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Prevalence and Predictors of Infant Mortality of Respiratory Distress Syndrome in Beijing and Jiangxi Provinces of PR China: A Retrospective Cohort Analysis

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Abstract

Background: Like any other countries, respiratory distress syndrome is a major cause of infantile mortality in China, especially in low birth weight infants.
Objectives: The study aimed to determine the incidence of respiratory distress syndrome and identify some predictors of mortality in Chinese infants with confirmed respiratory distress syndrome (Level of Evidence: III).
Methods: We retrospectively analyzed the demographic characteristics, perinatal risk factors, and clinical manifestations of 600 infants with Downes' score of $\geq$ 4 admitted to the Affiliated BaYi Children's Hospital, China, and the Second Affiliated Hospital of Nanchang University, China, from 1 January 2013 to 1 December 2018. Infants were divided into two cohorts, non-survivors (who died, n = 109) and survivors (who survived, n = 491). Factors predicting infant mortality were determined using univariate and multivariate logistic regression analysis at a 95% confidence level.
Results: Infants of the non-survivor cohort were more likely to have severer respiratory distress (P = 0.003), to be of low birth weight (< 1,000 g, P = 0.028), to undergo cesarean delivery (P = 0.005), and to be born preterm (P = 0.0001) than those of the survivor cohort. Downes' score of > 6, extreme low birth weight (< 1,000 g, P = 0.001), preterm delivery (gestational age < 37 weeks, P = 0.003), and cesarean delivery (P = 0.002) were found to be the independent risk factors of infant death.
Conclusions: Preterm delivery, extremely low birth weight, and cesarean section were the risk factors of infant death from respiratory distress syndrome.

Keywords: Birth Weight, Cesarean Section, Extremely Low Birth Weight, Gestational Age, Incidence, Infant Mortality, Newborn, Pregnancy, Preterm Delivery, Respiratory Distress Syndrome, Risk Factors

1. Background

Pulmonary surfactants (phospholipid/protein mixture) prevent the alveolar collapse at the end of expiration in infants (1). Their metabolic cycles maintain alveolar homeostasis (2). Hyaline membrane disease or respiratory distress syndrome occurs due to pulmonary surfactant deficiency and genetic mutations (3). Infants born to Chinese ladies, due to low body weight, develop respiratory distress syndrome (4). Respiratory distress syndrome could lead to short-term and long-term complications in infants, which increase hospital stay and/or death (5). It is one of the leading causes of death in infants around the globe, especially in poor healthcare resource settings (6, 7). Surfactant deficiency is the pathophysiological basis of respiratory distress syndrome in infants, which is closely associated with the gestational age (2) and birth weight (8). Despite the availability and understanding of pathophysiology and management of respiratory distress syndrome, the literature suggests that about 20% - 43% of infants with respiratory distress syndrome die due to several reasons including late identification of infants with severe respiratory distress syndrome and high probability of adverse outcomes (6), making it as one of the leading causes of death in infants (9).

European Consensus Guidelines have identified various predictors of respiratory distress syndrome in infants, including maternal age, number of children, sepsis, and other factors (9). However, there is sparse literature about the predictors of death due to respiratory distress syndrome in infants. Timely diagnosis and proper manage-

ment of respiratory distress syndrome could reduce the risk of mortality. Therefore, it is essential to understand the factors predicting Chinese infants with respiratory distress syndrome who are at a high risk of mortality.

2. Objectives

The objective of the current retrospective analysis was to determine the incidence of respiratory distress syndrome and identify some predictors of mortality in infants with confirmed respiratory distress syndrome in Beijing and Jiangxi Provinces of PR China at the level III evidence, without conflicts of interest.

3. Methods

3.1. Ethical Approval and Consent to Participate

The protocol (SZSM201606088/CL/5/11 dated 22 December 2012) of the study was approved by the Affiliated BaYi Children's Hospital, Southern Medical University review board. The study adhered to the law of China, the strengthening the reporting of observational studies in epidemiology (STROBE) statement, and the 2008 Helsinki Declaration. Informed consent forms were signed by the parents of all the enrolled infants regarding the publication of the study in all formats including personal images and data (if any) irrespective of time and language. Data were collected for observational parameters, and no element of specific intervention was used in the protocol. Therefore, the Chinese clinical trial registration was waived.

3.2. Inclusion Criteria

Infants aged less than three years with respiratory complications and not discharged against medical advice were included in the analysis. We only included infants whose Downes' score was 4 or more in the study.

3.3. Exclusion Criteria

Infants aged greater than three years who had Downes' score of 0 - 3 and those who were unstable at discharge were excluded from the analysis.

3.4. Data Collection

The severity of respiratory distress was assessed by Downes' score as a comprehensive and appropriate tool for infants at any gestational age (10). We collected the data regarding maternal age, weight, height, smoking, alcohol habits, abuse of other drugs, history of cesarean section, history of gestational diabetes, history of any major medical interventions, and information about the use of antenatal corticosteroids. We extracted the data of infant gender, weight at birth, gestational age, vital parameters (heart rate, respiratory rate, capillary refill time, and temperature), sepsis, perinatal asphyxia, anemia, polycythemia, congenital malformation, meconium aspiration syndrome, jaundice, hyaline membrane disease, congenital or acquired pneumonia, cardiac shock, or congenital heart disease, hyperventilation, seizures, and inborn errors of metabolism. The hospital setting provided 24 hours of access to clinicians and laboratory investigations. Data were collected as per the descriptive epidemiologic survey methodology (11).

3.5. Characteristics Definition

Based on the gestational age, preterm babies are defined as babies born alive before 37 weeks of pregnancy (12). Preterm birth is further categorized as per the institutional Gynecology and Obstetrics guidelines into moderate-to-late preterm (gestational age: 32 - 36 weeks) (13), very preterm (gestational age: 28 - 32 weeks) (13), and extremely preterm (gestational age: less than 28 weeks) (14). Based on birth weight, 2,500 to 4,500 g was considered a normal birth weight (15) and less than 2,500 g was considered a low birth weight (16). Low birth weight was further categorized into low birth weight (1,501 - 2,499 g) (15), very low birth weight (1,000 - 1,500 g) (17), and extremely low birth weight (< 1,000 g) (18).

The severity of respiratory distress was defined as mild, moderate, and severe according to the Downes' score as 4 - 5, 6, and $\geq$ 7, respectively (grading was given based on the guidelines of the institutional review board) (19).

3.6. Cohorts

Infants with respiratory distress syndrome were classified into survivors and non-survivors. Infants with respiratory distress syndrome who died during hospital stay were considered non-survivors and infant with respiratory distress syndrome who survived until discharge were considered survivors. All deaths reported in the study were confirmed by physicians and they were based on information in the hospital medical records.

3.7. Statistical Analysis

Descriptive data were reported as means $\pm$ standard deviation (SD), numbers and percentages (%), and median and interquartile range (IQR). Categorical variables were tested using the Fischer exact test and continuous variables were tested by the Mann-Whitney U test. Baseline demographic characteristics, laboratory findings, clinical presentation, bacteriology, and predisposing factors were compared between non-survivors and survivors. Logistic regression analysis was performed to assess the predictors

of mortality in infants with respiratory distress syndrome. Univariate logistic regression was performed first to identify significant predictors. Then, all factors that were significant in the univariate model were entered into the multivariate model to adjust for confounding effects. The results of logistic regression were presented as odds ratio (OR) and 95% confidence intervals (CI). The results were considered significant at a 95% confidence level. Statistical analyses were performed using R version 3.3.3 software (R-project, Vienna, Austria) (12).

4. Results

4.1. The Clinical Manifestations

In total, 713 infants were admitted to the neonatal intensive care units of Affiliated BaYi Children's Hospital, Clinical Medical College in PLA Army General Hospital, Southern Medical University, Beijing, China, and the Second Affiliated Hospital of Nanchang University, Nanchang, China, (private institutes) from 1 January 2013 to 1 December 2018. The infants suffered from tachypnea (> 60/min), respiratory retractions, increase chest on respiration, expiratory grunting, nasal flaring, and/or central cyanosis.

Among the infants, 77 had no respiratory distress (Downes' score $\leq$ 3), and 14 had an age that could not be affected by respiratory distress syndrome (age > 3 years); so, they were excluded from the study. Moreover, 82 infants were unstable at discharge time. Therefore, they were excluded from the analysis because the survival outcomes were not known. Finally, data of 600 infants with confirmed respiratory distress syndrome were included in the analysis. Pre-designed data collection forms were used to extract the data from individual infant medical records of the institutes. The demographic characteristics, perinatal risk factors, and clinical manifestations of the infants were analyzed. The flow diagram of the study is presented in Figure 1.

Among the enrolled infants 499 (83%) had tachypnea, 344 had respiratory retractions, and 164 had expiratory grunting. Other clinical manifestations presented by infants with respiratory distress are shown in Table 1.

Table 1. Clinical Parameters of Infants at the Time of Enrollment[a]

Clinical Manifestations	No. (%)
Infants included in the study	600 (100)
Tachypnea, > 60/min	499 (83)
Retractions	344 (57)
Expiratory grunting	164 (27)
Nasal flaring	209 (35)
Central cyanosis	93 (16)
Bradypnea, < 30 breaths/min	84 (14)
Respiratory pauses (apnea)	118 (20)
Intercostal recessions	157 (26)
Xyphoid recessions	66 (11)
Thoraco-abdominal asynchrony	102 (17)
Hypoxia	52 (9)
Fetal heartbeat[b]	12 (2)
Meconium-stained amniotic fluid	15 (3)

[a] Values are expressed as No. (%).
[b] > 160 beats/min or < 120 beats/min.

4.2. Infant Risk Factors

In total, 347 (58%) male and 253 (42%) female infants were included in the analysis. There were 29 (5%) infants with Downes' score of 7 or more, 205 (34%) infants with Downes' score of 6, and 365 (61%) infants with Downes' score of 4 or 5 at the time of assessment. Among the infants, 331 (55%) had a birth weight of 1,500 g to 2,500 g, 167 (28%) a birth weight of 1,500 g to 1,000 g, and 102 (17%) birth weight of less than 1,000 g. Overall, 109 infants died during hospital stays. Therefore, the infants were divided into two cohorts, non-survivors (who died, n = 109) and survivors (who survived and stable at discharge, n = 491).

The survivor cohort had more male infants than the non-survivor cohort (P = 0.024) while infants of the non-survivor cohort had more severity of respiratory distress (P = 0.003). The non-survivor cohort had a more percentage of infants with a body weight of less than 1,000 g (P = 0.028). The non-survivor cohort had more numbers of infants who needed immediate medical help (APGAR score < 7 at the first minute, P = 0.002). The differences in other demographic parameters between the cohorts are presented in Table 2.

4.3. Perinatal Risk Factors

The maternal age was higher in the survivor cohort than in the non-survivor cohort (P = 0.028). Cesarean deliveries were higher in the non-survivor cohort than in the survivor cohort (P = 0.005). A preterm gestational age (< 37 weeks) was more frequently noted in the non-survivor cohort (P = 0.0001). The other maternal risk factors are highlighted in Table 3.

4.4. Predictors of Death in Infants

Significant demographic parameters of infants and the perinatal risk factors reported for non-survivors during analysis were subjected to univariate and multivariate logistic regression models. Among significant factors screened out in the analysis, severe respiratory distress

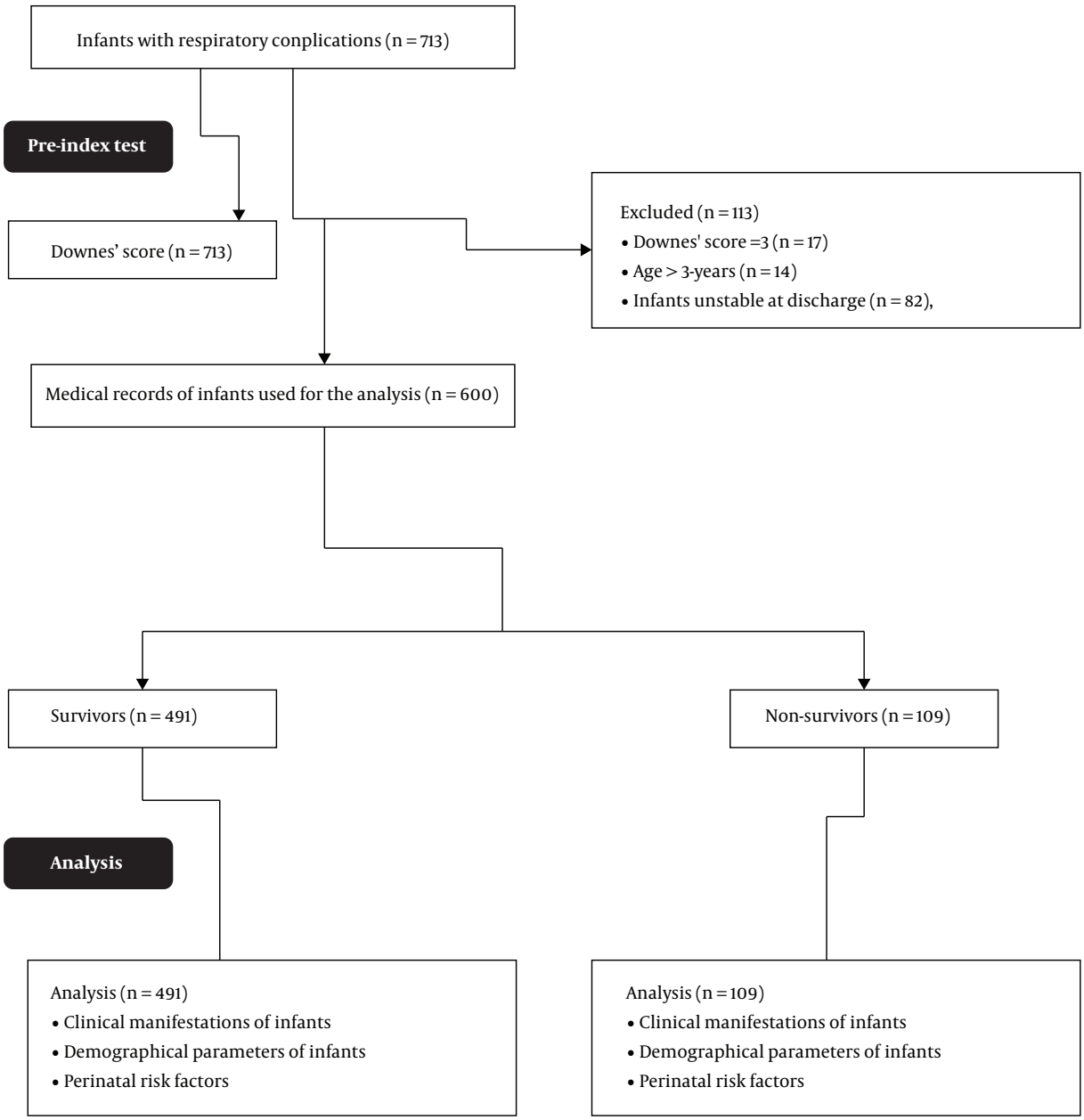

Figure 1. The flow diagram of the study

syndrome (Downes' score > 7, P = 0.003), moderate-to-severe respiratory distress syndrome (Downes' score = 6 - 7, P = 0.045), extremely low birth weight (< 1000 g, OR: 2.57, P = 0.001), preterm gestational age (< 37 weeks, P = 0.002), and delivery by a cesarean section (OR 2.32, P = 0.002) were found to be the significant predictors of death in infants with respiratory distress syndrome. The results were stable when these significant predictors from the univariate analysis were assessed using the multivariate model as shown in Table 4.

5. Discussion

The analysis showed that 18% of infants with respiratory distress syndrome died by the time of discharge due to respiratory distress or subsequent immediate complica-

Table 2. Demographical Parameters of Infants at the Time of Enrollment[a,b]

Parameters	Cohort		P Value[c]
	Survivors	Non-Survivors	
Infants	491	109	
Gender			0.024
Male	295 (60)	52 (48)[d]	
Female	196 (40)	57 (52)	
Age at the time of discharge or death, days			0.076
Minimum	1	1	
Maximum	22	22	
Mean ± SD	10.12 ± 5.12	9.12 ± 6.13	0.003
[b]Severity of respiratory distress (Downes' score)[e]			
Mild (4 - 5)	313 (64)	52 (48)	
Moderate (6)	159 (32)	46 (43)	
Severe (≥ 7)	19 (4)	10 (9)	
Birth weight			0.058
Normal birth weight (2,500 - 4,500 g)	93 (19)	12 (11)	
Low birth weight (1,501 - 2,499 g)	182 (37)	38 (35)	
Very low birth weight (1,000 - 1,500 g)	135 (27)	31 (28)	
Extremely low birth weight (< 1,000 g)	81 (17)	28 (26)[d]	
Sepsis[f]	64 (13)	22 (20)	0.069
APGAR score < 7 at the first minute	11 (2)	10 (9)[d]	0.002
Hospitalization duration, days			0.0016
Minimum	1	1	
Maximum	15	12	
Mean ± SD	9.51 ± 4.31	8.12 ± 3.21	

[a] Values are expressed as No. (%) or mean ± SD.
[b] Fischer exact test was used for categorical and the Mann-Whitney U test was used for continuous data.
[c] Comparisons between cohorts.
[d] Significant demographic parameters of non-survivor infants
[e] According to the institutional review board guidelines.
[f] Pathogens in the blood or other tissues and the body's response to their presence.

tions. Infants of the non-survivor cohort were more likely to be of low birth weight, to undergo cesarean delivery, and to be born preterm than infants of the survivor cohort were. Adverse outcomes are frequent in infants suffering from respiratory distress syndrome (8), which may increase the hospital length of stay and even the death rate (5). Despite available treatment options for respiratory distress syndrome (Ambroxol, Betamethasone, and Dexamethasone), a high death rate is reported in PR China (20). The results of the present study are consistent with available retrospective analyses that reported the death rate of 24.5% (range 20% - 45%) (6), as well as with a survey in the northwest regions of PR China that reported a 15% incidence of death (11). A retrospective analysis reported a slightly higher incidence of death in infants with respiratory distress syndrome than the present analysis. The difference in the observed incidence of death may be due to differences in the severity of respiratory distress syndrome in the infants of study, changes in practice over time, the sample size of the study, and the difference in approach to infant management. To the best of our knowledge, to date, there are a few surveys reporting the predictors of mortality in Beijing and Jiangxi provinces of PR China in infants with respiratory distress syndrome. Therefore, the present analysis adds significant values to the prevention of death as an adverse outcome in Chinese infants with respiratory distress and can inform the policymakers of PR China about prioritization in the management of respira-

Table 3. Perinatal Risk Factors for Infants at the Time of Enrollment[a,b]

Parameters	Survivors	Non-Survivors	P Value[c]
Infants	491	109	
Maternal age	29.71 ± 8.52	27.75 ± 7.56[d]	0.028
Maternal height, cm	155.45 ± 7.12	154.51 ± 6.45	0.205
Maternal weight, kg	54.12 ± 5.15	54.65 ± 6.14	0.349
Maternal body mass index, kg/m^2	23.15 ± 2.85	23.45 ± 2.98	0.325
Another drugs abuse	1 (1)	1 (1)	0.331
Ethnicity	449 (90)	96 (88)	0.116
Han Chinese			
Mongolian	39 (9)	10 (9)	
Tibetan	3 (1)	3 (3)	
Smoking status	132 (27)	25 (23)	0.47
Alcohol status	86 (18)	14 (13)	0.259
History of cesarean section	15 (3)	3 (3)	0.999
History of gestational diabetes	129 (26)	32 (29)	0.55
Maternal diabetes	156 (32)	40 (37)	0.367
Mode of delivery[d]			
Vaginal (normal delivery)	262 (53)	36 (33)	0.0005
Planned caesarian section	121 (25)	41 (38)	
Unplanned caesarian section	108 (22)	32 (29)	
Gestational age[d]			
Term/post-term (≥ 37 weeks)	384 (78)	66 (60)	0.0001
Preterm (< 37 weeks)	89 (18)	29 (27)	
Moderate to late preterm (32 - 36 weeks)			
Very preterm (28 -	14 (3)	9 (8)	
Extremely preterm (< 28 weeks)	4 (1)	5 (5)	

[a] Values are expressed as No. (%) or mean ± SD.
[b] Fischer exact test was used for categorical and the Mann-Whitney U test was used for continuous data.
[c] Comparisons between cohorts.
[d] Significant perinatal risk factors for non-survivors.

tory distress syndrome.

The analysis found that moderate or severe respiratory distress (Downes' score ≥ 6) to the infant was a significant predictor of the infant's death. The early identification of infants with respiratory distress syndrome is very important to plan the management of infants (9). The results of the study were in line with those of a cross-sectional study (21). Treating physicians could screen for the predictors identified in this analysis and plan a careful management strategy to monitor infants closely and prevent death in infants with respiratory distress syndrome.

Preterm gestational age (< 37 weeks) was more frequently noted in the non-survivor cohort. The results of the study were consistent with those of a case-control cohort study (2), a retrospective analysis (6), and a prospective study (22). Babies born with preterm delivery have structural and functional immaturity, lung deficiencies, and a low level of surfactants (6). The term of delivery is a significant predictor of death in infants.

The analysis found that extremely low birth weight (< 1,000 g) but not a low birth weight (1,501 - 2,499 g) was a significant predictor of infant death. A retrospective analysis (6) and a cross-sectional study (21) reported that low birth weight (< 2,500 g) is a significant predictor of death in infants with respiratory distress syndrome. The early use of non-invasive ventilation in low birth weight infants (1000 - 2499 g) may reduce the death rate (22). The results of the analysis are in line with a prospective study (22). Efforts are

Table 4. Prediction of Death in Infants[a]

Characteristics	Univariate Model		Multivariate Model[b]	
	95% CI, OR (IQR)	P Value	95% CI, OR (IQR)	P Value
Gender	1.89 (1.61 - 2.89)	0.061	NA	NA
Maternal age	1.95 (1.82 - 2.81)	0.075	NA	NA
APGAR score < 7 at the first minute (for infants)	1.96 (1.83 - 2.79)	0.071	NA	NA
Gestational age				
Very to extremely preterm (≤ 32 weeks)	2.33 (1.50 - 3.62)	0.0001	2.18 (1.42 - 3.43)	0.001
Preterm (< 37 weeks)	2.04 (1.27 - 3.28)	0.003	3.22 (1.43 - 7.26)	0.002
Respiratory distress syndrome (Downes' score)				
Severe (> 7)	1.80 (1.19 - 2.74)	0.001	1.94 (1.36 - 2.36)	0.003
Moderate to severe (6 - 7)	2.26 (1.03 - 4.94)	0.038	2.48 (1.60 - 3.85)	0.045
Mild (4 - 5)	2.31 (1.01 - 3.91)	0.035	3.45 (1.69 - 2.25)	0.07
Extremely low birth weight (< 1,000 g)	2.57 (1.61 - 4.09)	0.0001	2.72 (1.37 - 4.11)	0.001
Caesarian vs. vaginal delivery	2.32 (1.49 - 3.59)	0.0005	2.25 (1.26 - 3.78)	0.002

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, Odds ratio; N/A, not applicable.
[a] A $p < 0.05$ was considered significant.
[b] Multivariate model is adjusted for all the maternal and infant demographic characteristics.

required in nutritional management and clinical support of Chinese pregnant women and infants.

The analysis found that cesarean section delivery was a significant predictor of death in infants (P = 0.002). The results of the study are in line with those of retrospective analyses (6, 11). Unlike vaginal delivery, cesarean section delivery may not reduce lung water and catecholamine levels. Also, not possible to secrete pulmonary surfactants into the alveolar space, which leads to unsuccessful pulmonary vasodilatation (23). However, in women waiting for the onset of spontaneous labor pain, there may be increases in emergency cesarean sections, mortality, morbidity, and anxiety, which lead to the distrust of obstetricians (23). The study advises obstetricians to perform the cesarean section following the onset of labor pain in women with a planned cesarean section.

The analysis reported that the number of male infants (P = 0.061), maternal age (P = 0.075), and APGAR score < 7 at the first minute (for infants, P = 0.071) had no associations with the death of infants. The results of the study were in line with those of a retrospective analysis (6) and a prospective study (22). However, a high number of male infants survived because even at preterm delivery, pulmonary maturation is achieved in male infants due to the higher concentration of androgens (6). The gender of infants, maternal age, and initial critical conditions of infants were independent factors predicting the death of babies with respiratory distress syndrome.

The present analysis has certain limitations; for examples, participants were recruited from two hospital settings only; thus, the results might not be generalizable. The present study was a retrospective medical record-based analysis. Therefore, there is the possibility of bias due to reporting and assessment error. The study used only Downes' score despite the fact that the newborns were preterm (gestational age: 28 - 36 weeks). In the literature, most authors dedicate the Silverman-Anderson score to assess respiratory distress in very preterm and extremely preterm infants. However, Silverman-Anderson score has many subjective parameters such as retractions. Moreover, it requires intensive training for accurate assessment (24). Downes' score has lower inter-observer variability, better accuracy (25), and easy application (24). Downes' score is not comparable to Silverman-Anderson score even in very preterm and extremely preterm infants for health care providers.

5.1. Conclusions

This retrospective analysis screened and identified maternal and infant characteristics predicting death as an outcome in Chinese infants with respiratory distress syndrome. Preterm delivery (gestational age < 37 weeks), severe or moderate respiratory distress (Downes' score ≥ 6) to the infant, extremely low birth weight (< 1,000 g) of the infant, and cesarean section delivery were the predictors of death in Chinese infants with respiratory distress syndrome.

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Footnotes

Authors' Contribution: All authors reviewed and approved the submitted manuscript for publication. JingHua Luo was the project administrator and contributed to the design, data curation, and literature review of the study. Jia Chen contributed to the conceptualization, literature review, and data curation of the study. Jian Ming Yu contributed to the conceptualization, software, and literature review of the study. Qiuping Li contributed to the conceptualization, data curation, and literature review of the study. Zhichun Feng contributed to funding, literature review of the study, drafting, reviewing, and editing of the manuscript for intellectual content. The author agrees to be accountable for all the aspects of work ensuring integrity and accuracy.

Conflict of Interest: The authors report no conflict of interests associated with this work.

Ethical Approval: The protocol (SZSM201606088/CL/5/11 dated 22 December 2012) of the study had been approved by the Affiliated BaYi Children's Hospital, Southern Medical University review board.

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