

Risk Factors of Respiratory Distress Syndrome in Premature Infants at Prof Dr. I. G. N. G Ngoerah Hospital, Denpasar, Bali

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Abstract: *Introduction:* Respiratory distress syndrome (RDS) previously known as hyaline membrane disease (HMD), is one of the most common respiratory disorders in preterm neonates, appearing in the first few hours or immediately after delivery. The lack of pulmonary surfactant caused by immaturity of the lung is the etiology of RDS. Risk factors of RDS include maternal (sociodemographic and obstetric abnormalities), intrapartum and fetal factors. *Objectives:* To know the risk factors of RDS in preterm neonates at Prof. DR. I. G. N. G. Ngoerah Hospital Denpasar, Bali. *Methods:* This study was a retrospective study with design of case control study that conducted from January 2021 until February 2022. Samples of this study is neonates born prematurely with diagnosed of RDS at Prof. DR. I. G. N. G. Ngoerah Hospital during this study periode. All the data were analyzed by SPSS version 25. *Result:* The total sample of this study was 170 subjects, consisting of 85 subjects with RDS and 85 subjects as control. Multivariate analysis with logistic regression showed that gestational age < 34 weeks (OR 4.6; 95% CI 1.882-11.346; p = 0.001), APGAR score < 7 (OR 2.7; 95% CI 1.216-6.295; p = 0.015) and maternal preeclampsia (OR 3.58; 95% CI 1.09-11.75; p = 0.03) were statistically significant as the risk factors of RDS. *Conclusion:* Respiratory Distress Syndrome still occurs often in preterm newborns younger than 34 weeks of gestation. The incidence of RDS in preterm newborns was significantly increased by gestational age less than 34 weeks, APGAR score less than 7, and maternal preeclampsia. In particular, prospective cohort studies with bigger, more focused sample sizes are required in order to generate more accurate study.

Keywords: Respiratory Distress Syndrome, Risk Factor, Preterm Neonates

1. Introduction

Respiratory distress syndrome (RDS) previously known as hyaline membrane disease (HMD), is one of the most common respiratory disorders in preterm neonates, appearing in the first few hours or immediately after delivery. According to the Vermont Oxford Network diagnosis for RDS, infants must demonstrate central cyanosis in room air, arterial oxygen tension (PaO₂) 50 mmHg, and a distinctive chest radiography picture (uniform reticulogranular pattern to lung fields and air bronchogram) [1-4].

The pathogenesis of RDS is a surfactant deficit brought on by lung immaturity. In the case of developing lungs, it results from either insufficient surfactant synthesis or surfactant inactivation. Both of these variables are impacted by prematurity, which directly contributes to RDS. Birth weight and gestational age have an inverse relationship with its occurrence. The incidence of RDS is around 85% at 28 weeks of gestation and rises to 95% at 24 weeks, whereas it was 5% at 34 weeks and less than 1% at 37 weeks. Additionally, RDS affects 9.9 to 11.5% of newborns with birthweights above 2500g and 42% of neonates with low

birthweights [1, 3-6].

One of the leading causes of illness and death in infants is respiratory distress syndrome. According to a review study by Joel *et al.*, the prevalence of neonatal respiratory distress (NRD) ranged from 0.21 to 8.48%, with Saudi Arabia and Iraq having the highest prevalence (78.5% and 84.8%, respectively), and India, Ethiopia, and Sudan having the highest case fatality rates (47.1%, 45%, and 36%) [7]. Neonatal sepsis (42.7%), RDS (24.4%), perinatal asphyxia (15.9%), congenital abnormalities (13.4%), and meconium aspiration syndrome (MAS) (3.7%) are risk factors that lead to NRD mortality. However, studies conducted in Iraq by Fadhil revealed that RDS (67.1%), perinatal asphyxia (18.4%), congenital abnormalities (6.6%), sepsis (4.6%), and MAS (3.3%) were the leading causes of mortality in NRD [8].

Risk factors of RDS include maternal (sociodemographic and obstetric abnormalities), intrapartum and fetal factors. According to various studies, the risk factors for RDS include gestational age, birth weight under 1500 grams, vitamin D status, male babies, previous births of children with HMD, cesarean delivery, perinatal asphyxia, cold stress, perinatal infection, maternal diabetes, and abnormal placental implantation [2, 8, 9].

Identification the risk factor of RDS is very important to determine the initial therapy and to assess the prognosis of the baby. This study attempts to identify the factors that increase the incidence of RDS in preterm newborns.

2. Methods

This was an analytical observational study with case control design by collecting secondary data through medical records. Target population was neonates born prematurely who diagnosed with RDS. Accessible population was neonates born prematurely with RDS at neonatology ward Prof. Dr. I. G. N. G Ngoerah Hospital from January 2021 until February 2022. Inclusion criteria was all neonates born prematurely (gestational age < 37 weeks) who diagnosed with RDS at neonatology ward Prof. Dr. I. G. N. G Ngoerah Hospital. Exclusion criteria were infants with congenital anomalies and missing data. The sample size was calculated based on the formula for different proportion, two independent group as follows:

$$n1 = n2 = \frac{Z\alpha\sqrt{PQ} + Z\beta\sqrt{P1Q1+P2Q2^2}}{P1-P2}$$

In a previous study by Birihaane in 2021 about associated factors of RDS in preterm infants found that the proportion of effects in the control group was 0.189 (P2) and the OR was 2.6 (risk factor for gestational age <34 weeks to RDS). By entering the values above in the formula, we get the minimum sample size is 85 cases and 85 controls, the total sample is 170 infants.

2.1. Operational Definition of Variables

A) Respiratory distress syndrome, according to the Vermont Oxford Network, includes: Symptoms of respiratory distress at

≤ 28 days of age (tachypnea, expiratory grunting, nasal flaring, chest wall retraction); Arterial oxygen pressure (PaO₂) < 50 mmHg or central cyanosis on room air, PaO₂ >50 mmHg maintained with oxygen supplementation or peripheral oxygen saturation > 85%; Chest radiograph presenting uniform reticulogranular pattern, air bronchogram, bilateral symmetric lung consolidation, or effacement of pulmonary vessels [1]; Variable is presented in nominal scale, which are divided into (1) RDS, and (2) No RDS; B) APGAR score (expanded) is a standardized assessment for infants after delivery. The Apgar score comprises 5 components: (1) color; (2) heart rate; (3) reflexes; (4) muscle tone; and (5) respiration. The Apgar score provides an accepted and convenient method for reporting the status of the newborn infant immediately after birth and the response to resuscitation. The Apgar score is assigned at the 1st, 5th, 10th and 20th minute after delivery. Variable is presented in ordinal scale, which are divided into (1) APGAR score < 7, (2) APGAR score ≥ 7; C) Birth weight is the weight of the neonate that weighed within the first hour of birth. Low birth weight was defined as infants with a birth weight of < 2500 gram, very low birth weight: 1000 - <1500 gram, extremely low birth weight: < 1000 gram. Variable is presented in ordinal scale, divided into (1) birth weight below 1500 grams and; (2) birth weight ≥1500 gram; D) Premature infant is an infant born at gestational age < 37 weeks. Gestational age was assessed using *New Ballard Score* (physical and neuromuscular assessment) or *Finstrom score*. Variable is presented in nominal scale, which is divided into (1) premature and (2) not premature; E) History of antenatal corticosteroids (ANC) are antenatal corticosteroid therapy (long-acting glucocorticoids) administered intramuscularly to pregnant women at risk of preterm labor with a gestational age of 24 weeks to 34 weeks + 6 days. Variable is presented as nominal scale, divided into (1) History of ANC (2) No ANC; F) Sectio caesarea is an assisted delivery procedure in which the fetus is delivered through an incision made on anterior abdominal wall and uterine wall in the absence of labor signs. Variable is presented in nominal scale, which were divided into (1) Yes, (2) No; G) Maternal diabetes: mother with history of fasting plasma glucose >126 mg/dl or casual plasma glucose >200 mg/dl either before or during pregnancy; 8) Preeclampsia is a disorder of pregnancy associated with new-onset hypertension (systolic blood pressure of 140 mmHg or more or diastolic blood pressure of 90 mmHg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure) accompanied by new-onset proteinuria, or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following: thrombocytopenia (platelet count less than 100 x 10⁹/L); renal insufficiency, impaired liver function, pulmonary edema, new-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms; H) Gestational hypertension is defined as a systolic blood pressure 140 mmHg or more or a diastolic blood pressure of 90 mmHg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with a previously normal blood pressure; I) Premature rupture of

membranes: spontaneous leakage of amniotic fluid before apparent signs of labor. Preterm Premature Rupture of the Membranes (PPROM), when it occurs at gestational age < 37 weeks; J) Congenital anomalies also called birth defects, congenital disorders, or congenital malformations are structural or functional anomalies that occur during intrauterine life. It can involve many different parts of the body, including the brain, heart, lungs, liver, bones and intestinal tract. These conditions develop prenatally and may be identified before or at birth, or later in life.

2.2. Statistical Analysis

Categorical data are presented as frequencies and proportions, whereas numerical data is presented as mean if normally distributed or median if the distribution is not normal. Bivariate analysis was performed using chi-square or Fisher's Exact test if chi-square test conditions are not fulfilled. Odds ratio analysis (a measurement in case-control study to quantifies the odds of an exposure in case group relative to the control group). The relationship is considered significant if p value $\leq 0,05$ with 95% confidence interval. Multivariate analysis was used logistic regression test. This research has been approved by the Research Ethics Commission of the Faculty of Medicine, Udayana University/ Prof. Dr. I. G. N. G Ngoerah Hospital Denpasar with the ethical clearance number 1869/UN 14.2.2. VII.14/LT/2022.

3. Results

Among 170 preterm neonates, 85 subjects with RDS and 85 subjects without RDS. Subject with RDS mostly were male (54.1%), born by caesarean method (74.1%), very low birth weight (58.8%), gestational age < 34 weeks (85.9%), APGAR score <7 (74.1%) and mechanical ventilation < 14 days (57.6%). The characteristic of the subjects shown in Table 1.

The chi-square test was used to analyze the risk factors for gender, mode of delivery, gestational age, birth weight, APGAR score, ANC, and maternal preeclampsia. The results are shown in Table 2 as a large effect odds ratio (OR) with a 95% confidence interval (CI). In this study, the risk factors that significantly increased the likelihood of developing RDS were gestational age < 34 weeks (OR 10.60; 95% CI 4.99-22.5; $p=0.0001$), birth weight < 1500 gram (OR 6.67; 95% CI 3.29-13.5; $p=0.0001$), APGAR score < 7 (OR 6.87; 95% CI 3.51-13.48; $p=0.0001$), ANC (OR 1.86; 95% CI 0.96-3.64; $p=0.066$) and maternal preeclampsia (OR 3.05; 95% CI 1.13-8.23; $p=0.022$).

Variables having a p value of 0.25 in the bivariate analysis were subjected to multivariate analysis with logistic regression. The results were shown in Table 3. Gestational age < 34 weeks, APGAR score <7 and maternal preelampsia were significant increasing risk of RDS in premature infants.

Table 1. Characteristic of subjects.

Characteristics	RDS (n=85)	No RDS (n=85)	Total (n=170)
Gender, n (%)			
Male	46 (54.1)	50 (58.8)	96 (56.5)
Female	39 (45.9)	35 (41.2)	74 (43.5)
Delivery method, n (%)			
Caesarean	63 (74.1)	63 (74.1)	126 (74.1)
Spontaneous	22 (25.9)	22 (25.9)	44 (25.9)
Gestational age, n (%)			
< 34 weeks	73 (85.9)	31 (36.5)	104 (61.2)
≥ 34 weeks	12 (14.1)	54 (63.5)	66 (38.8)
Birth weight, n (%)			
< 1500 gr	50 (58.8)	15 (17.6)	65 (38.2)
≥ 1500 gr	35 (41.2)	70 (82.4)	105 (61.8)
APGAR score < 7, n (%)			
Yes	63 (74.1)	25 (29.4)	88 (51.8)
No	22 (25.9)	60 (70.6)	82 (48.2)
Antenatal corticosteroids, n (%)			
Yes	31 (36.5)	20 (23.5)	51 (30)
No	54 (63.5)	65 (76.5)	119 (70)
Maternal comorbidities, n (%)			
Diabetes			
Yes	2 (2.4)	3 (3.5)	5 (3)
No	83 (97.6)	82 (96.5)	165 (97)
Preeclampsia			
Yes	6 (7.1)	16 (18.8)	22 (12.9)
No	79 (92.9)	69 (81.2)	148 (87.1)
Gestational hypertension			
Yes	2 (2.4)	1 (1.2)	3 (1.8)
No	83 (97.6)	84 (98.8)	167 (98.2)
PPROM			
Yes	10 (11.8)	8 (9.4)	18 (10.6)
No	75 (88.2)	77 (90.6)	152 (89.4)
Ventilator use, n (%)			

Characteristics	RDS (n=85)	No RDS (n=85)	Total (n=170)
<14 days	49 (57.6)	14 (16.5)	63 (37.1)
≥14 days	12 (14.1)	6 (7.1)	18 (10.6)
No	24 (28.3)	65 (76.4)	89 (52.3)
Outcome, n (%)			
Alive	59 (69.4)	79 (92.9)	138 (81.2)
Died	26 (30.6)	6 (7.1)	32 (18.8)

Table 2. Bivariate analysis the risk factors of RDS.

Variable	RDS (n = 85)	Control (n = 85)	OR (95% CI)	P value
Gender				
Male, n (%)	46 (54.1)	50 (58.8)	0.826	0.536
Female, n (%)	39 (45.9)	35 (41.2)	(0.45 - 1.515)	
Birth weight				
<1500 gr, n (%)	50 (58.8)	15 (17.6)	6.67	0.0001
≥1500 gr, n (%)	35 (41.2)	70 (82.4)	(3.29 - 13.5)	
Gestational age, n (%)				
< 34 weeks	73 (85.9)	31 (36.5)	10.60	0.0001
≥ 34 weeks	12 (14.1)	54 (63.5)	(4.99 - 22.51)	
APGAR score				
< 7, n (%)	63 (74.2)	25 (29.4)	6.87	0.0001
≥ 7, n (%)	22 (25.8)	60 (70.6)	(3.51 - 13.48)	
Delivery method, n (%)				
Normal delivery	22 (25.9)	22 (25.9)	1	1
Caesarean section	63 (74.1)	63 (74.1)	(0.5 - 1.99)	
Antenatal corticosteroids, n (%)				
Yes	31 (36.5)	20 (23.5)	1.866	0.066
No	54 (63.5)	65 (76.5)	(0.96 - 3.64)	
Maternal preeclampsia, n (%)				
Yes	6 (7.1)	16 (18.8)	3.053	0.022
No	79 (92.9)	69 (81.2)	(1.132-8.236)	

OR = Odds Ratio; CI = Confidence Interval

Table 3. Multivariate analysis the risk factor of RDS.

Variable Penelitian	Sig.	Exp (B)	95% CI	
			LL	UL
Gestational age < 34 weeks	0.001	4.517	1.825	11.180
Birth weight < 1500 gram	0.289	1.659	0.651	4.230
APGAR score < 7	0.013	2.904	1.254	6.724
Maternal preeclampsia	0.035	3.589	1.095	11.757

LL = Lower Limit; UL = Upper Limit

4. Discussion

In this study, preterm neonates with RDS mostly are male (54.1%). The risk factors for RDS that Tochie et al discovered in Cameroon, Ethiopia, France, and South Africa have shown that male's gender is a significant risk factor for RDS [11]. According to Aynalem et al., male newborns had a 2.4 times greater chance of developing RDS than female neonates [9]. Since male newborns' lungs develop more slowly during the neonatal period as a result of greater levels of androgens, male neonates have a higher prevalence of RDS [7, 9, 12]. Zhao D et al. discovered a significant association between RDS and male gender. The enhancing impact of estrogens on alveolar growth and surfactant production can be used to explain why female gender has a protective effect. Estradiol and progesterone have a significant role in the development of the fetal lung, and it has been suggested that this involvement is mediated

by an increase in vascular endothelial growth factor (VEGF), which promotes the growth and maturation of alveolar type II cells [12].

Preterm neonates with birth weight <1500 gram were more at risk of suffering RDS (OR 6.67; 95% CI 3.29-13.5; $p=0.0001$). This result was similar with previous study. Birihaane et al discovered that newborns weighing less than 1500 gram (AOR 2.4; 95% CI 1.3-4.3) were predictors of HMD [2]. A scoping review by Tochie et al discovered a statistically significant association between RDS and low birth weight (birth weight < 2500 grams) [7]. Additionally, Permana et al. reported a favorable correlation between birthweight and RDS as well as between birthweight and gestational age [4]. Preterm birth (short gestation of less than 37 full weeks), intrauterine growth restriction (IUGR, also known as fetal growth restriction), or both can lead to low birth weight. Both of these causes result in organ immaturity, including respiratory distress [13]. Low birth weight newborns may also be associated with a higher risk of RDS

since preterm births are linked to low birth weight infants. All newborns with RDS are born at a lower weight (58.8%) than newborns without RDS. As reported by Nam et al., newborns with low birth weight are more likely to develop respiratory failure [14].

We found in bivariate analysis that gestational age < 34 weeks was one significant risk factor of RDS in preterm neonates (OR 10.60; 95% CI 4.99-22.51; $p=0.0001$) and confirmed in multivariate analysis (OR 4.51; 95% CI 1.82-11.18; $p=0.001$). Similar findings were seen in studies conducted in China, India, and Ethiopia (AOR 2.6; 95% CI 1.5-4.7; $p=0.005$) [2, 16, 17]. Additionally, Altman M discovered that a low gestational age was linked to a higher incidence of RDS [15]. According to a large systematic review, late preterm infants had a 17.3 times higher risk of developing RDS than term newborns. This is a result of the immature lung architecture, the lack of surfactants, and the lack of typical hormonal changes that occur at term and encourage the removal of lung fluid. Thyroid-Stimulating Hormone (TSH) levels rise with increasing gestational age, which has an effect on reducing the risk of RDS. Additionally, the likelihood of having a baby with a low Apgar score rises as gestational age decreases. As gestational age decreases, the risk of RDS rises (relative risk [RR] of 10.9 in 36-week infants, 28.6 in 35-week infants, and 48.4 in 34-week infants) [1, 2, 18, 19].

APGAR score < 7 (OR 2.9; 95% CI 1.25-6.72; $p=0.013$) were significantly as risk factors of RDS in preterm neonates. This result was in line with study in Ethiopia, UK, USA, Cameroon, China and Adis Ababa [2, 9, 16, 20-22]. Infants with Apgar scores under 6 were more likely than those with higher Apgar scores to have respiratory distress. Catecholamines are likely to have a role in how hypoxia affects the microcirculation and further reduces cardiac output. One of the most significant adverse effects of intrapartum hypoxia is hypovolaemia, which significantly reduces the newborn's peripheral blood flow and cardiac output. Following hypovolaemia, plasma expands, resulting in a lower oxygen carrying capacity. Hypovolemia and hypoxia working together might seriously hinder a newborn's ability to adjust their cardiorespiratory system to life outside the womb [2, 23].

This study found that infants from preeclampsia mothers had a higher risk of suffering RDS (OR 3.05; 95% CI 1.13-8.23; $p=0.022$). This result was supported by multivariate analysis, which revealed that maternal preeclampsia increased the risk of RDS (OR 3.58; 95% CI 1.09-11.75; $p=0.035$). This result was similar with previous study. Chang et al in their historic cohort study found the risk of RDS significantly increase in patients with preeclampsia (OR 1.35; 95% CI 1.03-1.78) [24]. Yu-Hua Wen et al in Taiwan also found that maternal preeclampsia slightly increase the risk of RDS (OR 1.16; 95% CI 1.02-1.31; $p=0.026$) [25]. Preeclampsia is characterized by an unbalanced maternal angiogenic state that causes generalized endothelial dysfunction, elevated levels of the maternal antiangiogenic factor soluble (mfs)-like tyrosine kinase-1 (sFlt-1), and

decreased levels of the angiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor in the free circulating state. Normal lung vasculature and the generation of surfactant proteins depend on VEGF, whereas sFlt-1, a VEGF antagonist, can prevent VEGF signaling and affect the production of surfactant proteins. RDS is related to surfactant deficiency, and RDS severity in premature newborns has been linked to low VEGF concentrations [25].

An earlier study showed that giving ANC to pregnant women who were at risk for preterm birth before 34 weeks of gestation reduced the incidence of HMD by 50% and its severity in newborns. In the event of preterm labor occurring before 34 weeks of gestation, the term before fetal lung maturation is complete, the administration of synthetic glucocorticoids (dexamethasone and betamethasone) within 24 to 48 hours to no longer than seven days can hasten fetal lung maturation by increasing the formation and release of surfactant. The administration of ANC did not show any protective impact for the development of RDS in a prospective cohort study carried out in France in 2012 to identify both risk factors and protective variables for RDS in intermediate preterm neonates using a logistic regression analysis. In this study we found that ANC had no protective effects for RDS. This result could be due to many preterm infants were not exposed to a complete course of ANC administration and short of ANC administration to delivery interval (<24 hours) [4, 7, 26].

Several studies showed that caesarean delivery was one of the risk factor of RDS in preterm neonates. Cesarean sections hinder the physiological changes that occur during labor and are essential for the newborn's normal cardiorespiratory adaptation, including the release of catecholamines and glucocorticoids, which cause pulmonary fluid resorption, the release of surfactant and pulmonary vasodilation, the mechanical compression of lung fluid during passage through the birth canal, and the molecular promotion of alveolar fluid drainage by activation of sodium channels [7, 15]. In this study we found that caesarean delivery was not associated with RDS in preterm neonates.

The goal of RDS management is to offer therapies that will increase survival while minimizing any potential side effects, including as bronchopulmonary dysplasia (BPD). The management consist of respiratory support by giving continuous positive airway pressure (CPAP) or mechanical ventilation (MV), surfactant replacement, fluid and nutritional support, antibiotic and sedation [1, 10]. In this study, 61 (71.7%) infants with RDS were using MV, 49 (57.6%) of them used less than 14 days.

Infants with RDS are now more likely to survive. Birth weight and gestational age have a significant impact on survival with or without respiratory and neurologic complications. For the tiniest newborns, major morbidity and poor postnatal development remain to be frequent [1]. In this study, 59 (69.4%) preterm neonates with RDS were survive while 26 (30.6%) were died.

5. Conclusion

Respiratory Distress Syndrome still occurs often in preterm newborns younger than 34 weeks of gestation. The incidence of RDS in preterm newborns was significantly increased by gestational age less than 34 weeks, APGAR score less than 7, and maternal preeclampsia. In particular, prospective cohort studies with bigger, more focused sample sizes are required in order to generate more accurate study findings.

Conflict of Interest

All the authors do not have any possible conflict of interest.

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