Martono Utomo <mrmartono73@gmail.com>

Thu, Jan 6, 2022 at 12:31 PM

Dari: **Paul L. Tahalele** <admin-journal@ukwms.ac.id>
Date: Kam, 2 Sep 2021 pukul 22.45
Subject: [JWM] Submission Acknowledgement

To: Martono Tri Utomo

Martono Tri Utomo

Thank you for submitting the manuscript, "THE CORRELATION BETWEEN APGAR
SCORE AND GESTATIONAL AGE WITH NEONATAL SEPSIS AND ASSOCIATED MORTALITY" to
JURNAL WIDYA MEDIKA. With the online journal management system that we are
using, you will be able to track its progress through the editorial process
by logging in to the journal web site:

Manuscript URL:
http://journal.wima.ac.id/index.php/JWM/author/submission/3388
Username: nabilaannisa

If you have any questions, please contact me. Thank you for considering
this journal as a venue for your work.

Paul L. Tahalele
JURNAL WIDYA MEDIKA

_____
JURNAL WIDYA MEDICA
http://journal.wima.ac.id/index.php/JWM

M Gmail

Martono Utomo <mrmartono73@gmail.com>

Perbaikan makalah

2 messages

Mon, Sep 27, 2021 at 5:15 PM

Yth Lukas Slamet Rihadi,
Terimakasih untuk masukan yang disampaikan, bersama ini saya lampirkan makalah yang telah
direvisi dengan parafrase pada bagian method dengan similiarity index yang menurun dari 13 menjadi
12% dan sudah memenuhi kriteria jurnal yaitu <20%.
Terima Kasih

Salam hormat,
dr Martono

**The Correlation Between Apgar Score and Gestational Age with Neonatal Sepsis and Associated
Mortality revision 1.docx**
62K

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

Nabila Annisa Harum[1], Martono Tri Utomo#[2], Aditiawarman[3], Prastiya Indra Gunawan[4]

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 was 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

---

[1] *Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*

[2,4] *Department of Paediatrics, Faculty of Medicine Universitas Airlangga - Dr. Soetomo Academic Hospital, Surabaya, Indonesia*

[3] *Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Airlangga - Dr. Soetomo Academic Hospital, Surabaya, Indonesia*

Corresponding author: +6281703667063, mrmartono73@gmail.com

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.

INTRODUCTION

Sepsis caused approximately 15% of all neonatal deaths worldwide in 2018.[1] In developing countries, one of the three leading causes of mortality in neonates is sepsis.[2] In Asia, neonatal sepsis is estimated to have an incidence of 7–38 per 1000 live births.[3] 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.[4–6]

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.[7] 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.[8] 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. [5,9–11]

Birth asphyxia is estimated to be responsible for 30–35 percent of newborn death.[12] 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.[13] 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).[14] Previous studies found that newborns with previous history of low Apgar score have a higher chance of deficiency in long-term cognitive[15] and neurological outcomes such as cerebral palsy and epilepsy.[16] A prospective observational study conducted in India found that newborns with a low Apgar score had 2.23 times greater risk of neonatal mortality than newborns with a high Apgar score.[17]

Indonesia is ranked 5th out of countries with the highest total number of premature infants (675,700 infants).[18] Immature immune systems in premature infants caused by a deficiency of IgG antibodies can have a greater risk of neonatal sepsis.[19] A national cohort study in Norway found high mortality in premature infants with neonatal sepsis up to 40%.[20] 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.[21]

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 Dr. Soetomo Hospital neonatal care unit between January 1st 2019 – December 31st 2019. The newborns were divided into two groups. A case group was selected by 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, mother with chorioamnionitis, intrapartum fever

>38⁰C, urinary tract infection were excluded as they may contribute to neonatal sepsis.[8] 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).[13] Birth prior to 37 weeks gestation was considered preterm[22]. Data was analyze with SPSS version 25.0. The correlation between neonatal sepsis with Apgar score and gestational age was analyzed with 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 (≥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 f (%)	Non-Neonatal Sepsis f (%)
Gender		
Male	62 (57.41%)	56 (51.85%)
Female	46 (42.59%)	52 (48.15%)
Total	108 (100%)	108 (100%)
Gestational Age at Birth		
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%)
Birth Weight		
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%)
Mode of Delivery		
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%)
Referral Case		
Yes	25 (23.15%)	1 (0.93%)
No	83 (76.85%)	107 (99.07%)
Total	108 (100%)	108 (100%)
Outcome		
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 ≥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**		
First minute Apgar score				
<7	73 (67.59%)	12 (11.11%)	<0.001	16.69 (8.10 – 34.38)
≥7	35 (32.41%)	96 (88.89%)		
Total	108 (100%)	108 (100%)		
Fifth minute Apgar score				
<7	54 (50.00%)	3 (2.78%)	<0.001	35.00 (10.46 – 117.14)
≥7	54 (50.00%)	105 (97.22%)		
Total	108 (100%)	108 (100%)		
Gestational age at birth				
< 37 weeks	79 (73.15%)	28 (25.93%)	<0.001	7.78 (4.25 – 14.26)
≥ 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.

Infants born extreme and moderate preterm had higher rates of death than survival (15.91% and 43.18%) compared to

Table 3. Analysis of correlation between Apgar score and gestational age with outcome in neonatal sepsis patients

| | Outcome | | p-value | Odds ratio |
	Dead	Alive		(95% CI)
First Minute Apgar score				
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 %)		
Fifth Apgar score				
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%)		
Gestational age at birth				
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 significant at 5 percent significance level (p<0.05).

(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. [23,24] 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 firsy and fifth minute measurement increased neonatal sepsis risk 2.05 and 2.35 times, respectively.[9] 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 .[5] 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.[5,25] 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. [26]

A study that assessed neonatal asphyxia by examining Apgar score found a 17.308 higher risk of neonatal sepsis than infants without asphyxia.[27] The concentration of oxygen in the body affects host-pathogen interactions. In certain conditions, hypoxia-enhanced release of neutrophils can also inhibit microbicidal activity and drive tissue damage.[28] However, this study's findings differed from those of 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).[10] Differences from maternal and or neonatal risk factors of 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. [29]

In this study, preterm newborns (born at 37 weeks gestation) were 7.78 times more likely than aterm births (born at 37 weeks gestation) to develop neonatal sepsis. This finding is similar to studies by Jaya and Roeslani.[5,6] 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.[30] Furthermore, during neonatal care, very preterm newborns are subjected to numerous invasive procedures. [31] 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. [32] A study by Madeiros in Brazil found arterial umbilical catheter had 8.5 times higher risk of late-onset sepsis. [33]

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.[6,34] However,

this finding is two times higher compared to the neonatal sepsis mortality rate of other middle-income countries (17.6%).[3] 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.[35] 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.[36] 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.[37] Prematurity is associated with mortality in neonatal sepsis due to insufficiencies in immunoglobulin synthesis, complement system (C3 and C5), phagocytosis, and opsonization ability.[38]

Previous studies have linked a low Apgar score at the fifth-minute measurement to a higher risk of neonatal death.[26,39] 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).[17] 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 risk of mortality.

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.[40] 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.

REFERENCES

1. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). Levels and trends in child mortality: report 2019 [Internet]. estimates developed by the United Nations Inter-agency Group for Child Mortality Estimation. 2019 [cited 2021 Aug 20]. Available from: https://www.unicef.org/sites/default/files/019-10/UN-IGME-child-mortality-report-2019.pdf

2. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet. 2016;388(10063):3027–35.

3. Fleischmann C, Reichert F, Cassini A, Horner R, Harder T, Markwart R, et al. Global incidence and mortality of neonatal sepsis: A systematic review and meta-analysis. Arch Dis Child. 2021;745–52.

4.   Putra PJ. Insiden dan Faktor-Faktor yang Berhubungan dengan Sepsis Neonatus di RSUP Sanglah Denpasar. Sari Pediatri. 2012;14:205–10.

5.   Roeslani RD, Amir I, Nasrulloh MH, Suryani. Penelitian awal: Faktor Risiko Pada Sepsis Neonatorum Awitan Dini. Sari Pediatri. 2013;14:363–8.

6.   Jaya I, Suryawan IW, Rahayu, PP. Hubungan prematuritas dengan kejadian sepsis neonatorum yang dirawat di ruang perinatologi dan neonatal intensive care unit (NICU) RSUD Wangaya kota Denpasar. Intisari Sains Medis. 2019;10:18–22.

7.   Ershad M, Mostafa A, Cruz M Dela, Vearrier D. Neonatal Sepsis. Curr Emerg Hosp Med Rep. 2019;7(3):83–90.

8.   Araújo BC, Guimarães H. Risk factors for neonatal sepsis: an overview. J Pediatr Neonatal Individ Med. 2020;9(2):1–15.

9.   Adatara P, Afaya A, Salia SM, Afaya RA, Konlan KD, Agyabeng-Fandoh E, et al. Risk Factors Associated with Neonatal Sepsis: A Case Study at a Specialist Hospital in Ghana. Parker MM, editor. Sci World J. 2019;2019:9369051.

10.   Carolus W, Rompis J, Wilar R. Hubungan Apgar Skor Dan Berat Badan Lahir Dengan Sepsis Neonatorum. e-CliniC. 2013;1(2):1–7.

11.   Hasanah N, Lestari H, Rasma R. Analisis Faktor Risiko Jenis Kelamin Bayi, BBLR, Persalinan Prematur, Ketuban Pecah Dini dan Tindakan Persalinan dengan Kejadian Sepsis Neonatus di Rumah Sakit Bahteramas Provinsi Sulawesi Tenggara Tahun 2016. J Ilm Mhs Kesehat Masy Unsyiah. 2016;1(3):185324.

12.   Lawn JE, Blencowe H, Oza S, You D, Lee ACC, Waiswa P, et al. Every newborn: Progress, priorities, and potential beyond survival. Lancet. 2014;384(9938):189–205.

13.   WHO. International Statistical Classification of Diseases and Related Health Problems (ICD-10) 10th revision [Internet]. 2019 [cited 2021 Aug 6]. Available from: https://icd.who.int/browse10/2019/en.

14.   American College of Obstetricians and Gynecologists, American Academy of Pediatrics. The Apgar Score (Committee Opinion No.644). Obstet Gynecol. 2015;126:52–5.

15   Odd DE, Rasmussen F, Gunnell D, Lewis G, Whitelaw A. A cohort study of low Apgar scores and cognitive outcomes. Arch Dis Child Fetal Neonatal Ed. 2008;93(2):115–20.

16.   Persson M, Razaz N, Tedroff K, Joseph KS, Cnattingius S. Five and 10 minute Apgar scores and risks of cerebral palsy and epilepsy: Population based cohort study in Sweden. BMJ. 2018;360:1–8.

17.   Sharma D, Choudhary M, Lamba M, Shastri S. Correlation of Apgar Score

with Asphyxial Hepatic Injury and Mortality in Newborns: A Prospective Observational Study from India. Clin Med Insights Pediatr. 2016;10:CMPed.S38503.

18. WHO. Preterm Birth Fact Sheets [Internet]. 2018. [cited 2021 Aug 10]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/preterm-birth

19. Kosim, MS, Yunanto, A, Dewi R, Sarosa GI, Usman A, Buku Ajar Neonatologi. Jakarta:Badan Penerbit IDAI;2012

20. Rønnestad A, Abrahamsen TG, Medbø S, Reigstad H, Lossius K, Kaaresen PI, et al. Septicemia in the first week of life in a Norwegian national cohort of extremely premature infants. Pediatrics. 2005;115(3).

21. WHO. Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions [Internet]. 2020. [cited 2021 Aug 11]. Available from: http://apps.who.int/bookorders.%0Ahttps://apps.who.int/iris/bitstream/handle/10665/334216/9789240010789-eng.pdf

22. Martin JA, Hamilton BE, Osterman MJK. Births in the United States, 2018. NCHS Data Brief. 2019;346:1–8. PMID: 31442195.

23. WHO. Improving the prevention, diagnosis and clinical management of sepsis [Internet]. 2017. [cited 2021 Aug 12]. Available from: http://apps.who.int/gb/ebwha/pdf_files/EB 140/B140_R5-en.pdf?ua=1

24. Weiss SL, Fitzgerald JC, Balamuth F, Alpern ER, Lavelle J, Chilutti M, et al. Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. Crit Care Med. 2014;42(11):2409–17.

25. Widayati K, Kurniati D, Windiani G. Faktor Risiko Sepsis Neonatorum di Ruang Perinatologi Rumah Sakit Umum Pusat Sanglah Denpasar. Public Heal Prev Med Arch. 2016 Jul 1;4:67.

26. Dalili H, Sheikh M, Hardani AK, Nili F, Shariat M, Nayeri F. Comparison of the combined versus conventional apgar scores in predicting adverse neonatal outcomes. PLoS One. 2016;11(2):1–11.

27. Dwilda Ferdinandus E, Devianti Putri B. Early-Onset Neonatal Sepsis in Low-Birth-Weight and Birth-Asphyxia Infants at Haji Hospital Surabaya, Indonesia. Indian J Public Heal Res Dev. 2020;11(1):1076.

28. Lodge KM, Cowburn AS, Li W, Condliffe AM. The impact of hypoxia on neutrophil degranulation and consequences for the host. Int J Mol Sci. 2020;21(4).

29. Nilasari N, Kharisma B, Puti A. Analisis Faktor Penyebab Kejadian Asfiksia pada Bayi Baru Lahir. J ners Dan Kebidanan. 2019;6(2):251–62.

30. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M.

IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012;2012:985646.

31. Vinall J, Miller SP, Bjornson BH, Fitzpatrick KPV, Poskitt KJ, Brant R, et al. Invasive procedures in preterm children: Brain and cognitive development at school age. Pediatrics. 2014;133(3):412–21.

32. Urzedo JE, Levenhagen MMMD, Pedros RS, Abdallah VOS, Sabino SS, Brito DVD. Nosocomial infections in a neonatal intensive care unit during 16 years: 1997-2012. Rev Soc Bras Med Trop. 2014;47(3):321–6.

33. Medeiros F do VA, Alves VH, Valete COS, Paiva ED, Rodrigues DP. A correlação entre procedimentos assistenciais invasivos e a ocorrência de sepse neonatal TT - The correlation between invasive care procedures and the occurrence of neonatal sepsis. Acta paul enferm. 2016;29(5):573–8.

34. Pinilih A, Ranto H. Profil dan Faktor Risiko Kematian Sepsis Neonatus di RSUD Sukadana Lampung Timur. J Ilmu Kedokt dan Kesehat. 2019;6:290–5.

35. WD B. Public Health Implications of Very Preterm Birth. Clin Perinatol. 2018;45(3):565–77.

36. Zhu Z, Yuan L, Wang J, Li Q, Yang C, Gao X, et al. Mortality and Morbidity of Infants Born Extremely Preterm at Tertiary Medical Centers in China from 2010 to 2019. JAMA Netw Open. 2021;1–15.

37. Howse JL, Katz M. Conquering prematurity. Pediatrics. 2013;131(1):1–2.

38. Silva SM ary. R, de Cássia Pinheiro da Motta G, Nunes CR aup., Schardosim JM achad., da Cunha ML uzi. C. Late-onset neonatal sepsis in preterm infants with birth weight under 1.500 g. Rev Gaucha Enferm. 2015;36(4):84–9.

39. Iliodromiti S, MacKay DF, Smith GCS, Pell JP, Nelson SM. Apgar score and the risk of cause-specific infant mortality: A population-based cohort study. Lancet. 2014;384(9956):1749–55.

40. Mu Y, Li M, Zhu J, Wang Y, Xing A, Liu Z, et al. Apgar score and neonatal mortality in China: an observational study from a national surveillance system. BMC Pregnancy Childbirth. 2021;21(1):1–12.