidence of BPD in the preterm infants with RDS as compared with that with both RDS and ARDS (14:87 vs 43:125, 95%CI:0.24-0.91, $P=0.023$). (table 2)

Discussion

In the retrospective study, we aimed to report the effects of PRF on the transition from RDS to RDS combined with ARDS, and to clarify whether preterm infants with RDS, as compared with both RDS and ARDS, is associated with the decreased incidence of BPD. As a result, we found that PRF were not related to the increased conversion from RDS to RDS and ARDS. But, comparing with preterm neonates with both RDS and ARDS, that with RDS was related to the decreased incidence of BPD (22:79 vs 61:107, 95%CI:0.27–0.85, $P = 0.010$), especially in the subgroup of severe BPD (3:98 vs 17:151, 95%CI:0.08–0.95, $P = 0.032$).

We also showed that the effects of RDS and RDS combined with ARDS on the incidence of BPD were partially associated with the exogenous surfactant replacement. When only one of surfactant was administrated, no difference in the incidence of BPD was found between the two groups. But when more than two of surfactant was needed, there was decreased incidence of BPD in the preterm infants with RDS as compared with that with RDS and ARDS (14:87 vs 43:125, 95%CI:0.24–0.91, $P = 0.023$). To our knowledge, this is the first study to assess the effects of surfactant on BPD between preterm infants with RDS and RDS combined with ARDS. The result suggests that preterm infants with both RDS and ARDS is associated with the increased incidence of BPD as compared with that with RDS when two or more of surfactant were needed.

Besides caffeine [17], early use of NCPAP has been proved to be one of the most effective pathways to reduce the incidence of BPD. Supplying with an intermittent peak pressure on NCPAP, NIPPV is considered as a strengthened version of NCPAP with increased flow delivery in the upper airway, increased minute volume and functional residual capacity and recruitment of collapsed alveoli, improved stability of the chest wall and reduced asynchrony of thoraco-abdominal movement [18–21]. And it should be related to the decreased incidence of BPD. However, several studies have compared the effects of NIPPV and NCPAP on the incidence of BPD, and the results were no advantages of NIPPV over NCPAP. Meneses J et al [22] indicated that NIPPV did not significantly reduce the incidence of BPD comparing with NCPAP, of which mean gestational ages were about 30 weeks. Our previous study did not also show differences in the incidence of BPD [23], which was consistent with the meta-analyses [24, 25]. The largest multi-centered study on the comparison of NIPPV and NCPAP also showed that, in very preterm infant, there was no significant difference on the rate of intubation and survival to 36 weeks of post-menstrual age without BPD [26]. And the authors suggested that there might be some subtle but important differences between extremely preterm and preterm infants, but they did not tell us what the differences were.

One important cause to induce the difference may be the diagnosis of RDS and ARDS. the above studies were mainly performed in the pre-neonatal acute respiratory distress syndrome (ARDS) era, in which ARDS was usually considered as severe RDS or severe respiratory failure. Actually, ARDS and RDS are two diseases according to their etiological and pathological characteristics. To further reduce the heterogeneities and exclude the potential effects of RDS on outcomes in neonates with ARDS, the keywords "severe RDS" or "severe respiratory distress" were hypothetically regarded as ARDS. An interesting result was that, as compared with conventional mechanical ventilation, high-frequency oscillatory ventilation reduced the mortality (2:9 vs 3:3, 95%CI 0.09–0.89, $P = 0.03$) (4:177 vs 13:179,

95%CI 0.10–0.94, P = 0.04) [27, 28], and the incidence of BPD at 36 weeks (13:173 vs 28:166, 95%CI 0.24–0.83, P = 0.01) [28], and improved long-term neurodevelopment outcomes [28]. Recently, we also reported a randomized controlled trial, and the result demonstrated that, compared with NCPAP, nasal high frequency oscillatory ventilation significantly reduced the need for endotracheal ventilation in the infants with ARDS and/or RDS (10:33 vs 21:15 95%CI 0.08–0.57, P = 0.002), but not in the neonates with RDS and ARDS (2:7 vs 11:6 95%CI 0.02-1.00, P = 0.097) [29]. And the result was consistent with the present study.

Another important cause to induce the difference might be the administration of surfactant. In fact, no studies have indicated beneficial effects of surfactant for adult and pediatric ARDS [5, 6], including meconium aspiration syndrome, and which is a subtype of ARDS. Cochrane review showed that, although reducing the severity of respiratory illness and decreased number of infants with progressive respiratory failure requiring support with extracorporeal membrane oxygenation in infants with meconium aspiration syndrome, surfactant administration does not reduce the incidence of BPD [30]. And they were consistent with the present study, in which two or more of surfactant was related to the increased incidence of BPD in the preterm infants with both RDS and ARDS as compared with that with RDS.

Furthermore, the exact rate of ARDS in neonates was unknown due to the substantial heterogeneity of ARDS [5]. Seung Hyun Lee, et al reviewed retrospectively 242 late preterm and term newborn infants who were admitted to NICU for acute respiratory distress within 24 h after birth, and the respiratory distress were divided into six diseases: RDS (21, 8.6%), TTN (132, 54.5%), atypical acute respiratory disorder (52, 21.5%), meconium aspiration syndrome (18, 7.4%), pneumonia (5, 2.1%), and the others(14, 5.8%). According to the figures, the estimated rate of ARDS was up to 36.8% after excluding RDS and TTN [31]. In the present study, the prevalence of RDS in preterm neonates was 34.7% (269/775) and the conversion incidence from RDS to RDS and ARDS was 21.7% (168/775). Even so, the rate of ARDS was thought to be under-recognized. An observational study in 2016 including 459 ICUs in fifty countries showed that the clinical recognition rates ranged from 51.3% for mild ARDS to 78.5% for severe ARDS [32].

There were some basic limitations due to the observational nature of the present study. 1. there were small neonates with PRF. 2. the severity of ARDS was not measured quantitatively. These factors could induce potential bias, including restricted application scope and size effect. These problems could be overcome in additional prospective studies. A definitive answer to whether PRF increased the conversion from RDS to RDS and ARDS and incidence of BPD would require a larger sample size in randomized controlled trials.

Conclusions

In summary, preterm infants with both RDS and ARDS were associated with the increased incidence of BPD, especially in the subgroup of severe BPD and two or more of surfactant as compared with preterm neonates with RDS. But, PRF was not related to the increased conversion from RDS to RDS and ARDS.

Due to small neonates with PRF, the relationship between PRF and the conversion from RDS to RDS and ARDS need further assessment.

Declarations

Acknowledgement

Not applicable

Author's contributions

LC conceptualized the study, accomplished the clinical trial, drafted the initial manuscript and reviewed the manuscript. JX revised the manuscript, accomplished the registration of clinical trial, and reviewed the manuscript. JYG carried out the initial analyses and reviewed the manuscript. JL designed the data collection instruments, and reviewed the manuscript. YS reviewed the manuscript for important intellectual content. LB conceptualized and designed the study and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Funding

This work was supported by Clinical Medical Study Program of Children's Hospital of Chongqing Medical University (YBXM-2019-013), the Technology Innovation and Application Demonstration Program of Chongqing Science and Technology Commission, China (No. cstc2018jscx-msybX0040), "guan'ai" preterm Study Program of Renze Foundation of Beijing (K022), Medical Science Study Program of Chongqing Hygiene and Health Commission (No. 2017MSXM018).

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due hospital policy but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Children's Hospital of Chongqing Medical University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

bronchopulmonary dysplasia

BPD

respiratory distress syndrome

RDS

acute respiratory distress syndrome

ARDS

nasal continuous positive airway pressure

NCPAP

nasal intermittent positive pressure ventilation

NIPPV

transient tachypnea of newborn

TTN

neonatal intensive care unit

NICU

pregnancy risk factor

PRF

gestational diabetes mellitus

GDM

hypertensive disorder complicating pregnancy

HDCP

intrahepatic cholestasis during pregnancy

ICP

premature rupture of membrane

PROM

pernicious placenta previa

PPP

retinopathy of prematurity

ROP

necrotizing enterocolitis
NEC
intraventricular hemorrhage
IVH

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Tables

Table 1. The baseline characteristics of neonates with RDS and neonates with RDS and ARDS

	RDS (n=101)	RDS and ARDS (n=168)	RR or MD	95%CI	p-value
Gestational age (weeks)	31.8±2.6	31.9±2.8	-0.21	(-4.94)- 4.51	0.930
Gender (male), No. (%)	57 (56.4)	104 (61.9)	0.80	0.48-1.32	0.376
Caesarean (yes), No. (%)	65 (64.4)	107 (63.7)	1.03	0.62-1.72	0.912
Birth weight (g)	1.73±0.53	1.72±0.61	0.01	(-0.13)- 0.15	0.898
Apgar, 1 min	7.3±2.4	7.0±2.5	0.29	(-0.32)-0.91	0.351
Apgar, 5 min	8.8±1.3	8.5±1.5	0.26	(-0.10)-0.63	0.150
Apgar, 10 min	9.1±1.0	8.9±1.2	0.16	(-0.11)-0.44	0.245
Antenatal corticoids (yes), No. (%)	41 (40.6)	58 (34.5)	1.30	0.78-2.16	0.317
GDM (yes), No. (%)	4 (4.0)	2 (1.2)	3.42	0.61-19.03	0.202
PROM (yes), No. (%)	41 (40.6)	53 (31.5)	1.48	0.89-2.48	0.132
ICP (yes), No. (%)	1 (1.0)	1 (0.6)	1.67	0.10-27.00	1.000
PPP (yes), No. (%)	5 (5.0)	13 (7.7)	0.62	0.22-1.80	0.456
HDCP (yes), No. (%)	3 (3.0)	15 (8.9)	0.31	0.09-1.11	0.077
Primary modes (NIV, IV, %)	85:16(84.2%)	127:41(75.6%)	1.72	0.91-3.25	0.123
Primary modes-NIV (NCPAP, NIPPV, %)	81:4(98.8%)	103:24(81.1%)	19.57	2.59-147.70	0.000

GDM: gestational diabetes mellitus; PROM: premature rupture of the membrane; ICP: intrahepatic cholestasis of pregnancy; pernicious placenta previa:PPP; respiratory distress syndrome: RDS; acute respiratory distress syndrome: ARDS; nasal continuous positive airway pressure: NCPAP; nasal intermittent positive pressure ventilation: NIPPV; NIV: noninvasive ventilation; MD: mean difference; CI: confidence interval.

Table 2. The primary and secondary outcomes

	RDS (n=101)	RDS and ARDS (n=168)	RR or MD	95%CI	p-value
BPD (yes), No. (%)	22 (21.8)	61 (36.7)	0.48	0.27-0.85	0.010
Severe	3 (3.0)	17 (10.1)	0.27	0.08-0.95	0.032
Moderate	12 (11.9)	32 (19.0)	0.57	0.28-1.17	0.124
Mild	7 (6.9)	12 (7.1)	0.97	0.37-2.55	0.948
0 dose of surfactant	2 (2.0)	7 (4.2)	0.47	0.10-2.28	0.491
1 dose of surfactant	6 (5.9)	11 (6.5)	0.90	0.32-2.52	1.000
≥2 doses of surfactant	14 (13.9)	43 (25.6)	0.47	0.24-0.91	0.023
Death (yes), No. (%)	0 (0.0)	3 (1.8)	1.02	1.00-1.04	0.294
Surfactant use (yes), No. (%)	86 (85.1)	106 (75.2)	1.89	0.97-3.69	0.059
1 dose	70 (70.0)	56 (39.3)	3.43	2.00-5.89	0.000
≥2 doses	16 (15.8)	50 (47.2)	0.34	0.18-0.65	0.001
Frequency of surfactant	1.2±0.5 (86)	1.6±0.7 (106)	-0.39	(-0.56)- (-0.21)	0.000
Intubation (yes), No. (%)	17 (14.4)	42 (20.0)	0.67	0.36-1.25	0.206
<32w	4 (7.3)	21 (19.4)	0.32	0.11-1.00	0.041
32-36w	13 (28.3)	21 (35.0)	0.73	0.32-1.68	0.461
IVH (yes), No. (%)	23 (22.8)	51 (30.4)	0.68	0.38-1.20	0.177
>2 nd stage	4 (4.0)	8 (4.8)	0.82	0.24-2.81	1.000
ROP>2 nd stage (yes), No. (%)	1 (1.0)	2 (1.2)	0.83	0.07-9.27	1.000
Air leak (yes), No. (%)	1 (1.0)	4 (2.4)	0.41	0.05-3.72	0.653
NEC ≥2 nd stage (yes), No. (%)	9 (8.9)	11 (6.5)	1.40	0.56-3.50	0.474
Hospital stay (days)	30.8±19.9	31.9±23.2	-1.09	(-6.75)- 4.58	0.695

BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage; MD: mean difference; CI: confidence interval.

Figures

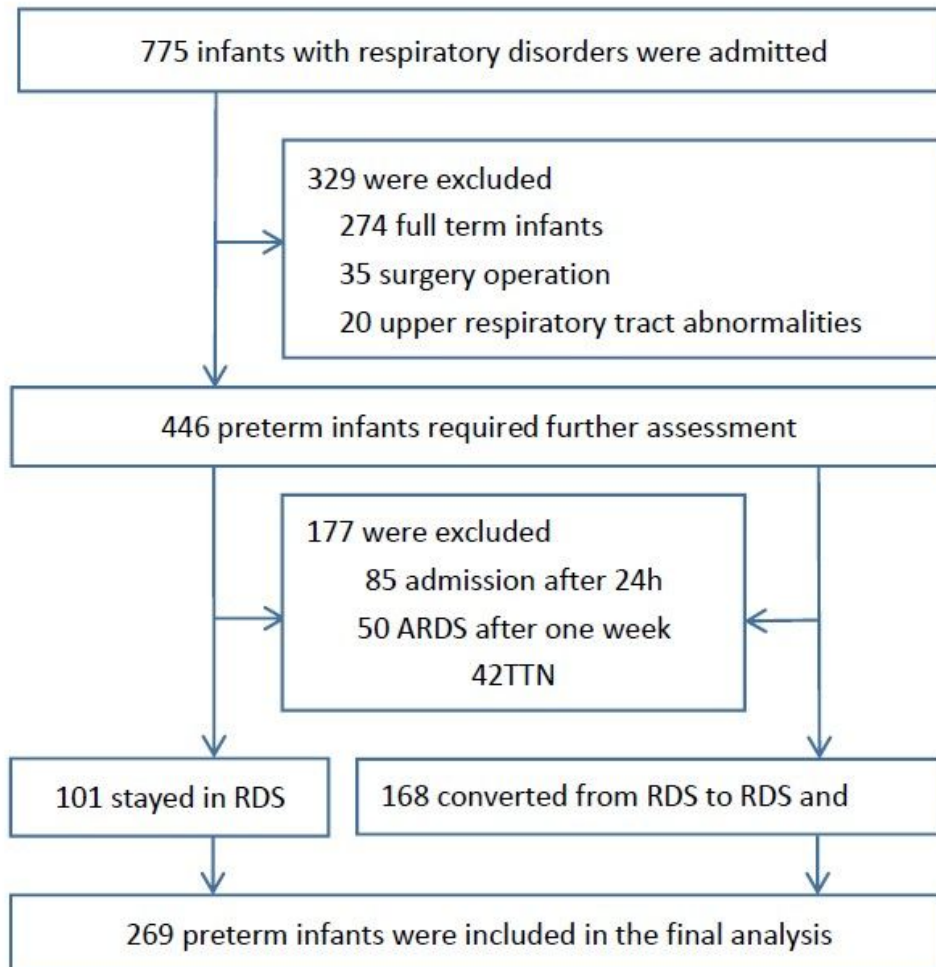


Figure 1

Flowchart of study enrollment: a total of 775 newborn infants were screened and 269 subjects were included in the analysis.