

The Effect of Asphyxia on Neonatal Death: A Meta-Analysis

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ABSTRACT

Background: Asphyxia is the second leading cause of neonatal death in the world. The indicator for the diagnosis of asphyxia in newborns is the APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score. APGAR score at the fifth minute of life correlated with the asphyxia degree. This study aimed to estimate how great the effect of asphyxia on neonatal death based on the results of some previous studies.

Subjects and Method: This was a systematic and meta-analysis study. The articles used in this study were obtained from several databases including PubMed, Science Direct, and Google Scholar. The articles used in this study were articles that have been published from 2010-2020. The article was searched by considering the eligibility criteria defined using the PICO model. The population of this study was neonatal with intervention in the form of asphyxia, comparison, namely non-asphyxia, and outcome in the form of death. These articles were collected for 1 month. The keywords were "neonatal" AND "asphyxia" OR "APGAR score" AND "mortality",

"death neonatal asphyxia" OR "mortality asphyxia" AND "cross sectional". The articles included in this study were full-text articles with a cross-sectional study design. The articles were collected using PRISMA flow diagrams. The articles were analyzed using the Review Manager 5.3 application.

Results: 6 articles were reviewed in this study. This study showed that asphyxia increased the risk of neonatal death (aOR= 3.52; 95% CI= 1.05 to 11.82; p=0.040).

Conclusion: Asphyxia increases the risk of neonatal death.

Keywords: Asphyxia, APGAR score, neonatal mortality, neonatal death

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BACKGROUND

One of the Sustainable Development Goals (SDGs) is to end deaths from newborns and children under five years old by 2030. The SDGs stated that all countries must reduce neonatal death to 12 deaths per 1,000 births by 2030 (Hug et al., 2019).

The majority of neonatal deaths occurred in the first week of life and even around 1 million newborns died in the first 24 hours (WHO, 2019). UNICEF (2019) stated that 2.5 million children in 2018 died in the first month of life with 7,000 newborn deaths, one

third died on the day of birth, and almost three quarters died in the first week of life.

Neonatal mortality is 50 times greater in low- and middle-income countries (UNICEF, 2019). The highest number of neonatal mortality occurs in sub-Saharan Africa, Central, Asia, and South Asia.

WHO (2019) stated that sub-Saharan Africa in 2018 had a neonatal mortality rate of 28 deaths per 1,000 live births, while Central and South Asia had 25 deaths per 1,000 live births. One of the cause of neonatal death in this country was asphyxia (Shah, 2012).

Asphyxia is caused by fetal hypoxia in the uterus. Fetal hypoxia occurred due to disruption of oxygen exchange and transportation from mother to fetus so that the supply of oxygen to the fetus was reduced and carbon dioxide levels increased (Pitsawong and Panichkul, 2012; Listiani, 2018). Asphyxia was a serious threat to newborns that contributed to neonatal birth and death (Brucknerova et al., 2014).

According to a study conducted by Purwaningsih (2018), 24% of total neonatal deaths worldwide were caused by asphyxia. Study conducted by (Brucknerova et al., 2014), Asphyxia was the second highest causes of infant mortality after infection. In addition, it is estimated that about one million newborns die each year due to asphyxia

According to a study conducted by Ersdal (2012) in a Tanzanian hospital, 60% of the main causes of neonatal death were asphyxia. Based on a study conducted by Bazzano's (2019), 10 out of 13 deaths (76.92%) were premature neonatal deaths, 15.38% were late neonatal deaths, and one was still birth where 23% was caused by asphyxia. This study is in line with Halim (2016) that in Bangladesh, in 24 hours of birth, there were 6,748 neonatal deaths by 24.4 per 1,000 births, where 43% of deaths were caused by asphyxia.

The indicator for the diagnosis of asphyxia in newborns was the APGAR score assessment in the first minute of delivery (Mariati, 2015). APGAR score stands for Appearance, Pulse, Grimace, Activity, and Respiration (Ekwochi et al., 2017).

APGAR score is a simple method of assessing the health of a newborn during the first, fifth, and tenth minutes of life. APGAR scores at the fifth minute of life correlated best with the degree of asphyxia (Uchenna et al., 2017).

According to a study conducted by Seikku et al. (2016), low APGAR score at the

fifth and tenth minutes of birth reflected asphyxia which could predict neonatal mortality. Another study conducted by Sharma et al (2012) found that low APGAR score in neonates had a 2.23 times risk of having neonatal death compared to neonates with high APGAR score. The low APGAR score reflected the level of service availability and service standards that were not appropriate during delivery (Berglund et al., 2010).

The high rate of neonatal mortality caused by asphyxia which was supported by several studies encouraged the researchers to combine and analyze the results of existing studies and draw conclusions from studies that discuss the effect of asphyxia on neonatal death.

SUBJECTS AND METHOD

1. Study Design

This study was a systematic and meta-analysis study. The articles used in this study were obtained from several databases including PubMed, Science Direct, and Google Scholar. These articles were collected for 1 month. The keywords to search for articles were as follows: "neonatal" AND "asphyxia" OR "APGAR score" AND "mortality", "death neonatal asphyxia" OR "mortality asphyxia" AND "cross sectional".

2. Population and Sample

The articles were searched by considering the eligibility criteria defined using the PICO model. The population of the study was neonatal with intervention in the form of asphyxia, comparison, namely non-asphyxia, and outcomes in the form of death.

3. Inclusion Criteria

The articles included in this study were full paper articles with a cross-sectional study design. Selected articles were about asphyxia with neonatal mortality outcomes. The intervention given in the article was an APGAR score <7 in 5 minutes of life. The articles

were published in English. The analysis used multivariate with Adjusted Odds Ratio (AOR).

4. Exclusion Criteria

The articles published in this study were articles with random controlled trial design, case-control, quasi-experiment, protocol study, and pilot study. The articles were not published in English. The statistical results reported were not AOR. The AOR results obtained were overestimated and the 95% CI was too wide.

5. Operational Definition of Variables

Asphyxia was a lack of oxygen before, during, and after the delivery process. The instrument used was the APGAR score with a categorical measuring scale.

Death was the permanent loss of all signs of

life at any time after live birth. The instrument used was in the form of medical records with a categorical measuring scale.

6. Data Analysis

The data processing was carried out by the Review Manager (RevMan 5.3) by calculating the effect size and heterogeneity to determine the study model that was combined and formed the final meta-analysis result.

RESULTS

The articles were searched through a database with journals as seen in Figure 1. Figure 2 shows the areas where the articles were drawn according to the inclusion criteria. The articles were obtained from 2 continents, namely South America and Africa.

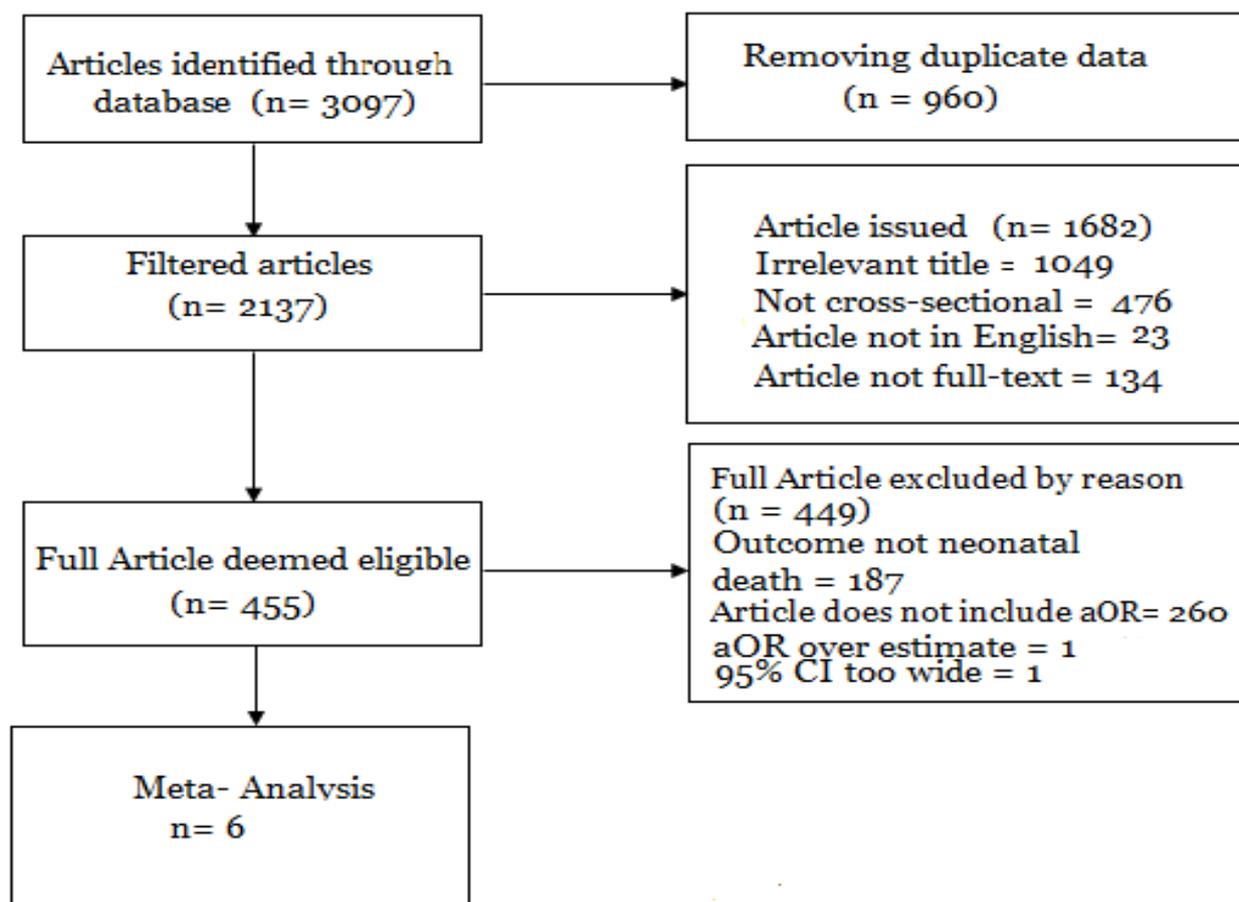


Figure 1. Flowchart of the Review Process



Figure 2. Map of the Study Area

a. Forest plot

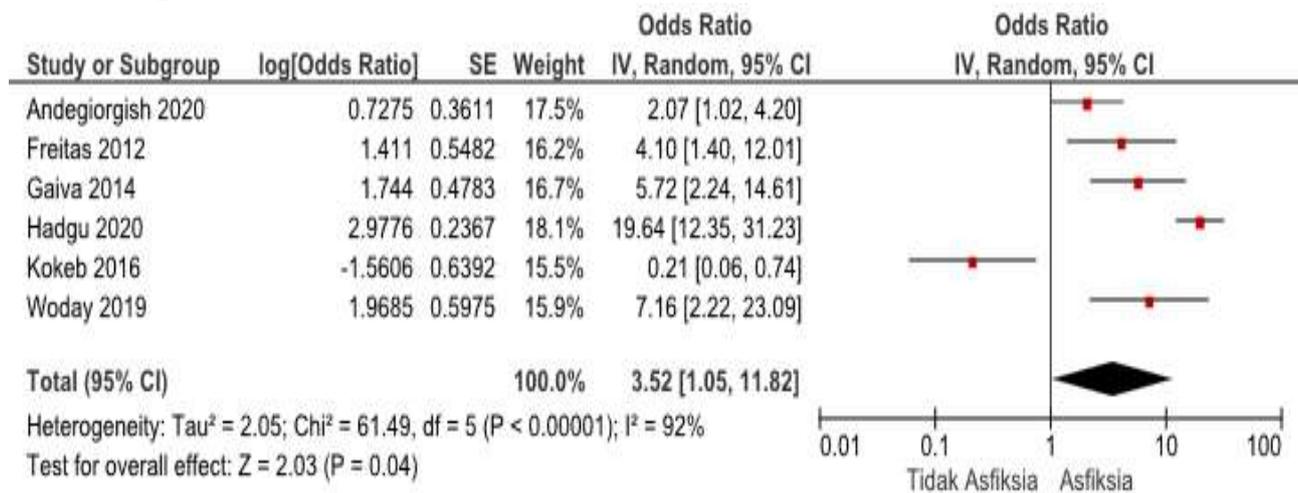


Figure 3. The forest plot of the effect of asphyxia on neonatal death

b. Funnel plot

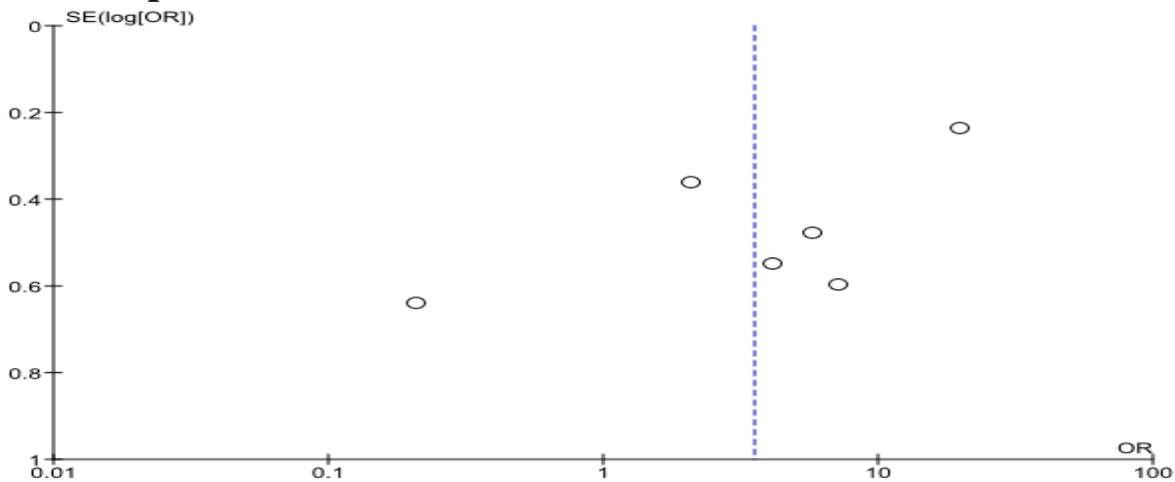


Figure 4. The funnel plot of the effect of asphyxia on neonatal death

c. Asphyxia on neonatal death

Six cross-sectional articles proved the association between asphyxia and neonatal death.

Table 1. The description of the primary study that was included in the meta-analysis

Author (year)	Country	Study Design	S	P	I	C	O
Woday <i>et al.</i> (2019)	Ethiopia	Cross sectional	403	Neonatal	Male, ANC follow-up, delivery place at home, premature pregnancy, temperature ≥ 36.5 , had asphyxia*, had RDS, hospitalized for ≥ 5 days	Female, did not do ANC follow-up, delivery place at the hospital, aterm pregnancy, no asphyxia, no RDS, hospitalized for < 5 days	Neonatal Mortality
Hadgu <i>et al.</i> (2020)	Ethiopia	Cross sectional	1,785	Neonatal	Parity > 2 , delivery place at a hospital, birth weight $< 1,500$ g, gestational age > 28 weeks, had asphyxia*, had RDS, had jaundice, had congenital abnormalities, had sepsis, length of stay > 7 days, abnormal temperature	Parity < 2 , delivery place at home, birth weight $> 1,500$ g, gestational age < 28 weeks, no asphyxia, no RDS, no jaundice, no congenital abnormalities, no sepsis, < 7 days of stay, normal temperature	Neonatal Mortality
Andegiorgish (2020)	Eritrea	Cross sectional	1,204	Neonatal	Low birth weight, gestational age < 37 weeks, APGAR score $< 7^*$, had congenital abnormalities, had pregnancy complications, multigravida, ANC follow-up	Normal birth weight, gestational age > 37 weeks, APGAR score > 7 , no congenital abnormalities, no pregnancy complications	Neonatal Mortality
Kokeb <i>et al.</i> (2016)	Ethiopia	Cross sectional	325	Neonatal	Low birth weight, prematurity, hypothermia, hypoglycemia, had asphyxia*, had neonatal sepsis, had meningitis, had seizures, had hyaline membrane disease, had meconium aspiration, had congenital abnormalities, had hemorrhagic, delivery place at home	Normal birth weight, no hypothermia, no hypoglycemia, no asphyxia, no neonatal sepsis, no meningitis, no seizures, no hyaline membrane disease, no meconium aspiration, no congenital abnormalities, no hemorrhagic, delivery place was not at home	Neonatal Mortality
Gaiva <i>et al.</i> (2014)	Brazil	Cross sectional	771	Neonatal	Prenatal visit < 7 , gestational age < 37 weeks, APGAR score $< 7^*$, congenital abnormalities	Prenatal visits ≥ 7 , gestational age > 37 weeks, APGAR score > 7 , no congenital abnormalities	Neonatal Mortality
Freitas <i>et al.</i> (2012)	Brazil	Cross sectional	502	Neonatal	Had sepsis, gestational age < 28 weeks, small gestational age, APGAR score $< 7^*$, had necrotizing enterocolitis (NEC)	No sepsis, gestational age > 28 weeks, aterm pregnancy, APGAR score > 7 , no necrotizing enterocolitis	Neonatal death

*variables included in the meta-analysis study

d. Forest plot

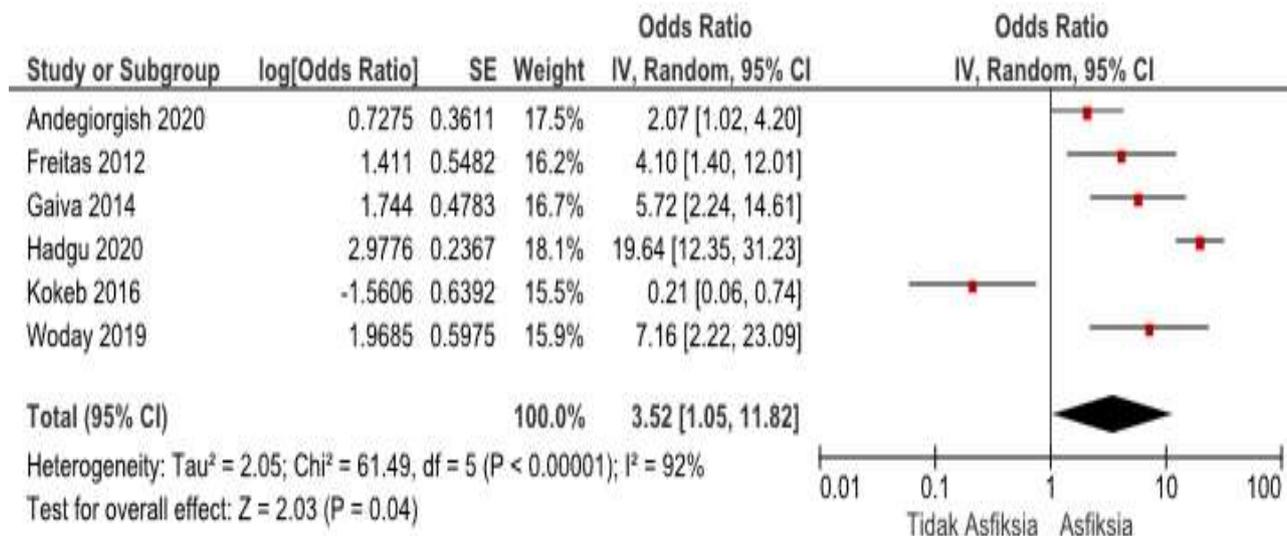


Figure 3. The forest plot of the effect of asphyxia on neonatal death

e. Funnel plot

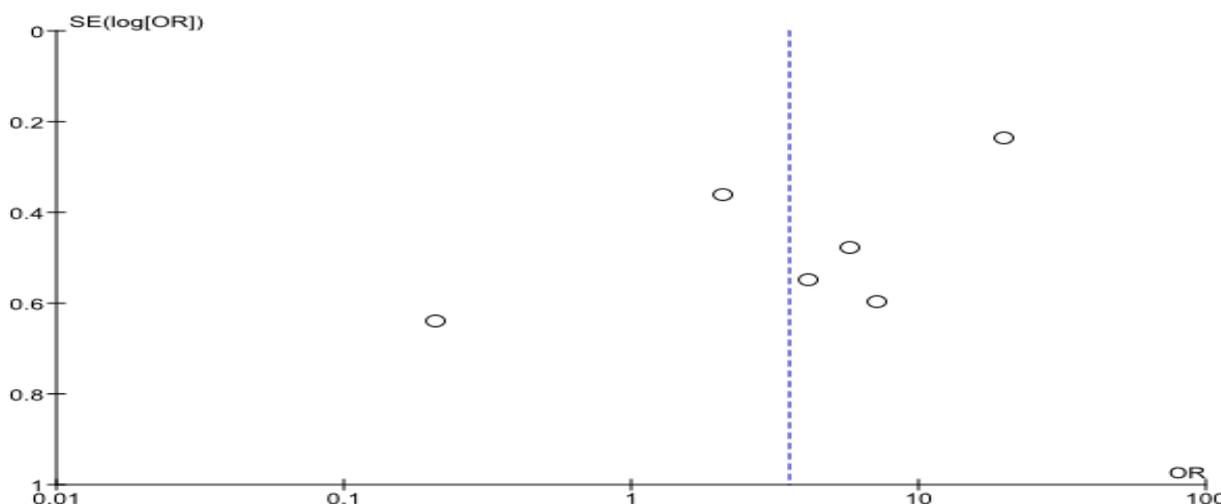


Figure 4. The funnel plot of the effect of asphyxia on neonatal death

Based on the results of the forest plot (Figure 3), asphyxia could increase neonatal death by 3.52 times compared to neonatal without asphyxia, and it was statistically significant ($p=0.040$). The heterogeneity of the study data showed $I^2=92\%$ so that the distribution of the data was stated as heterogeneous (random effect model). The funnel plot (Figure 4) shows a publication bias that was characterized by an asymmetry of the right and left plots where 4 plots were on the right

and 2 plots were on the left. The plots on the left of the graph had a standard error between 0.2 and 0.8 and the plot on the right had a standard error between 0.2 and 0.6. Bias also occurred from an imbalance between the distances among studies both right and left side of the funnel plot.

DISCUSSION

This systematic review and meta-analysis study raised the theme of the effect of asphy-

xia on neonatal death. The independent variables analyzed were asphyxia. A study that discussed data on neonatal mortality was considered important because of its scarcity. The number of the relevant studies published and accessible was still small and also had data access problems (data duplication) (Murti, 2018). Most of the statistical results reported were in the total percent or a crude odd ratio (cOR), where the study did not control the confounding factors.

Confounding factors affected the relationship or effect of exposure to the occurrence of disease estimated by the study was not the same as the relationship or effect that occurred in the target population, or invalid (Murti, 2018). This systematic and meta-analysis study used a study that controlled the confounding factors which could be seen from the study inclusion requirements, namely multivariate analysis. The statistical result reported was the adjusted odd ratio (aOR).

The estimation of the combined effect of asphyxia and neonatal death were processed using the RevMan 5.3 application with the generic inverse variance method. This method was used to analyze the data in the form of rate, time-to-event, hazard ratio, ordinal scale, adjusted estimate, difference of mean, or ratio of mean.

The results of the systematic and meta-analysis study were presented in the form of a forest plot and a funnel plot. The forest plot showed an overview of information from each of the studies examined in the meta-analysis and the estimation of the overall results (Murti, 2018). The forest plot showed the amount of variation (heterogeneity) of each study results visually (Akobeng in Murti, 2018).

Funnel plot was a diagram in a meta-analysis used to demonstrate possible publication bias. The funnel plot showed the relationship between the effect size of the study

and the sample size or standard error of the effect size of the various studies studied (Murti, 2018).

The funnel plot showed the amount of variation (heterogeneity) visually (Akobeng, 2005 in Murti, 2018). Funnel plot showed the relationship between the effect size of the study and the sample size of the various studies studied, which could be measured in many different ways (Murti, 2018).

Asphyxia on neonatal death

The results of the forest plot showed that the neonatal that had asphyxia was 3.52 times more likely to have neonatal death than those who did not have asphyxia.

According to a study conducted by Listiani et al. (2018), neonates with asphyxia had an increased risk of neonatal death caused by fetal hypoxia in the womb. Fetal hypoxia occurred due to impaired exchange and transport of oxygen from mother to fetus, so that the oxygen supply to the fetus decreased and the carbon dioxide levels increased. The asphyxia on neonatal could cause organ system dysfunction.

This study is in line with the study conducted by Adetola et al. (2011) that neonatal mortality caused by asphyxia occurred due to congenital malformation and the need for positive-pressure ventilation resuscitation to maintain neonatal oxygen. Severe asphyxia (APGAR score ≤ 3) had the highest risk of death in neonates. Most (82%) of the neonatal deaths occurred within 7 days of life, 56% of deaths within the first 24 hours of life, 26% between 2 and 7 days of life.

Another study conducted by Lee et al. (2008) stated that deaths that occurred due to birth with asphyxia were 9.7 per 1,000 live births. It was 30% of neonatal deaths. The risk factors such as antepartum, health facilities, fever in mother, swelling of the mother's face, hands, and feet were the significant factors for neonatal mortality caused by asphyxia. Premature infants (<37 weeks) had a

higher risk (RR=2.28; 95%CI=1.69 to 3.09; p= 0.050) and the combination of maternal fever and premature affected the association between the risk of death and the incidence of asphyxia (RR=7.12; 95% CI= 4.25 to 11.90; p= 0.050).

Ehrenstein (2009) stated that the indicator for the diagnosis of asphyxia in newborns was the APGAR score assessment. There was a consistent association between low APGAR score and an increased risk of infant and neonatal mortality and the incidence of neurological disabilities, including cerebral palsy, epilepsy, and cognitive impairment. An APGAR score <7 at five minutes increased the risk of neurological disability and neonatal death.

This is in line with a study conducted by Seikku et al. (2016) that low APGAR scores at 5 and 10 minutes reflected asphyxia and perinatal acidosis and predicted neonatal birth and mortality. Neonatal mortality that occurred due to asphyxia was associated with decreased umbilical arterial pH and increased acidosis.

A low APGAR score was a predictor that was more closely associated with neonatal mortality. An APGAR score <7 at 5 minutes of life was considered as the most accurate index for the neurological prognosis of health and neonatal death (Gaiva, 2014).

AUTHOR CONTRIBUTION

Silvalia was the main researcher who selected topics, explored, and collected the data. Hanung Prasetya and Bhisma Murti played a role in analyzing the data and reviewing the documents

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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