

## ***THE CORRELATION BETWEEN APGAR SCORE AND GESTATIONAL AGE WITH NEONATAL SEPSIS AND ASSOCIATED MORTALITY***

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### ***ABSTRACT***

***Background:*** Neonatal sepsis is increasingly recognized as an important global health problem that challenges neonatal survival. In 2018, sepsis caused approximately 15% of all neonatal deaths worldwide. Recent data regarding preterm birth and low Apgar score as risk factors for neonatal sepsis-related death have not been reported in Indonesia. ***Methods:*** This was a case-control study carried out in Dr. Soetomo Hospital. A case group was obtained from medical records by a total sampling of all neonates diagnosed with neonatal sepsis in 2019, and a control group of non-neonatal sepsis cases was taken by random sampling. The data were analyzed using the chi-square test and logistic regression analysis. ***Results:*** Statistical analysis showed a significant correlation between one and five-minute Apgar score <7 ( $p < 0.001$ , OR=16.69, 95% CI 8.10 - 34.38 and  $p < 0.001$ , OR=35.00, 95% CI 10.46 - 117.14 respectively) and preterm birth <37 weeks gestation ( $p < 0.001$ , OR=7.78, 95% CI 4.25 - 14.26) with neonatal sepsis. The mortality rate of neonatal sepsis was 40.74%. Mortality was strongly associated with one and five-minute Apgar score 0 – 3 ( $p=0.047$ , OR=4.59, 95%CI 1.05 – 20.06 and  $p=0.024$ , OR=3.12 1.09 - 8.92 respectively), extreme preterm born <28 weeks gestation ( $p=0.043$ , OR=4.59, 95% CI 1.05 - 20.06 ) and very preterm born 28 - <32 weeks gestation ( $p=0.032$ , OR=3.12 1.09 – 8.92). ***Conclusion:*** Low Apgar score and preterm birth could make neonates more at risk of neonatal sepsis. Mortality in neonatal sepsis was significantly related with one and five-minute Apgar score 0 - 3 (severe birth asphyxia) and preterm birth <32 weeks gestation.

***Keywords:*** Neonatal Sepsis, Apgar Score, Preterm Birth, and Neonatal Mortality.

### ***ABSTRAK***

***Latar Belakang:*** Sepsis neonatorum semakin diakui sebagai masalah kesehatan global penting yang menantang kelangsungan hidup neonatus. Pada tahun 2018,

sepsis menyebabkan sekitar 15% dari seluruh kematian neonatal di seluruh dunia. Data terbaru mengenai kelahiran prematur dan skor Apgar rendah sebagai faktor risiko kematian terkait sepsis neonatorum belum dilaporkan di Indonesia. **Metode:** Penelitian ini merupakan studi kasus-kontrol di Rumah Sakit Umum Daerah Dr. Soetomo. Kelompok kasus didapatkan dari rekam medis secara *total sampling* seluruh neonatus yang terdiagnosis sepsis neonatorum pada tahun 2019, dan kelompok kontrol diambil secara *random sampling*. Uji *chi-square* dan regresi logistik digunakan untuk menganalisis data. **Hasil:** Didapatkan 108 sampel untuk setiap kelompok. Analisis statistik menunjukkan korelasi yang signifikan antara skor Apgar menit ke-1 ( $p < 0,001$ , OR=16,69, 95% CI 8,10 - 34,38), ke-5 kurang dari 7 ( $p < 0,001$ , OR=35,00, 95% CI 10,46 - 117,14), dan kelahiran prematur <37 minggu kehamilan ( $p < 0,001$ , OR=7,78, 95% CI 4,25 - 14,26) dengan sepsis neonatorum. Angka kematian sepsis neonatorum sebesar 40,74%. Mortalitas pada sepsis neonatorum berhubungan dengan skor Apgar menit ke-1 dan ke-5 0 - 3 ( $p=0,047$ , OR=4,59, 95%CI 1,05 - 20,06 dan  $p=0,024$ , OR=3,12 1,09 - 8,92), kelahiran prematur ekstrim <28 minggu kehamilan ( $p=0,043$ , OR=4,59, 95%CI 1,05 - 20,06 ) dan kelahiran sangat prematur 28 - <32 minggu kehamilan ( $p=0,032$ , OR=3,12 1,09 - 8,92 ). **Kesimpulan:** Skor Apgar rendah dan kelahiran prematur dapat membuat neonatus lebih berisiko mengalami sepsis neonatorum. Mortalitas pada sepsis neonatorum berhubungan dengan skor Apgar menit ke-1 dan ke-5 0 - 3 dan kelahiran prematur <32 minggu kehamilan.

**Kata kunci:** Sepsis Neonatorum, Skor Apgar, Kelahiran Prematur, dan Mortalitas Neonatal.

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## INTRODUCTION

Sepsis caused approximately 15% of all neonatal deaths worldwide in 2018.<sup>1</sup> In developing countries,

sepsis is one of the three leading causes of mortality in neonates.<sup>2</sup> In Asia, neonatal sepsis is estimated to have an incidence of 7–38 per 1000

live births.<sup>3</sup> Astoundingly, a higher number of neonatal sepsis incidence has been reported in Indonesia. Several referral hospitals in Indonesia reported an incidence rate of 46–98 per 1000 live births.<sup>4-6</sup>

Neonatal sepsis is an infection involving blood circulation that affects neonates aged less than 28 days old, resulting in a potentially severe and fatal condition.<sup>7</sup> Birth asphyxia, preterm birth, meconium-stained amniotic fluid, low Apgar score, and low birth weight have all been recognized as newborn risk factors for neonatal sepsis.<sup>8</sup> However, preceding studies concerning consequences of birth asphyxia and preterm birth still have conflicting results. Some studies found a significant correlation between birth asphyxia and preterm birth with neonatal sepsis, but some conclude otherwise.<sup>5,9-11</sup>

Birth asphyxia is estimated to be responsible for 30–35 percent of newborn death.<sup>12</sup> Severe birth asphyxia has the criteria of Apgar score 0–3 in the first minute, and score 4–7 is considered mild and moderate asphyxia.<sup>13</sup> Apgar score is a method used to identify the

requirement of resuscitation in newborns and consists of five parameters (appearance, pulse, grimace, activity, and respiration).<sup>14</sup> Previous studies found that newborns with a previous history of the low Apgar score have a higher chance of deficiency in long-term cognitive<sup>15</sup> and neurological outcomes such as cerebral palsy and epilepsy.<sup>16</sup> A prospective observational study conducted in India found that newborns with a low Apgar score had a 2.23 times greater risk of neonatal mortality than newborns with a high Apgar score.<sup>17</sup>

Indonesia is ranked 5th out of countries with the highest number of premature infants (675,700 infants).<sup>18</sup> Immature immune systems in premature infants caused by a deficiency of IgG antibodies can have a greater risk of neonatal sepsis.<sup>19</sup> A national cohort study in Norway found high mortality in premature infants with neonatal sepsis up to 40%.<sup>20</sup> However, recent data regarding preterm birth and low Apgar score as risk factors for sepsis-related death have not been reported in Indonesia. Although survival of preterm and asphyxia neonates has

increased over the years, this group frequently needs hospitalization, putting them at risk of developing late-onset sepsis from hospital-acquired infection.<sup>21</sup>

There is still a significant rate of neonatal sepsis-related death. This indicates that efforts to reduce mortality have not been entirely effective. It is critical to recognize risk factors that contribute to neonatal mortality. Therefore, identifying the correlation between Apgar score, gestational age, neonatal sepsis, and neonatal mortality in Dr. Soetomo Hospital was the purpose of this study.

## METHODS

This study was a retrospective, observational, and analytical investigation of cases and controls carried out from medical records of neonates admitted to Dr. Soetomo Hospital neonatal care unit between January 1st, 2019 and December 31st, 2019. The newborns were divided into two groups. A case group was selected by a total sampling of all neonatal sepsis patients admitted in 2019, and the control group of non-neonatal sepsis cases was selected by random sampling. The Ethical

Committee of Dr. Soetomo Hospital approved this study's ethical clearance, number 0371/105/XI/2020. Inclusion criteria in this study were neonates less than 28 days old. Fetal congenital abnormalities, preterm rupture of membranes > 18 hours, a mother with chorioamnionitis, intrapartum fever >38°C, urinary tract infection were excluded as they may contribute to neonatal sepsis.<sup>8</sup> The dependent variable of this study was neonatal sepsis and outcome upon hospital discharge. The independent variable of this study was Apgar score and gestational age. Apgar score was divided into low (0–6) and normal (7–10) and was further categorized based on the severity of birth asphyxia 0–3 (severe), 4–7 (mild and moderate), and 8–10 (normal).<sup>13</sup> Birth prior to 37 weeks gestation was considered preterm<sup>22</sup>. Data were analyzed with SPSS version 25.0. The correlation between neonatal sepsis with Apgar score and gestational age was analyzed with the Chi-square test. Logistic regression was used to examine the correlation between prematurity and Apgar score with neonatal mortality in neonatal sepsis

patients. All tests were carried out with a 95% confidence level. Significant p-values were defined as those less than 0.05.

## RESULTS

The number of cases of neonatal sepsis at Dr. Soetomo Hospital in the period of January 1st, 2019 – December 31st, 2019 was 242 cases. Among the 242 cases, 44 had congenital abnormalities, 19 had mothers with PROM > 18 hours, 56 had incomplete medical record data, and 15 had incomplete medical record data with congenital abnormalities. Thus, 108 were included in the study as the case group, and 134 were excluded. A total of 1478 deliveries of non-neonatal sepsis patients born in obstetric gynecology emergency rooms were registered during this study. Among

the 1478 newborns, 108 were randomly sampled as the control group.

As shown in Table 1, there was a noticeable difference in the characteristic distribution between the two groups. A majority of the neonatal sepsis group were male (57.4%). The cases of preterm birth (born <37 weeks gestation) cases were close to 3 times greater in the neonatal sepsis group (73.15%) than the non-neonatal sepsis group (35.93%). The majority of newborns with neonatal sepsis were born weighing <2500 grams. (46.30%) which is close to 2 times higher than normal birth weight ( $\geq 2500$  grams) cases. Both groups were most frequently born by cesarean section (64.81% and 53.70%, respectively). The mortality rate in sepsis cases was high (40.74%).

**Table 1.** Characteristics of Neonates That were Admitted in Dr. Soetomo General Hospital January 1st, 2019 - December 31st, 2019

Characteristics of Samples	Neonatal Sepsis n (%)	Non-Neonatal Sepsis n (%)
<b>Gender</b>		
Male	62 (57.41%)	56 (51.85%)
Female	46 (42.59%)	52 (48.15%)
Total	108 (100%)	108 (100%)
<b>Gestational Age at Birth</b>		
Extreme preterm (< 28 weeks)	11 (10.18%)	0 (0%)
Very preterm (28 – <32 weeks)	35 (32.42%)	5 (4.63%)
Moderate preterm ( 32 – <37 weeks )	33 (30.55%)	23 (21.30%)
Aterm ( 37 – 42weeks)	29 (26.85%)	80 (74.07%)
Total	108 (100%)	108 (100%)
<b>Birth Weight</b>		
ELBW (<1000 grams)	10 (9.25%)	0 (0%)
VLBW (<1500 grams)	23 (21.30%)	1 (0.93%)
LBW (<2500 grams)	50 (46.30%)	33 (30.56%)
NBW (≥2500 grams)	25 (23.15%)	74 (68.51%)
Total	108 (100%)	108 (100%)
<b>Mode of Delivery</b>		
Spontaneous Vaginal Delivery	34 (31.48%)	40 (37.04%)
Forceps Extraction	4 (3.71%)	10 (9.26%)
Caesarean Section	70 (64.81%)	58 (53.70%)
Total	108 (100%)	108 (100%)
<b>Referral Case</b>		
Yes	25 (23.15%)	1 (0.93%)
No	83 (76.85%)	107 (99.07%)
Total	108 (100%)	108 (100%)
<b>Outcome</b>		
Live	44 (40.74%)	0 (0%)
Death	64 (59.26%)	108 (100%)
Total	108 (100%)	108 (100%)

\*ELBW: Extremely Low Birth Weight, VLBW: Very Low Birth Weight, LBW: Low Birth Weight, NBW: Normal Birth Weight.

Table 2 compared characteristics of Apgar score and gestational age between neonatal sepsis and non-neonatal sepsis group. Infants with Apgar score <7 at first and fifth-minute measurement were significantly higher in neonatal sepsis (67.59% and 50.00%, respectively) compared to the non-neonatal sepsis group (11.11% and 2.78%, respectively). The cases of preterm

birth were found close to 3 times higher in neonatal sepsis (73.15%) compared to the non-neonatal sepsis group (25.93%). Statistical analysis with chi-square test presented a significant correlation between first and fifth minute Apgar score and gestational age with neonatal sepsis ( $p < 0.001$ ). Infants with a first minute Apgar score <7 had a 16.69-fold greater risk (95% CI 8.10 – 34.38) of

neonatal sepsis compared with infants with an Apgar score  $\geq 7$ , while infants with Apgar score  $< 7$  at the fifth minute had a 35-fold greater risk (95% CI 10.46 – 117.14). Preterm

birth (born  $< 37$  weeks gestation) had 7.78-fold greater risks (95% CI 4.25 – 14.26) of neonatal sepsis than neonates born aterm.

**Table 2.** Analysis of Correlation Between Apgar Score and Gestational Age with Neonatal Sepsis

	Neonatal sepsis		p-value	Odds ratio (95% CI)
	Yes	No		
<b>First minute Apgar score</b>				
$< 7$	73 (67.59%)	12 (11.11%)	$< 0.001$	16.69 (8.10 – 34.38)
$\geq 7$	35 (32.41%)	96 (88.89%)		
Total	108 (100%)	108 (100%)		
<b>Fifth minute Apgar score</b>				
$< 7$	54 (50.00%)	3 (2.78%)	$< 0.001$	35.00 (10.46 – 117.14)
$\geq 7$	54 (50.00%)	105 (97.22%)		
Total	108 (100%)	108 (100%)		
<b>Gestational age at birth</b>				
$< 37$ weeks	79 (73.15%)	28 (25.93%)	$< 0.001$	7.78 (4.25 – 14.26)
$\geq 37$ weeks	29 (26.85%)	80 (74.07%)		
Total	108 (100%)	108 (100%)		

Description : \*Chi-square test significant at 5 percent significance level ( $p < 0.05$ ).

Infants with one and five-minute Apgar score of 0–3 (severe asphyxia) and 4–7 (mild and moderate asphyxia) in the neonatal sepsis group had higher mortality (47.73%; 22.73%) and (50.00%; 54.54%), respectively compared to survival.

Meanwhile, most neonatal sepsis cases who had an Apgar score of 8–10 at first and fifth-minute measurement had higher percentages of survival (15.62% and 43.75%, respectively) than death.

**Table 3.** Analysis of Correlation Between Apgar Score and Gestational Age with Outcome in Neonatal Sepsis Patients

	Outcome		p-value	Odds ratio (95% CI)
	Dead	Alive		
<b>First Minute Apgar score</b>				
0 – 3	21 (47.73%)	24 (37.50%)	0.047	8.75 (1.03 – 74.18)
4 – 7	22 (50.00%)	30 (46.88%)	0.066	7.33 (0.87 – 61.58)
8 – 10	1 (2.27%)	10 (15.62%)		Reference
Total	44 (100%)	64 (100 %)		
<b>Fifth Apgar score</b>				
0 – 3	10 (22.73%)	7 (10.94%)	0.024	4.00 (1.20 – 13.36)
4 – 7	24 (54.54%)	29 (45.31%)	0.068	2.32 (0.94 – 5.71)
8 – 10	10 (22.73%)	28 (43.75%)		Reference
Total	44 (100%)	64 (100%)		
<b>Gestational age at birth</b>				
Extreme preterm (< 28 weeks)	7 (15.91%)	4 (6.25%)	0.043	4.59 (1.05 – 20.06)
Very preterm (28 – <32 weeks)	19 (43.18%)	16 (25.00%)	0.032	3.12 (1.09 – 8.92)
Moderate preterm ( 32 – <37 weeks )	10 (22.73%)	23 (35.94%)	0.814	1.14 (0.38 –3.44)
Aterm ( 37 – 42 weeks)	8 (18.18%)	21 (32.81%)		Reference
Total	44 (100%)	64 (100%)		

Description : \*logistic regression analysis was significant at a 5 percent significance level (p<0.05).

Infants born extreme and moderate preterm had higher rates of death than survival (15.91% and 43.18%) compared to (6.25% and 25.00%), respectively. Statistical analysis with regression logistic presented significant correlation between first and fifth minute Apgar score 0 – 3 (p=0.047, OR=8.75, 95%CI 1.03–74.18; p=0.024 and OR=4.00, 95%CI 1.20 – 13.36, respectively), extreme preterm (born <28 weeks gestation) (p=0.043, OR=4.59, 95%CI 1.05 –

20.06) and very preterm (born 28 – <32 weeks gestation) (p=0.032, OR=3.12, 95%CI 1.09 – 8.92) with neonatal sepsis-associated deaths (Table 3).

## DISCUSSION

Understanding risk factors helps early prediction, diagnosis, and appropriate empirical antibiotic treatment. This is important to decrease infant morbidity and mortality in a "time-critical illness" like sepsis.<sup>23,24</sup> Low Apgar score



both at first and fifth-minute measurement, and preterm birth significantly increased the odds of neonatal sepsis in this study. This result is similar to a study by Adatara in Ghana where low Apgar scores at first and fifth-minute measurement increased neonatal sepsis risk 2.05 and 2.35 times, respectively.<sup>9</sup> A low Apgar score has also been identified to increase the risk of neonatal sepsis in a study conducted at Cipto Mangunkusumo Hospital with a 5.59 greater risk.<sup>5</sup> Both studies were conducted in specialist and referral hospitals where patients frequently have more severe and complicated illnesses that need advanced intervention and tools.

Intervention procedures, namely mechanical ventilation and umbilical catheter insertion in the delivery room, were found high neonates with a first minute Apgar score <7, thereby increasing the risk of sepsis due to pathogen contamination leading to nosocomial infection.<sup>5,25</sup> A study by Dalili in a tertiary referral hospital in Iran found that low Apgar scores at five-minute measurements have increased the

likelihood of requiring mechanical ventilation by 18-fold higher.<sup>26</sup>

A study that assessed neonatal asphyxia by examining Apgar score found a 17.308 higher risk of neonatal sepsis than infants without asphyxia.<sup>27</sup> The concentration of oxygen in the body affects host-pathogen interactions. In certain conditions, the hypoxia-enhanced release of neutrophils can also inhibit microbicidal activity and drive tissue damage.<sup>28</sup> However, this study's findings differed from Carolus's study in Manado, which found that Apgar score was not significantly linked to a higher risk of neonatal sepsis. ( $p=0.067$  and  $p=0.355$ , respectively).<sup>10</sup> Differences from maternal and or neonatal risk factors of the low Apgar score may explain the different findings. There were 79 (73.1%) preterm births in this study and 83 (76.9%) LBW infants with neonatal sepsis. Premature and LBW infants tend to have lower Apgar scores than term infants due to underdeveloped neurological systems that affect tone muscles and slow reflexes and cause a bluish red color to the skin.<sup>29</sup>

In this study, preterm newborns (born at 37 weeks gestation) were 7.78 times more likely than term births (born at 37 weeks gestation) to develop neonatal sepsis. This finding is similar to studies by Jaya and Roeslani.<sup>5,6</sup> Premature infants were predisposed to neonatal sepsis because of their relative immunodeficiency condition. In preterm infants, passive transport of IgG across the placenta from the mother to fetus in late pregnancy does not occur. Therefore, preterm infants can present hypogammaglobulinemia that unavoidably exposes them to a greater risk of infection.<sup>30</sup> Furthermore, during neonatal care, very preterm newborns are subjected to numerous invasive procedures.<sup>31</sup> Parental feeding, mechanical ventilation, orogastric catheter usage, antimicrobial treatment, central venous catheter use are all variables that appear to be linked to a higher risk of hospital-associated infections.<sup>32</sup> A study by Madeiros in Brazil found arterial umbilical catheter had an 8.5 times higher risk of late-onset sepsis.<sup>33</sup>

A total of 44 deaths out of 108 neonatal sepsis cases were reported in

this study, giving weighted neonatal mortality of 40.74%, similar to the rate reported in several hospitals in Indonesia.<sup>6,34</sup> However, this finding is two times higher compared to the neonatal sepsis mortality rate of other middle-income countries (17.6%).<sup>3</sup> This study further explores the association of neonatal mortality with preterm gestational age categorization and degree of perinatal asphyxia based on the Apgar score. Extreme and very preterm and Apgar score 0 – 3 (severe asphyxia) were strongly associated with neonatal death.

Even though extreme and very preterm births account for a relatively small number of newborns globally, they have a greater risk of mortality and morbidity.<sup>35</sup> In a multicenter cohort study by Zhu in China, the overall morbidity of extremely preterm infants was up 72.4%, only 9.4% survived without any major morbidity.<sup>36</sup> However, public health initiatives to prevent preterm birth born <34 weeks of gestation have not been effective, owing to a lack of knowledge of the complex reasons of extreme and very preterm birth.<sup>37</sup> Prematurity is associated with mortality in neonatal sepsis due to

insufficiencies in immunoglobulin synthesis, complement system (C3 and C5), phagocytosis, and opsonization ability.<sup>38</sup>

Previous studies have linked a low Apgar score at the fifth-minute measurement to a higher risk of neonatal death.<sup>26,39</sup> A study in India conducted by Sharma found a significant correlation between severely asphyxiated (one-minute Apgar score 0–3 and mild/moderately asphyxiated neonates (one-minute Apgar score 4–7) compared to normal Apgar score with neonatal mortality ( $p=0.03$  and  $p=0.04$ , respectively).<sup>17</sup> However, no studies have classified the risk of neonatal mortality depending on the severity of asphyxia in neonatal sepsis patients using the Apgar score classification.

It is necessary to note that in this study, the neonatal sepsis-related mortality to Apgar score is different between severe and mild/moderate asphyxia. Although newborns with an Apgar score of 4–7 had the highest percentage of neonatal sepsis-related death, infants with an Apgar score of 0–3 had a higher mortality risk.

With advancements in technology, there are certainly more

precise evaluation approaches, such as indicators of metabolic acidosis, including umbilical cord, base excess, blood pH, arterial lactate, and other markers.<sup>40</sup> However, most Indonesian hospitals do not have access to these indicators and are only available in a select few advanced hospitals. A majority of rural hospitals, on the other hand, are unable to take advantage of these advanced indicators. The Apgar score has a benefit over these advanced indicators in that it may be utilized as an assessment for prompt intervention therapy when resuscitation is required, and the results can be acquired on-site.

## CONCLUSION

In summary, low Apgar score and preterm birth could make neonates more at risk of neonatal sepsis. Mortality in neonatal sepsis was significantly related with first and fifth minute Apgar score 0 – 3, and preterm birth born <32 weeks gestation. Prevention of nosocomial infection is strongly suggested to prevent late-onset sepsis in infants born with low Apgar score and preterm birth.

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