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Survival of Respiratory Failure within the First 72 Hours in Preterm Infants with Respiratory Distress Based on the Downes Score Assessment

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ABSTRACT

Background: Respiratory distress in neonates is the most common condition of preterm infants receiving treatment in the neonatal intensive care unit. As a clinical assessment of respiratory distress, the Downes score can predict the risk of respiratory failure. The present study aimed to determine the survival of respiratory failure in the first 72 h in preterm infants with respiratory distress based on the Downes score assessment.

Methods: A prospective cohort survival analysis was performed at three hospitals in Indonesia (Al-Islam Hospital, Bandung, Al-Ihsan Hospital, Bandung, and Cibabat Hospital, Cimahi) from April to July 2021. Subjects were infants aged 28-36 weeks, with respiratory distress based on the Downes score within the first 2, 6, 12, 24, 48, and 72 h after delivery. The analyzed variables included birth weight ([BW], <1500 vs. 1500-2500 g), gestational age ([GA], 28-32 vs. 32-37 weeks), and 5-min APGAR score (<7 vs. >7). Bivariate and multivariate analyses were conducted with Cox regression proportional hazard and the Kaplan-Meier estimate of survival rate was also performed. In addition, the adjusted hazard ratio (aHR) was calculated, and a P-value of less than 0.05 was considered statistically significant.

Results: Of the 89 subjects who met the criteria, 20 (22.47%) experienced respiratory failure. The multivariate analysis including BW (aHR: 1.846, 95%CI: 0.570-5.979, P> 0.05), GA (aHR: 2.273, 95 %CI: 0.697-7.416, P>0.05), and the 5-min APGAR score (aHR: 2.049, 95%CI: 0.811-5.179, P>0.05) estimated the survival rate for respiratory failure at the age of 72 h at 74.7% (standard error: 0.05%).

Conclusion: A GA of <32 weeks, a BW of <1500 g, and the condition of asphyxia simultaneously increased the aHR of respiratory failure, with an estimated survival rate of 74.7%.

Keywords: Downes score, Preterm infants, Respiratory failure

Introduction

The neonatal period is highly vulnerable since the risk of death is the highest during the first month of life. (1) In 2012, the neonatal mortality rate in Indonesia was 19 per 1,000 live births; however, it dropped to 15 per 1,000 live births in 2017. (3) Globally, the most common cause of neonatal death is a complication of premature birth (35%). (1,4) Premature births in 2015 amounted to 15.5 per 100 live births, placing Indonesia in the 9th position among 10 countries with the highest preterm births. (5)

Respiratory distress is the most common cause of newborn care in the neonatal intensive care unit (NICU). (6) Preterm infants often experience respiratory distress syndrome (RDS) caused by surfactant deficiency. (7) Clinically, infants with RDS have increased respiratory effort, characterized by tachypnoea, chest wall retraction, shortness of breath, and grunting. (8) Critically ill neonates in developing countries are monitored

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solely through observation due to limited facilities and a lack of supporting tools. (3) Respiratory distress in neonates can be assessed using the Downes score (Table 1). (9,10) A study done by Shashidhar showed that the Downes score was trustworthy, accurate, as well as more accessible and that it could be carried out faster by health workers. (11) Another study by Permatagalih revealed that the Downes score could be used to predict the need for respiratory support in the first 72 h after birth. (12) Downes et al., in their study, revealed that the Downes score could also predict prognosis. (13) Therefore, the present study aimed to determine the survival rate of respiratory failure in the first 72 h in preterm infants with respiratory distress, based on the Downes score in three hospitals with different setting areas during the COVID-19 pandemic.

Methods

The present study is based on survival analysis with a prospective cohort design, conducted at three hospitals in Indonesia (Al-Islam Hospital, Bandung, Al-Ihsan Hospital, Bandung, and Cibabat Hospital, Cimahi) from April to July 2021. A random sample of infants aged 28-36 weeks with gestational age (GA) of 28-36 weeks, who had respiratory distress based on the Downes Score (Table 1), were included in the study.

The dependent variable used in this study was the duration of respiratory failure within the first 72 h since the initial diagnosis of respiratory distress was observed within 2, 6, 12, 24, 48, and 72 h after birth. Clinical respiratory failure criteria are characterized by one or more of the following: 1) inadequate spontaneous breathing, 2) persistent bradycardia, 3) severe chest retractions, 4) severe tachypnoea, 5) desaturation, 6) apnoea, 7) nasal continuous positive airway pressure failure (Positive end-expiratory pressure of 8 cmH2O and an oxygen fraction requirement of 40%), and 8) the Downes score of >7. The dependent and independent variables were obtained from interviews and clinical assessments of patients with respiratory failure time (h) given a nominal scale status as follows: respiratory failure = 1, and no respiratory failure (censored) = 0.

The analysis was conducted in three stages. First, a univariate analysis was conducted to describe the subjects' characteristics. Afterward, bivariate and multivariate analyses were carried out with Cox regression proportional hazard to describe the relationship between the estimated survival function of respiratory failure at the time and the test results assessed by the adjusted hazard ratio (aHR). The analyzed multivariate variables included BW (1500 vs. 1500-2500 g), GA (28-32 vs. 32-37 weeks), and the 5-minute APGAR score (<7 vs. >7). Finally, the survival analysis was run using Kaplan-Meier curves to estimate the survival rate for respiratory failure. All data were recorded on the research form, tabulated, and statistically processed using the statistical software SPSS (version 25.0) for Windows.

Tabel 1. Downes Scores (9), (10)

	0	1	2
Respiratory rate	<60 min	60-80 min	>80 min
Retraction	No retraction	Mild retraction	Severe retraction
Cyanosis	No cyanosis	Cyanosis relieved by O2	Cyanosis on O2
Air Entry	Good bilateral air entry	Mild decrease in air entry	No air entry
Grunting	No grunting	Audible by stethoscope	Audible with ear

Results

During the study period, 89 preterm infants met the study criteria. The majority were born to median mothers aged 29±6.737 years old (57.3% multigravida and 80.9% singleton), who delivered their infants by cesarean section (48.3%), without complications during pregnancy (55.1%), and did not receive antenatal steroids (73%). Most of the infants born were girls (56.2%), with a median GA of 33.073±2.29 weeks, a mean BW of 1808.01±492.318 g, and the gestational maturity at the Appropriate for gestational age of 79.8%. Infants born with asphyxia based on the APGAR scores at 1 and 5 min (78.3% and 48.3%, respectively) underwent stages of positive pressure ventilation resuscitation (42.7%). Overall, 48.3% of the study subjects were diagnosed with RDS, 22.5% experienced respiratory failure, and 12.4% experienced early neonatal death (Table 2).

Based on the bivariate Cox regression proportional hazard analysis, there was an increased aHR of respiratory failure in the study subjects in the first 72 h of life, accompanied by statistically significant differences (P<0.05) in the variables of GA (aHR: 3.116, 95%CI: 1.288-7.539), BW (aHR: 2.740, 95%CI: 1.140-6.584), RDS (aHR: 8.078, 95%CI: 1.872-34.869), and neonatal mortality (aHR: 7.407, 95%CI: 3.079-17.821). Maternal age (aHR: 1.209, 95%CI: 0.506-2.886), multigravida (aHR: 1.096, 95% CI: 0.448-2.683), antenatal steroid administration (aHR: 1.211, 95%CI: 0.440-3.337), premature rupture of membranes (aHR: 1.520, 95%CI: 0.352-6.566), and the 5-min APGAR score (aHR: 1.741, 95%CI: 0.692-

Table 2. Subject Characteristics

Variables	Subjects	
	N(89)	%
Mother's age (years)		
Median	29±6.737	
<20	6	6.8
20-35	65	73.0
>35	18	20.2
Number of pregnancies		
Singleton	72	80.9
Twin	17	19.1
Gravida		
Primigravida	38	42.7
Multigravida	51	57.3
Abortion history		
Yes	12	13.5
Not	77	86.5
Type of delivery		
Vaginal Birth	46	51.7
Cesarian section	43	48.3
Maternal complications		
Normal	49	55.1
Antepartum hemorrhage	10	11.2
Prolonged labor (>18 hours)	5	5.6
Preeclampsia	5	5.6
Eclampsia	7	7.9
Fetal Emergency	7	7.9
Premature Contractions	6	6.7
Antenatal steroid administration		
Not given	65	73.0
Incomplete (<4×)	10	11.2
Complete (4×)	14	15.7
Premature rupture of membranes		
Yes	7	7.9
No	82	92.1
Sex		
Male	39	43.8
Female	50	56.2
BW (gram)		
Means	1808.01±492.318	
<1000 (extremely low BW)	4	4.5
1000-1499 (very low BW)	19	21.3
1500-2499 (low BW)	66	74.2
GA (weeks)		
Median	33.073±2.2932	
<30 (very early preterm)	8	9.0
30-33+6 (early preterm)	39	43.8
34-36+6 (late preterm)	42	47.2
Gestational maturity		
SGA	13	14.6
AGA	71	79.8
LGA	5	5.6
APGAR score 1 minute		
<7	70	78.3
>7	19	21.3
5-minute APGAR score		
<7	43	48.3
>7	46	51.7
Resuscitation stage		

Table 2. Continued		
Routine Care	13	14.6
Initial step	36	40.4
PPV	38	42.7
PPV+Chest Compression	2	2.2
Chest X-ray		
RDS	43	48.3
TTN	1	1.1
Normal lung findings	45	50.6
Respiratory failure		
Yes	20	22.5
No	69	77.5
Neonatal death		
Yes	11	12.4
No	78	87.4

GA: Gestational Age
BW: Birth Weight
SGA: Small for Gestational Age
AGA: Appropriate for Gestational Age
LGA: Large for Gestational Age
APGAR: Appearance, Pulse, Grimace, Activity, and Respiration
PPV: Positive Pressure Ventilation
RDS: Respiratory Distress Syndrome
TTN: Transient Tachypnea of the Newborn

4.378) were altered in the study subjects in the first 72 h of life; however, these variables were not accompanied by a statistically significant difference (P>0.05) (Table 3).

In the omnibus test coefficient model, it was found that a log level of 162.268 was statistically significant (P<0.05) on three variables (BW, GA, and the 5-min APGAR score), indicating that the Cox regression proportional hazard analysis with multivariate analysis was a good fit model. In Table 4, the multivariate Cox regression proportional hazard analysis shows that there was an increased aHR of respiratory failure in the study subjects in the first 72 h of life with BW (aHR: 1.846, 95%CI: 0.570-5.979, P>0.05), GA (aHR: 2.273, 95%CI: 0.697-7.416, P>0.05), and the 5-min APGAR score (aHR: 2.049, 95%CI: 0.811-5.179, P>0.05).

Table 3. Bivariate Analysis with Cox Regression Proportional Hazard

Variables	Respiratory Failure		No Respiratory Failure (censored)		aHR	P-Value	95%CI	
	N(20)	%	N(69)	%			Lower	Upper
Mother's age (years)								
<20/>35	8	40.0	16	23.2	1.209	0.669	0.506	2.886
20-35	12	60.0	53	76.8				
Gravida								
Multigravida	12	60.0	39	56.5	1.096	0.841	0.448	2.683
Primigravida	8	40.0	30	43.5				
Antenatal steroid administration								
Not given	15	75.0	50	72.5	1.211	0.706	0.440	3.337
Given (complete/incomplete)	5	25.0	19	27.5				
Premature rupture of membranes								
Yes	2	10.0	5	7.2	1.520	0.575	0.352	6.566
No	18	90.0	64	92.8				
Sex								
Male	8	40.0	31	44.9	0.767	0.561	0.313	1.878
Female	12	60.0	38	55.1				
BW (gram)								
<1500	10	50.0	14	20.3	2.740	0.024	1.140	6.584
1500-2499	10	50.0	55	79.7				
GA (weeks)								
<32	9	45.0	12	17.4	3.116	0.012	1.288	7.539
32-36+6	11	55.0	57	82.6				

Table 3. Continued								
Gestational maturity								
AGA	3	15.0	10	14.5	0.964	0.954	0.283	3.292
SGA / LGA	17	85.0	59	85.5				
1-minute APGAR score								
<7	13	65.0	57	82.6	0.622	0.314	0.247	1.566
>7	7	35.0	12	17.4				
5-minute APGAR score								
<7	13	35.0	30	43.5	1.741	0.239	0.692	4.378
>7	7	65.0	39	56.5				
Etiology of respiratory distress								
RDS	18	10.0	27	39.1	8.078	0.005	1.872	34.869
TTN / Others	2	90.0	42	60.9				
Neonatal death								
Yes	10	50.0	1	1.4	7.407	0.000	3.079	17.821
No	10	50.0	68	98.6				

GA: Gestational Age
BW: Birth Weight
SGA: Small for Gestational Age
AGA: Appropriate for Gestational Age
LGA: Large for Gestational Age
APGAR: Appearance, Pulse, Grimace, Activity, and Respiration

Table 4. Multivariate Analysis with Cox Regression Proportional Hazard (Variables in the Equation)

Variables	B	SE	Df	Sig	Exp (B)	95%CI	
						Lower	Upper
BW	0.613	0.600	1	0.307	1.846	0.570	5.979
GA	0.821	0.603	1	0.173	2.273	0.697	7.416
5-minute APGAR score	0.717	0.473	1	0.130	2.049	0.811	5.179

SE: Standard Error
BW: Birth Weight
GA: Gestational Age
APGAR: Appearance, Pulse, Grimace, Activity, and Respiration

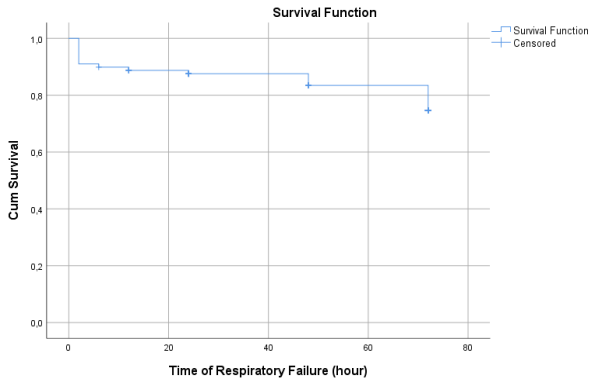

Figure 1. Kaplan Meier Curve Time of Respiratory Failure

Figure 1 shows the estimated survival rate for respiratory failure at the ages of 2 h [91.0%, standard error (SE): 0.030%], 6 h (89.9%, SE: 0.032%), 12 h (88.7%, SE: 0.034%), 24 hours (87.6%, SE: 0.035%), 48 h (83.4%, SE: 0.041%), and 72 h (74.7%, SE: 0.050%). In total, 20 cases of respiratory failure were managed with mechanical ventilation, but 8 (40%) subjects got surfactant therapy. There were not any co-morbidities, such as sepsis, in those infants who died

Discussion

Respiratory distress is the most common cause of newborn care in the NICU. (14) Approximately, 46.5% of neonates experience respiratory distress due to RDS. Respiratory distress in neonates is clinically characterized by increasing respiratory efforts, such as tachypnoea, grunting, cyanosis, chest wall retraction, and breath sounds on auscultation. A progressive increase in respiratory effort and oxygen fraction requirement to maintain target saturation can be used as a tool to assess disease progression (11,13).

Critically ill neonates in developing countries are monitored solely through clinical observation due to limited facilities and a lack of supporting equipment. Various studies have been conducted to train health workers to recognize respiratory distress, but very few studies have been undertaken on newborns. In limited health facilities, blood gas analysis cannot always be done for the monitoring and evaluation of the progress of respiratory distress due to limited tools and high costs. An easier, faster, and more accurate clinical assessment method is needed to evaluate the severity and risk of respiratory failure in neonates with respiratory distress. A previous study by Parappils has shown that low-cost techniques could save many infants (28-32 weeks of GA) and reduce mortality during hospitalization in low-income countries. (18)

Another study conducted by Downes et al.

revealed that the Downes score could predict prognosis, that is infants with a Downes score of >7 at the age of 12-24 and 24-30 h showed a survival rate of approximately 50% and 60%, respectively. (13) In a study by John BM, it was found that the Downes score 4 has a sensitivity of 59%, a specificity of 77.39%, and a positive predictive value of 50% in predicting the use of mechanical ventilation with an odds ratio of 4.94 (95%CI: 2.35-10.39). (19) In another study conducted by Rusmawati comparing the Downes score assessment with oxygen saturation examination, the sensitivity was 88% (95%CI: 79-99) and the specificity was 81% (95%CI: 70-91). (20) The study by Permatagalih showed a correlation between the Downes scores monitored in 24 h and the risk of respiratory failure in the first 72 h starting at 2 h of age (aHR= 1.86, 95%CI, P<0.001). Moreover, there was an increased risk of respiratory failure with increasing age in h for neonates experiencing respiratory distress. (12) Therefore, the Downes score can be used for periodic monitoring of neonates with respiratory distress, assessing the need for respiratory support, and considering the timing of referrals.

The occurrence of RDS is influenced by maternal factors, GA, the condition of asphyxia, BW, histories of antenatal steroid administration, and surfactant administration (6,8,21). In this study, based on bivariate analysis, there was an increase in the incidence of respiratory failure, accompanied by a statistically significant difference (P<0.05) in GA, BW, RDS, and neonatal mortality. However, maternal age, multigravida, antenatal steroid administration, premature rupture of membranes, and 5-min APGAR score showed a statistically significant difference (P>0.05) for the increase in the incidence of respiratory failure. In total, 7 out of 32 studies reported that RDS impacts the survival of preterm infants, and preterm neonates with RDS were 3.2 times more likely to die than preterm neonates without RDS (95%CI: 1.96-5.25). (22) In this study, RDS increased the aHR of respiratory failure in preterm infants by 8.078 times (95%CI: 1.872-34.869). The risk of infant death from premature birth in infants with RDS was 7.7742 times higher than that in infants without RDS (95%CI: 4.7121-512.826). Meanwhile, in this study, the aHR for the occurrence of death in infants with respiratory failure was 7.407 times higher (95%CI: 3.079-17.821), compared to those without respiratory failure.

Yehuala et al. showed that the Kaplan-Meier curve for infants with respiratory distress and a BW of <1600 g was lower than that in infants with no RDS and a BW of >1600 g. (24) In this study, preterm infants with a GA of <32 weeks, a BW of <1500 g, and the condition of asphyxia experienced a simultaneous increase in the aHR of respiratory failure by 1.846, 2.273 and 2.049 times, respectively. In total, 9 out of 32 studies reported that birth asphyxia had a significant association with preterm mortality. The combined effect of birth asphyxia on the survival of preterm infants suggests that preterm neonates with birth asphyxia had 2.6 times (95%CI: 1.9-3.4) higher risk of death than preterm infants without birth asphyxia. (22) During the first day of hospitalization, the probability of survival for preterm infants was maximum (93.4%) with a SE of 0.0113, (23) while in this study, the survival rate of respiratory failure occurred at the age of 24 h in 87.6% of cases (SE: 0.035%), 48 h in 83.4% of subjects (SE: 0.041%), and 72 h in 74.7% of cases (SE: 0.050%).

Conclusion

The conclusion of this study shows that infants born at 32 weeks of gestation, with a BW of <1500 g and the condition of asphyxia have a simultaneously increased risk of respiratory failure in the first 72 h based on the Downes score assessment, with an estimated survival rate of 74.7%. Therefore, it is recommended to conduct further research with more subjects in a multicentre study.

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Conflicts of interest

The authors declared no conflict of interest.

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