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TIME TO DEATH AND ITS PREDICTORS AMONG ASPHYXIATED NEONATES ADMITTED TO JIMMA UNIVERSITY MEDICAL CENTER, SOUTHWEST ETHIOPIA: A RETROSPECTIVE COHORT STUDY.

BY:

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A RESEARCH THESIS SUBMITTED TO DEPARTMENT OF EPIDEMIOLOGY, FACULTY OF PUBLIC HEALTH, JIMMA UNIVERSITY; IN PARTIAL FULFILMENT FOR THE REQUIREMENT FOR MASTERS OF PUBLIC HEALTH IN EPIDEMIOLOGY.

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ABSTRACT

Background*: Perinatal asphyxia is a failure to initiate and sustain breathing at birth. It is the second leading cause of neonatal mortality in sub-Saharan African countries and accounts for 31% of neonatal mortality in Ethiopia. There is limited scientific evidence in Ethiopia on time to death and its predictors among asphyxiated neonates, especially at a referral hospital; therefore, the objective of this study was to assess time to death and its predictors among asphyxiated neonates admitted to Jimma University Medical Center, southwest Ethiopia.*

Methods: *A retrospective cohort study was conducted on all eligible 373 asphyxiated neonates admitted to Jimma University Medical Center from April 12/2019 to May 5 /2022. Data were extracted from May 18 to June 3/2022, entered into Epidata 3.1, and analyzed by R 4.2 version. A Kaplan Meier plot with a Log-rank test was used to evaluate the median survival time difference. Bivariable Cox regression was used to select variables for the final model at a p-value<0.25. Multivariable Cox regression was used to identify independent predictors of mortality of neonates considering a 95% confidence interval of adjusted hazard ratio and a corresponding p-value≤0.05.*

Result*: During a total of 2888 person-days, 84 neonates (22.52 % (95CI:18.38, 27.10)) died, yielding an incidence rate of 29.09 (95%CI: 23.20, 36.01) per 1000 person-days. The median survival time was 20 days(95%CI: 18, 23)). Almost half* (47.62%) of the death was during the first 7 days. Survival probability at the first, second, and third follow-up dates were 96.5%, 94.4%, and 92.3% respectively. *Stage III Hypoxic ischemic encephalopathy (AHR: 3.46(95%CI: 1.55, 7.70)), acute kidney injury (AHR: 2.82 (95%CI: 1.28, 6.23)), and stress ulcers (AHR: 2.24 (95%CI: 1.26, 3.97)) were independent predictors of time to death.*

Conclusion and recommendation: *The incidence of neonatal mortality was higher than in a previous study done in Ethiopia. Stage III Hypoxic ischemic encephalopathy, Acute kidney injury, and Stress ulcers were independent predictors of time to death, therefore, early identification and close follow-up are suggested for neonates who have those conditions.*

Keywords: *Asphyxiated, Predictors, Ethiopia, Time to death*

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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ABBREVIATIONS AND ACRONYMS

AHR	Adjusted Hazard Ratio
AKI	Acute Kidney Injury
ANC	Antenatal Care
APGAR	Appearance, Pulse, Grimace, Activity, Respiration
APH	Antepartum Hemorrhage
BW	Birth Weight
CHR	Crude Hazard Ratio
CPAP	Continuous Positive Airway Pressure
CS	Cesarean Section
DM	Diabetes Mellitus
EDHS	Ethiopian Demographic And Health Survey
HIE	Hypoxic-Ischemic Encephalopathy
HMD	Hyaline Membrane Disease
IDA	Iron Deficiency Anaemia
KMC	Kangaroo-Mother-Care
MAS	Meconium Aspiration Syndrome
MDG	Millennium Development Goal
NGO	Non-Governmental Organization
NICU	Neonatal Intensive Care Unit
NMR	Neonatal Mortality Rate
PNA	Perinatal Asphyxia
PROM	Premature Rupture Of Membrane
RBS	Random Blood Sugar
RDS	Respiratory Distress Syndrome
SDG	Sustainable Development Goal
SW	Southwest
SVD	Spontaneous Vaginal Delivery
UNICEF	United Nation Children Emergency Fund
WHO	Word Health Organization

CHAPTER ONE: INTRODUCTION

1. 1. Background

Children are most vulnerable to death during the first 28 days of life(1). Perinatal asphyxia is defined as a failure to initiate and sustain breathing at birth(2,3); it is a condition characterized by impaired blood gas exchange before, during, or immediately after birth(4,5). The "Diving reflex" physiology allows redistribution of cardiac output to vital organs in response to this condition(4,6), however, if the condition persists, this compensatory mechanism fails(6).

This interruption of oxygen and glucose flow causes a brain dysfunction called hypoxic-ischemic encephalopathy(HIE), which occurs in two phases; primary and secondary energy failure(7). Primary energy failure occurs as a result of the initial reduction of cerebral blood flow(4,5,8,9). Next, latent phase reperfusion occurs within six hours of primary neuron injury, which is the window period for intervention(4,8). If an intervention fails, secondary energy failure occurs over the next 24 to 48 hours. Then, it will then deteriorate, eventually leading to end-organ damage(4,8,9). As result, neonates might have a convulsion, loss of consciousness, and feeding difficulty within 12-72 hours(4).

The cause of this condition is usually not known(7). However, preeclampsia, gestational diabetes, placental abruption, maternal hypotension, chronic hypertension, and neonates airway disorder are among common risk factors for perinatal asphyxia(5,10).

Although the Sustainable Development Goal aims to reduce the neonatal mortality rate to 12 per 1000 live births by 2030G.C(11), 2.4 million neonates(6700 each day) died in 2020. The four leading causes of global neonatal mortality are preterm birth complications, perinatal asphyxia, infection, and birth defects. About 43% of global neonatal mortality occurs in sub-Saharan African countries(12), which is 10 times higher compared to high-income countries(13).

In 2019G.C, Ethiopia's neonatal mortality rate was 33 per 1000 live births(14), placing Ethiopia fourth among the top ten countries in the world with the highest neonatal mortality(12). Ethiopia's health sector transformation plan II agenda has set a goal of lowering the neonatal mortality rate to 21 per 1000 live births by 2025G.C(15). However, the rate of neonatal mortality stayed high(14), with preterm birth complications, perinatal asphyxia, and infection accounting for greater than 80% of the cause(16,17).

1.2. Statement of the problem

Perinatal asphyxia accounts for 25% of global neonatal death(3), particularly in sub-Saharan African countries, it is the second leading cause of neonatal mortality(18,19). It occurs more commonly in developing countries due to limited access to maternal and neonatal care(20).

In East and Central Africa, the pooled prevalence of perinatal asphyxia was 15.9% in 2020G.C(21). Moreover, in Ethiopia, although the prevalence varies by location, the pooled prevalence of perinatal asphyxia was 24.06% in 2020(22). In addition, it was 32.9% in Jimma Zone in 2015G.C(23) and was about 18% at Jimma University Medical Center in 2017 G.C(24).

In lower and middle-income countries, a neurologic complication related to perinatal asphyxia accounts for 80% of developmental delay in under-five children(36). Perinatal asphyxia was found to be responsible for 31% and 47.5% of neonatal mortality in Ethiopia and the Jimma zone respectively(17,25). Furthermore, nearly half(48.1%) of neonatal admission at Jimma University Medical Center were due to perinatal asphyxia(26).

After 72hours of occurrence of asphyxia, abnormal sucking, swallowing, and tongue movement cause feeding difficulty(4), as a result, gastrointestinal dysfunction like vomiting, abdominal distension, and gastric hemorrhage will occur(27). Providing hypothermia within 6 hours of birth for 72 hours at a temperature of 33.5 degrees Celsius reduced death and neurologic disability associated with HIE(28).

In addition to neuron injury, asphyxia might cause kidney injury, respiratory failure, and paralytic ileus due to mesenteric hypo-perfusion(4). Therefore, acute kidney injury was found to be common among asphyxiated neonates(29–33), which was higher among males, stage III HIE, and neonates born by cesarean section(34). A single dose of prophylactic theophylline was found to be effective in preventing acute kidney injury in asphyxiated neonates(4,35).

Stage I HIE may recover within 24 hours of starting treatment, but stage II and III will be hospitalized for several days to weeks due to complications(8). An estimated 15 to 20% of neonates who develop perinatal asphyxia will die, and 25% will survive with permanent neurologic deficits(20).

Asphyxiated neonates experience a gross motor delay from 3 months to 2 years of age(37). Moreover, at 18-22 months of age, epilepsy, blindness, severe hearing impairment, and disabling cerebral palsy were found in 16%, 14%, 6%, and 30% of asphyxiated neonates, respectively(38–40). Furthermore, asphyxiated neonates were found to have lower academic performance at around 8-9 years of age(41).

When analyzing follow-up study outcomes at different times, time-to-event analysis is essential. The inclusion of time information is the primary advantage of the time-to-event analysis(42), the other importance is treating lost to follow-up data as censored, unlike other models which exclude it from analysis potentially resulting in the loss of partial information collected and introduction of bias in inference made(43,44).

A study done in southern Ethiopia on the survival status of neonates with perinatal asphyxia found that pregnancy-induced hypertension, Cord prolapse, iron deficiency anemia, and convulsion were independent predictors of neonatal mortality (45). On the other hand, a hazard of mortality of asphyxiated neonates was found to differ according to the stages of HIE as a study done in Nigeria showed(46). Acute kidney injury was also found to be common among asphyxiated neonates(29–32). However, some variables such as stages of HIE, acute kidney injury, hypoglycemia, neonatal sepsis, stress ulcers, and hyaline membrane disease were not studied by previous research done in Southern Ethiopia.

Generally, little study has been done on the survival status of asphyxiated neonates in Ethiopia to the level of knowledge of the researcher. Particularly, at the referral hospitals where these neonates are taken for further management after receiving treatment at a lower unit health facility; there was no published scientific research finding in freely accessible journals at the time this study was planned to be conducted. Therefore, this study aimed to assess time to death and its predictors among asphyxiated neonates admitted to Jimma University Medical center, by adding those variables not assessed by a previous study done in Ethiopia.

1.3. Significance of the study

The findings of the present study added to the existing body of knowledge on complications of perinatal asphyxia and asphyxiated neonates who have a higher hazard of death. Therefore, the finding will be used by health facilities and program planners to recognize the high-risk neonates for whom to improve care for their survival and reduce further comorbidity and mortality associated with perinatal asphyxia. They can use the finding to reduce this stated morbidity and mortality by focusing on the indicated factors associated with early neonatal death and the specified time during which the probability of neonatal mortality was found to be high.

Furthermore, non-governmental organizations working in the country targeting improving neonatal survival will and reducing neonatal mortality use the finding as input for preventing perinatal asphyxia complications and improving the survival of neonates. Furthermore, it will also use as an input for further research conduction in the areas related to neonatal mortality.

CHAPTER TWO: LITERATURE REVIEW

2.1. Incidence of death and Survival time of asphyxiated neonates

A study conducted in Nigeria found that 25.3% of asphyxiated neonates died(46). However, a study done in southern Ethiopia identified that 7.85% of neonates died during a follow-up period(45).

Moreover, a study done in Nigeria reported an incidence rate of 28 per 1000 person-days, with the cumulative survival probability on the first, second, and third days of admission being 85.8%, 78.4%, and 75.6% respectively(46). However, a study done in southern Ethiopia found that survival probability at the first, second, and third follow-up dates was 95.21%, 92.82%, and 92.02% respectively(45).

2.2. Predictors of time to death among asphyxiated neonates

2.2.1. Socio-demographic and admission baseline factors

A study conducted in Nigeria found that being a female was associated with an increased risk of mortality(47). However, a study done in India, Congo, and southern Ethiopia found that the sex of the neonates has no significant effect on the hazard of neonatal death(45,48,49).

Furthermore, a study done in the Democratic Republic of Congo found that the risk of neonatal mortality was high among neonates admitted after one day(49), however, a finding of a study done in Nigeria found that the age of neonates at admission has no significant association with the risk of mortality(47).

A study done in Nigeria also found that the survival probability of neonates was associated with gestational age(50), but a study done in Enugu state in the same country and southern Ethiopia revealed that the risk of neonatal mortality has no significant association with gestational age(45,47). In addition, a study done in southern Ethiopia revealed that the hazard of neonatal mortality has no significant association with birth weight(45).

2.2.2. Maternal medical problem-related factors

A study conducted in India and southern Ethiopia identified that maternal iron deficiency anemia increased the hazard of neonatal mortality. However, the previous study done in southern Ethiopia found that the hazard of mortality of asphyxiated neonates had no

statistically significant association with maternal Diabetes, hypertension, hypothyroidism, and HIV status(45,48).

2.2.3. Maternal obstetric and gynaecologic related factors

A study done in India found that the absence of antenatal care(ANC) increased the risk of neonatal mortality(51), Whereas, a study done in southern Ethiopia found that the number of ANC visits has no significant association with the hazard of neonatal mortality(45).

In addition, a study done in India found that premature rupture of membrane increased the risk of neonatal mortality(51). A finding of study done at the Tertiary care teaching hospital in the same country states risk of neonatal mortality has no significant association with preeclampsia and gestational diabetes(48).

Moreover, a study conducted in southern Ethiopia found that pregnancy-induced hypertension and cord prolapse were statistically associated with an increased hazard of death in neonates(45).On the other hand, the finding of a study done in India, Nigeria, and Katihar hospital in India identified that home delivery was associated with an increased risk of neonatal mortality(51–53).

In addition, studies done in Nigeria found that being born outside of the treatment Center was associated with an increased risk of neonatal mortality(47,54). Furthermore, a study done in India found that instrumental delivery increased the risk of neonatal mortality(52). Moreover, another study done in India found that being primipara increased the risk of mortality in asphyxiated neonates(51). However, the finding of a study conducted in South Ethiopia indicates that the number of parity has no association with neonatal mortality(45).

2.2.4. Neonatal clinical conditions and comorbid diseases

A study done in India, Nigeria, and Congo found that having stage III HIE increased the risk of mortality of neonates(46,48,49,52). Furthermore, a study conducted in India and southern Ethiopia found that having a neonatal convulsion increased risk of neonatal mortality(45,48). In addition, having hypothermia was found to increase the risk of neonatal mortality as identified by a study done in Bangladesh and India(51,55).

A finding of a study conducted in Turkey, Kenya, and Tanzania indicates that having acute kidney injury was associated with a higher risk of neonatal mortality(56–58). Moreover, a study done in Congo stated that having neonatal sepsis increased the risk of mortality(49).

Moreover, a study done in India found that hypoglycemia and birth injury was associated with an increased risk of neonatal mortality(51). A study done in Nigeria indicates respiratory distress syndrome increased the risk of mortality in asphyxiated neonates(53).

2.3. Conceptual framework

This is a conceptual framework for the time to death of a neonate admitted with perinatal asphyxia. The independent variables were classified into socio-demographic and baseline-related variables, maternal medical condition, maternal obstetric care and gynecologic condition, and neonatal clinical condition-related variables; which was adapted and modified after reading different literature (45–48,51,52,54–56,59).

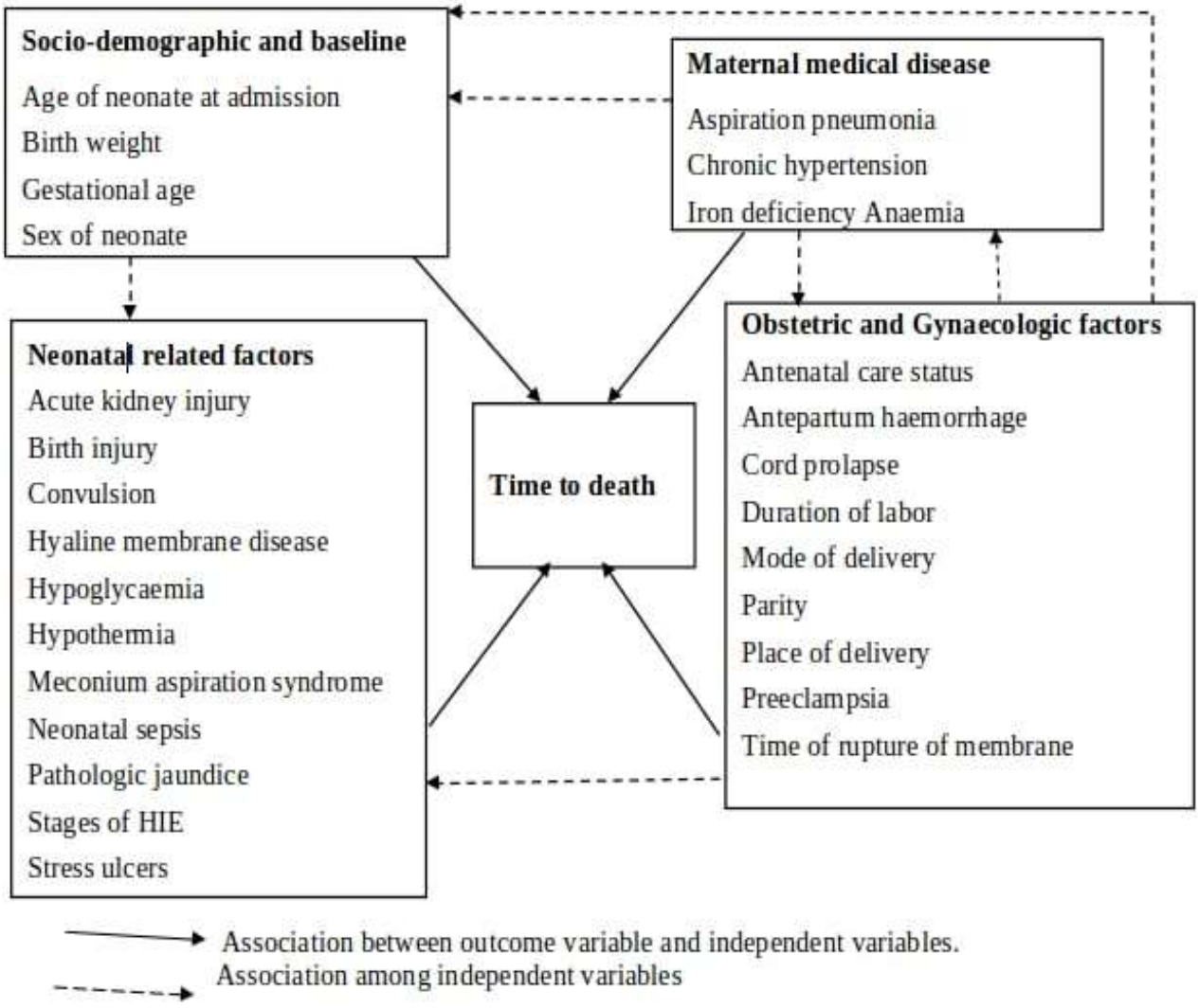

Figure 1: Conceptual framework of time to death of asphyxiated neonates admitted to Jimma University Medical Center, which was adapted from different literature and modified.

CHAPTER THREE: OBJECTIVE

3.1. General objective

To assess time to death and its predictors among asphyxiated neonates admitted to Jimma University Medical Center, Southwest Ethiopia from April 12/2019 to May 5 /2022

3.2. Specific objectives

- To determine the incidence of death among asphyxiated neonates admitted to Jimma University Medical Center
- To determine the time to death among asphyxiated neonates admitted to Jimma University Medical Center
- To identify predictors of time to death among asphyxiated neonates admitted to Jimma University Medical Center

CHAPTER FOUR: METHODS AND MATERIALS

4.1. Study area and period

The study was conducted at Jimma University Medical Center (JUMC) and data were extracted from May 18 to June 3/2022 G.C. Jimma University Medical Center is found in Jimma town in southwest Ethiopia about 352 kilometers from Addis Ababa. It is the only Tertiary and Referral hospital in southwest Ethiopia serving about 15 million people(66).

The neonatal intensive care (NICU) unit is situated adjacent to the labor ward of the hospital to suit the quick receiving of high-risk neonates from the ward. In addition to those born at this hospital, it gives service to neonates referred from different health public and private institutions found in southern Ethiopia. Currently, the NICU of the hospital is providing care for neonates using thirty-two staff(18 Bsc and 1Msc, 11 neonatal nurses, and 2 specialists), with available four CPAP machines, sixty warmers, one suction machine, four incubators, six phototherapies, and forty beds

4.2. Study design

An institution-based retrospective cohort study was conducted.

4.3. Population

4.3.1. Source population

All asphyxiated neonates who were admitted to Jimma University Medical Center from April 12/2019 to May 5 /2022 G.C.

4.3.2. Study population

All eligible asphyxiated neonates who were admitted to the Neonatal intensive care unit of Jimma University Medical Center from April 12/2019 to May 5 /2022 G.C.

4.3.2.1. Eligibility criteria

Inclusion criteria

Alive-born asphyxiated neonate admitted to neonatal intensive care Unit of Jimma University Medical Center from April 12/2019 to May 5 /2022 G.C whose medical record number was found in neonatal registry logbook of the hospital.

Exclusion criteria

Asphyxiated neonates whose record was lost from the record center of the hospital and had incomplete records were excluded from the study.

4.4. Sample size determination and sampling procedure

4.4.1. Sample size determination

The sample size for the study was estimated by STATA 15.0 version, taking into account a 95% confidence interval, a two-sided level of significance at 0.05, an 80% power, a 0.0785 probability of death of asphyxiated neonates, and an adjusted hazard ratio of 5.9 which was taken from a study done in southern Ethiopia(45). After adding 10% for incomplete records, the minimal sample size was 219 neonates, however, since it was manageable, all 373 eligible neonates found during the study period were included in the study.

Table 1: Sample size estimate for time to death and its predictors among asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, from April 12/2019 to May 5 /2022

S/N	Predictors	AHR	Death	Sample size	Reference
1	Neonatal convulsion	10.23	0.0785	116	(45)
2	Cord prolapse	6.5	0.0785	179	
3	Pregnancy-induced hypertension	25.4	0.0785	60	
4	Maternal iron deficiency anemia	5.9	0.0785	199	

4.4.2. Sampling procedure

All 373 eligible asphyxiated neonates admitted to the NICU of Jimma University Medical Center from April 12/2019 to May 5 /2022 G.C were included in the study.

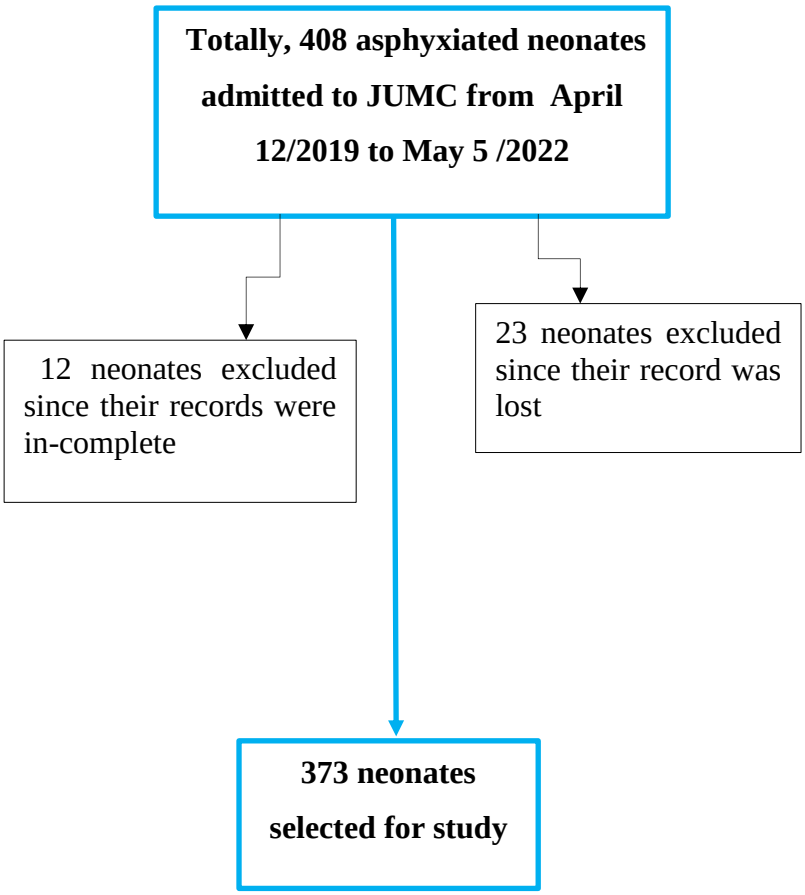

Figure 2: Case selection flow diagram to time to death and its predictors among asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

4.5. Data collection instrument and procedure

Data were collected using a data abstraction checklist adapted after reviewing different literature, previous related studies(45–48,51,52,54–56,59), and the standard Ethiopian neonatal registration logbook. It was prepared in the English language to facilitate the extraction of data on sociodemographic and baseline, maternal medical disease, maternal obstetric and gynaecologic conditions, and neonatal clinical conditions-related factors. Five BSc. nurses were recruited for data collection based on their prior experience, and the principal investigator supervised the data collection process.

4.6. Study variables

Dependent variable

- Time to death

Independent variables

Socio-demographic and baseline

Residence of the mother

Age of neonate in days, Birth weight, Gestational age, Sex of neonate, admission heart rate, admission respiratory rates, admission body temperature

Maternal medical disease

Aspiration pneumonia, Chronic hypertension, Iron deficiency Anaemia

Obstetric and Gynaecologic

Antenatal care status, Antepartum hemorrhage, cord prolapse, duration of labor, mode of delivery, Parity, Place of delivery, Preeclampsia, Time of rupture of membrane

Neonatal clinical condition

Acute kidney injury, Birth injury, convulsion, Hyaline membrane disease, Hypoglycaemia, Hypothermia, Meconium aspiration syndrome, Neonatal Sepsis, Pathologic jaundice, HIE stage, Stress ulcers.

4.7. Operational definition

Perinatal asphyxia: Was diagnosed if the neonate had a fifth-minute Apgar score<7, arterial cord PH<7, evidence of altered neurologic status, or multiorgan involvement(8).

Time-to-death: A time during which asphyxiated neonates developed an event of interest measured in days from the date of admission to the neonatal intensive care Unit of Jimma University Medical Center to the date of death

Death: It was an event of interest: neonates who suffered from perinatal asphyxia and died from any immediate cause secondary to asphyxia, for which a death summary was written.

Survival status: the outcome of asphyxiated neonates which was categorized as “death(coded 1)” or “censored(coded 0)” at discharge from the NICU of Jimma University Medical Center.

Censored: Asphyxiated neonates whose discharge status implies that they were either discharged to home, referred to other health institutions where the outcome was unknown, or left against medical advice by their family.

Follow-up period: time in days during which study participants were followed retrospectively for either to develop an event of interest or to be censored. The neonates were followed until 28 days of their age(date from birth to 28 days).

Neonatal comorbid disease*:* it was measured by a question that has dichotomy answers (yes or no), where "Yes" indicates neonate had specified comorbid disease and "No" indicates neonate has no indicated comorbid disease during the follow-up period(45).

Stress ulcers: Deep focal mucosal damage of gastroduodenal that occurs after major physiologic disturbance and associated gastrointestinal bleeding might occur from these sites(60,61).

Acute kidney injury: It is a rise of 3≥ milligrams per deciliter from baseline serum creatinine(4).

Hypoxic-ischemic encephalopathy (HIE) stage: Central nervous system dysfunction associated with perinatal asphyxia(8) which is categorized into three stages(stage I, III, and III HIE) according to the Sarnat scale and its modified criteria(4).

4.8. Data processing and analysis

Each checklist was checked, coded, and entered into Epidata 3.1 version, and exported to R 4.2 version for analysis. Missing values were replaced by the median value of a respective variable. Continuous variables were characterized by a median with an interquartile range, categorical variables were described by cross-tabulation of a category of survival status of neonates to the event and censored.

The incidence rate of neonatal mortality was estimated by dividing the total number of events that occurred during the study period by the total number of person-days at risk. The mean and median survival times were calculated using the Kaplan-Meier estimate, and the Kaplan Meier Survival and Cumulative Hazard Curves were drawn for overall strata and each category of predictors. The log-rank test was used to assess the median survival time difference between categories of covariates at the 0.05 level of significance.

Variable with p-value<0.25 in bivariable Cox regression were selected for multivariable cox regression. In multivariable Cox regression, variables whose 95% confidence interval of adjusted hazard ratio did not include one and respective P-value≤0.05 were taken as independent predictors of time to death. The effect measure modification of covariates was evaluated by including the interaction term of covariates in the final model, where a p-value>0.05 indicates an absence of effect measure modification(62).

Multicollinearity was tested by a variance inflation factor(VIF) where the value of variance inflation factor less than 10 was considered an acceptable level(Table 9 in annex I). Schoenfeld residual statistical test and graph were used to evaluate the proportional hazard assumption of each covariate included in the final model and for the overall Global test; the assumption was assumed to be satisfied if the corresponding p-value for the statistical test was >0.05 and independence between the Schoenfeld residual and transformed time(43,63)(Table 10 and Figure 9 in Annex I).

Moreover, influential points were checked by deviance residuals, where the roughly symmetric distribution of Deviance residual around the fitted line is indicative of the absence of influential observation poorly described by the model (Figure 10 in Annex I). Furthermore, the overall Goodness of fit test was assessed by regressing the CoxSnell residual against the Cumulative hazard, where the exponential distribution of the cumulative hazard at 45degree of the fitted line in the Coxsnell residual plot is indicative of well fit of the data by the model (43,63)(Figure 11 in Annex I). Finally, the finding of the study was presented using tables, graphs, and statements.

4.9. Data quality management

The adapted checklist was approved by advisors and two days of training were given to the data collectors on the objective of the study, and the study population's eligibility criteria before data collection. In addition, a pre-test was done on 19 neonates who were treated before April 12/2019G.C at JUMC(neonates who were treated before the beginning of the study period). Further modifications were made to the sequencing of questions and the content of the checklist. The principal investigator stored the collected data after checking its completeness and consistency to minimize the chance of loss of data. In addition, the pre-test data were not included in the final analysis.

4.10. Ethical consideration

An ethical clearance letter with reference number IHRPGD/606/22 was taken from the Ethical Review Board of the Institute of Health of Jimma University. A permission letter to proceed with the study was taken from the Chief clinical director of Jimma University Medical Center and the NICU head nurse. To ensure confidentiality, the name of the neonates, mothers, physicians, and other health care professionals who examined the patient was not recorded in the data abstraction checklist, and the collected data were kept confidential.

4.11. Dissemination plan

The result of the study was presented and submitted to the department of Epidemiology Faculty of the Public Health of Jimma University. The pertinent finding will be informed to Jimma University Medical Center, Jimma zone health office, and local NGOs. In addition, it will be published in an international journal.

CHAPTER FIVE: RESULTS

5.1. Socio-demographic characteristics and admission baseline

In the present study, 219 (58.71%) of study participants were males, and 322(86.33%) of them were born at 37-40 weeks, with a median gestational age of 37 and an interquartile range of 2 weeks. At birth, 289 (77.48%) weigh 2500 to 3999 grams and the median birth weight was 2930 grams with an interquartile range of 720. Furthermore, 4(57%) and 60(21%) neonates with birth weight <1500 and 2500-3999g respectively, have died. On the other hand, 5(62%) and 70(22%) neonates with admission pulse rates <100 and 100-160 pulse per minute respectively died(Table 2 below).

Table 2: Socio-demographic and baseline of asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Variables	Categories	Died(84)	Censored(289)	Total (373)
		Frequency (%)	Frequency (%)	Frequency (%)
Sex of neonate				
	Male	50(13.40)	169(45.31)	219(58.71)
	Female	34(9.12)	120(32.17)	154(41.29)
Residence of mother				
	Jimma district	21(5.63)	73(19.57)	94 (25.20)
	Other districts	58(15.55)	190(50.94)	248(66.49)
	SNNPR	4(1.07)	21(5.63)	25 (6.70)
	Gambella	1(0.27)	5(1.34)	6 (1.61)
Gestational age in weeks				
	<37	14(3.75)	27(7.24)	41(10.99)
	37 to 40	69(18.50)	253(67.83)	322(86.33)
	Above 40 weeks	1(0.27)	9(2.41)	10(2.68)
Birth weight in gram				
	<1500	4(1.07)	3(0.80)	7(1.88)
	1500 to 2499	20(5.36)	57(15.28)	77(20.64)
	2500 to 3999	60(16.09)	229(61.39)	289(77.48)
Age of neonate at admission in days				
	≤1 day	53(14.21)	166(44.50)	219(58.71)
	2 to 4 days	24(6.43)	77(20.64)	101(27.08)
	≥5 days	7(1.88)	46(12.33)	53(14.21)
Admission body temperature in degrees Celsius				
	≤35.5	32(8.58)	85(22.79)	117(31.37)
	35.6 to 37.4	48(12.87)	168(45.04)	216(57.91)
	≥37.5	4(1.07)	36(9.65)	40(10.72)

Admission Pulse rate in beats per minute			
<100	5(1.34)	3(0.80)	8(2.14)
100 to 160	70(18.77)	249(66.76)	319(85.52)
>160	9(2.41)	37(9.92)	46(12.33)
Admission respiratory rate in breaths per minute			
< 30	3(0.80)	18(4.83)	21(5.63)
30 to 60	42(11.26)	150(40.21)	192(51.47)
>60	39(10.46)	121(32.44)	160(42.90)

Other districts: Districts in Jimma Zone and surrounding Oromia region
SNNPR: Southern Nations, Nationalities, and people's region

5.2. Maternal medical diseases

Aspiration pneumonia and other diseases including iron deficiency anemia, chronic hypertension, epilepsy, asthma, HIV/AIDS, and acute febrile illnesses were found to be present in 16 (4.29%) and 12 (3.22%) of the mothers, respectively.

Table 3: Medical disease of mothers of asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Variables	**Categories**	**Died (84)**	**Censored(289)**	**Total (373)**
		Frequency (%)	Frequency (%)	Frequency (%)
Aspiration pneumonia				
	Yes	3(0.80)	13(3.49)	16(4.29)
	No	81(21.72)	276(73.99)	357(95.71)
Other medical diseases				
	Yes	3(0.80)	9(2.41)	12(3.22)
	No	81(21.72)	280(75.07)	361(96.78)

5.3. Obstetric and Gynaecologic conditions

It was identified that 193(51.74%) of mothers of study participants had one to three times antenatal care visits, and 254(65.68%) of a place of delivery was at other health facilities. In addition, 7(21%) of neonates whose mothers had no ANC visit and 28(19%) of those whose mothers had ANC visits of four and above times had died. Moreover, 20(22%) of those born by cesarean section and 8(24%) of neonates born by instrumental delivery had died(Table 4 on the next page).

Table 4: Obstetric and Gynaecologic conditions of mothers of asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Variables Categories	Died (84)	Censored(289)	Total (373)
	Frequency (%)	Frequency (%)	Frequency (%)
Number of antenatal care visits			
No ANC visit	7(1.88)	27(7.24)	34(9.12)
1 to 3 visits	49(13.14)	144(38.61)	193(51.74)
≥4 visits	28(7.51)	118(31.64)	146(39.14)
Place of delivery			
Inborn	32(8.58)	96(25.74)	128(34.32)
Referred	52(13.94)	193(51.74)	245(65.68)
Parity			
Primipara	45(12.06)	159(42.63)	204(54.69)
Multipara	30(8.04)	94(25.20)	124(33.24)
Grand multipara	9(2.42)	36(9.65)	45(12.07)
Preeclampsia			
Yes	4(1.07)	16(4.29)	20(5.36)
No	80(21.45)	273(73.19)	353(94.64)
Antepartum hemorrhage			
Yes	12(3.22)	11(2.95)	23(6.17)
No	72(19.30)	278(74.53)	350(93.83)
Time of rupture of membrane			
<12 hours	75(20.11)	241(64.61)	316(84.72)
≥ 12 hours	9(2.41)	48(12.87)	57(15.28)
Duration of labor in hours			
<4	17(4.56)	52(13.94)	69(18.50)
4-12	39(10.46)	111(29.76)	150(40.21)
>12	28(7.51)	126(33.78)	28(7.51)
Mode of delivery			
CS	20(5.36)	72(19.30)	92(24.66)
SVD	56(15.01)	191(51.21)	247(66.22)
Instrumental	8(2.14)	26(6.97)	34(9.12)

5.4. Clinical condition of the neonates

This study found that 186(49.87%) neonates had early-onset neonatal sepsis, and 116(31.10%) had meconium aspiration syndrome (MAS). In addition, 34(9.12%), 49(13.14%), and 17(4.56%) suffered stress ulcers, stage III HIE, and acute kidney injury respectively. In addition, 9(52%) of those who had and 75(21.07%) of those who do not

have acute kidney injury died, and 10(22%) of stage I and 20(41%) of stage III HIE have died(Table 5 below).

Table 5:Clinical conditions of asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Variables	Categories	Died (84)	Censored(289)	Total (373)
		Frequency (%)	Frequency (%)	Frequency (%)
Hypoglycemia				
	Yes	8(2.14)	7(1.88)	15(4.02)
	No	76(20.38)	282(75.60)	358(95.98)
Hypothermia				
	Yes	32(8.58)	85(22.79)	117(31.37)
	No	52(13.94)	204(54.69)	256(68.63)
Earl onset neonatal sepsis				
	Yes	38(10.19)	148(39.68)	186(49.87)
	No	46(12.33)	141(37.80)	187(50.13)
Meconium aspiration syndrome				
	Yes	30(8.04)	86(23.06)	116(31.10)
	No	54(14.48)	203(54.42)	257(68.90)
Jaundice				
	Yes	7(1.88)	29(7.77)	36(9.65)
	No	77(20.64)	260(69.71)	337(90.35)
Stress ulcers				
	Yes	17(4.56)	17(4.56)	34(9.12)
	No	67(17.96)	272(72.92)	344(92.23)
Hyaline membrane disease				
	Yes	7(1.88)	7(1.88)	14(3.75)
	No	77(20.64)	282(75.60)	359(96.25)
Acute kidney injury				
	Yes	9(2.41)	8(2.14)	17(4.56)
	No	75(20.11)	281(75.34)	356(95.44)
Birth injury				
	Yes	16(4.29)	56(15.01)	72(19.30)
	No	68(18.23)	233(62.47)	301(80.70)
Stage of hypoxic ischemic encephalopathy				
	Stage I	10(2.68)	35(9.38)	45(12.06)
	Stage II	54(14.48)	225(60.32)	279(74.80)
	Stage III	20(5.36)	29(7.77)	49(13.14)
Neonatal convulsion				
	Yes	13(3.49)	41(10.99)	54(14.48)
	No	71(19.03)	248(66.49)	319(85.52)
Other neonatal health problems				
	Yes	11(2.95)	6(1.61)	17(4.56)
	No	73(19.57)	283 (75.87)	356(95.44)

5.5. Treatments provided for neonates

This study found that about 84.99% and 81% were resuscitated and received antimicrobial therapy respectively. In addition, 5% received other treatments, such as cimetidine, kangaroo mother care, and blood transfusions (Figure 3 below).

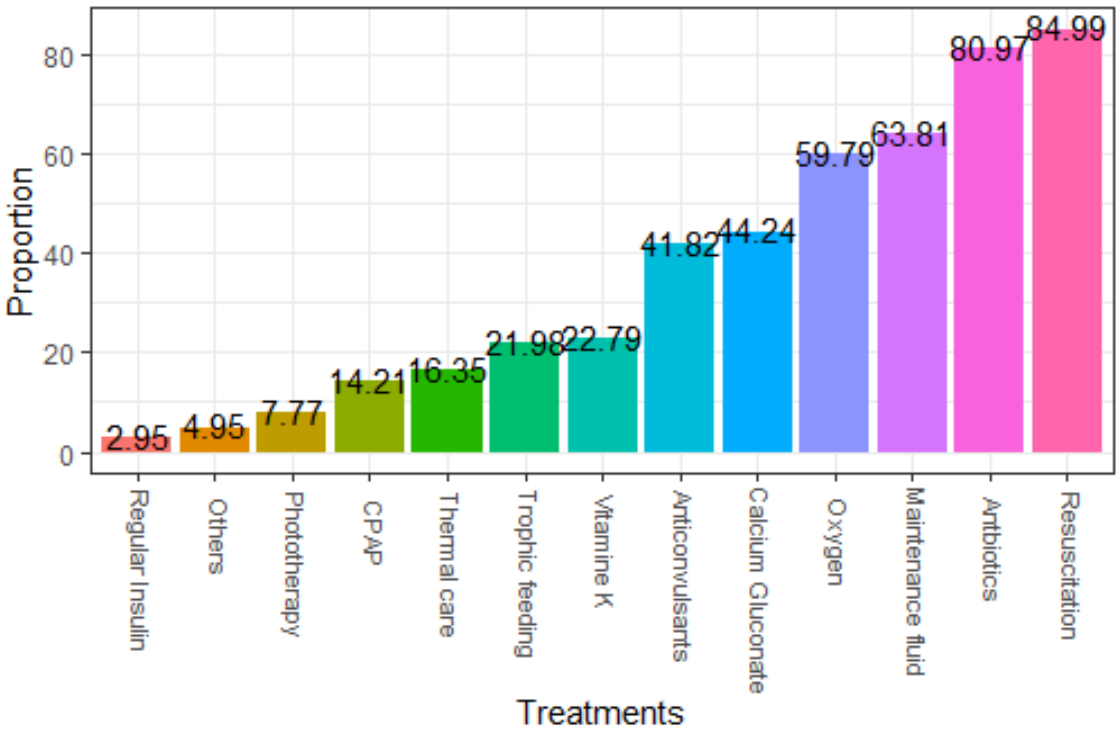

Figure 3: Treatments provided for asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

5.6. Survival status of the neonates

In the present study, 84 neonates (22.52 %(95CI:18.38, 27.10)) died, while the remaining 289(77.48%) were censored. The total person at risk was 2888 days, as result, the incidence rate of neonatal mortality was 29.09(95% CI: 23.20, 36.01) per 1000 person days.

5.6.1. Kaplan Meier survival and hazard function

In this study, the minimum and maximum survival times were 1 and 24 days respectively, and 40(47.62%) of the death of neonates occurred during the first 7 days. The survival probability was 96.5%, 94.4%, and 92.3% at the first, second, and third follow-up dates, respectively, and 9.90% at the twenty-fourth follow-up date. Furthermore, the neonates' median survival time was 20 days (95%CI: 18, 23) (Table 6 and Figure 4 on the next page).

Table 6: Life table of asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5/2022

Time	Number at risk	Number of death	Survival	Standard error	95% CI
1	373	13	0.9651	0.0095	0.9467 , 0.984
4	249	19	0.9007	0.0169	0.8683, 0.934
8	170	15	0.8301	0.0235	0.7853, 0.877
12	97	13	0.7421	0.0314	0.6830, 0.806
16	51	6	0.6712	0.0398	0.5975, 0.754
20	21	12	0.4381	0.0618	0.3324, 0.578
24	3	6	0.0993	0.0847	0.0187, 0.528

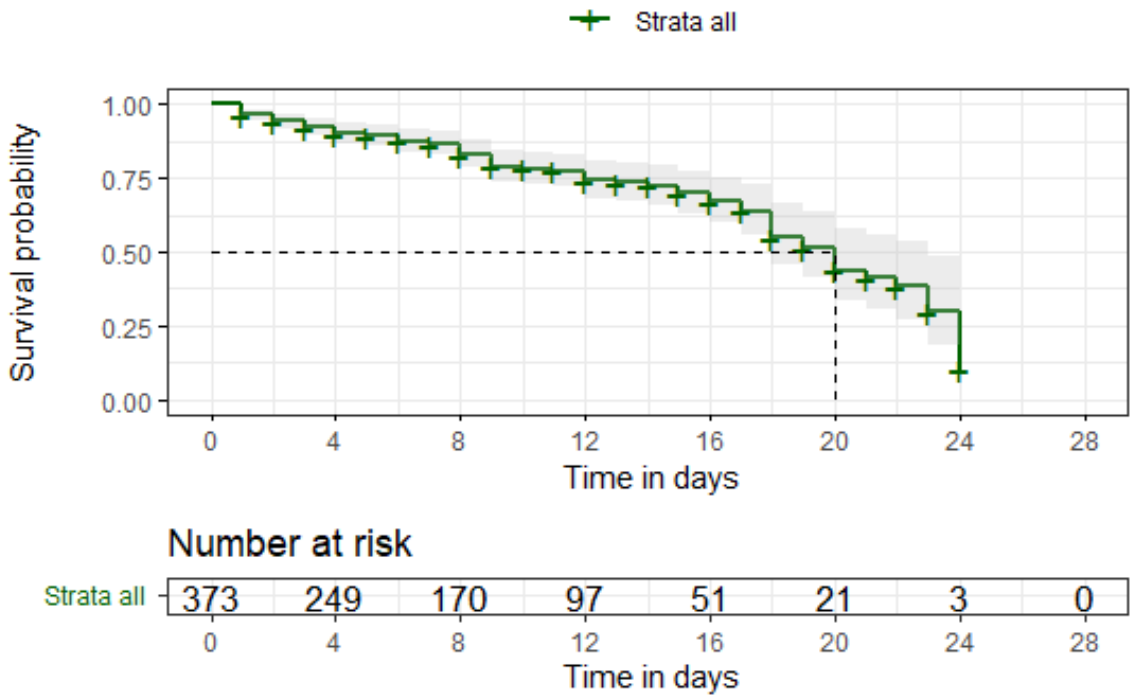

Figure 4: Kaplan Meier survival plot of asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

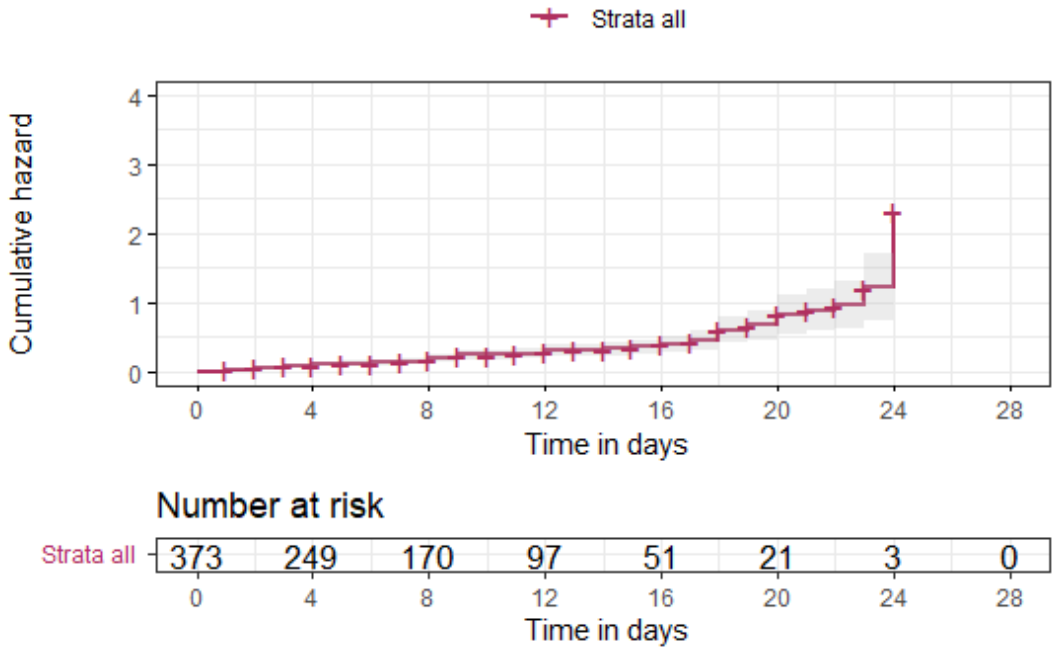

Figure 5: Kaplan Meier cumulative hazard plot of asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Furthermore, the median survival time of neonates in stages I, II, and III HIE was 24, 20, and 14 days, respectively, with a Log-rank test indicating a statistically significant survival time difference among HIE stages.

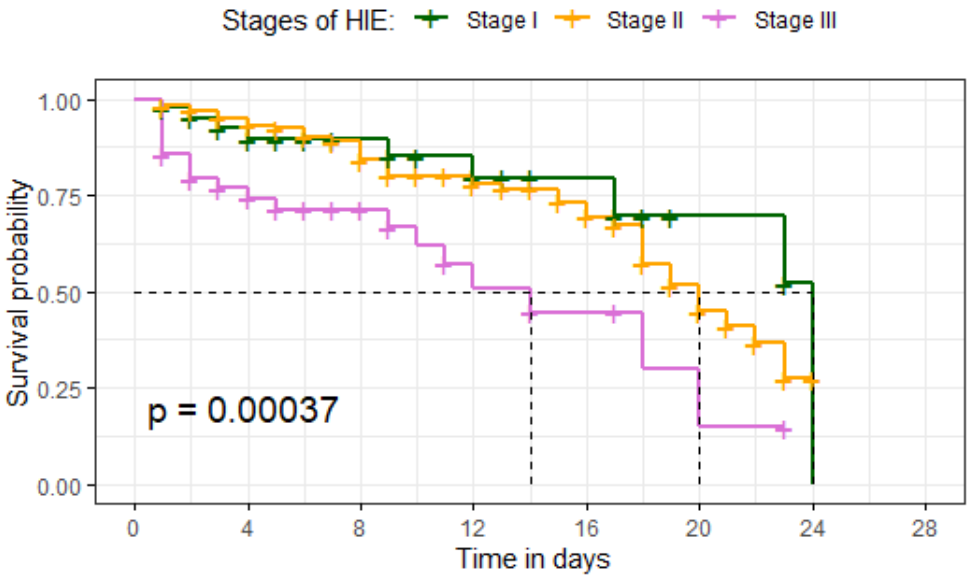

Figure 6: Kaplan-Meier survival plot for stages of HIE among asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

In addition, the median survival times for neonates with acute kidney injury and those who did not were about 8 and 20 days, respectively, with a log-rank P-value<0.05 indicating a significant difference in survival time.

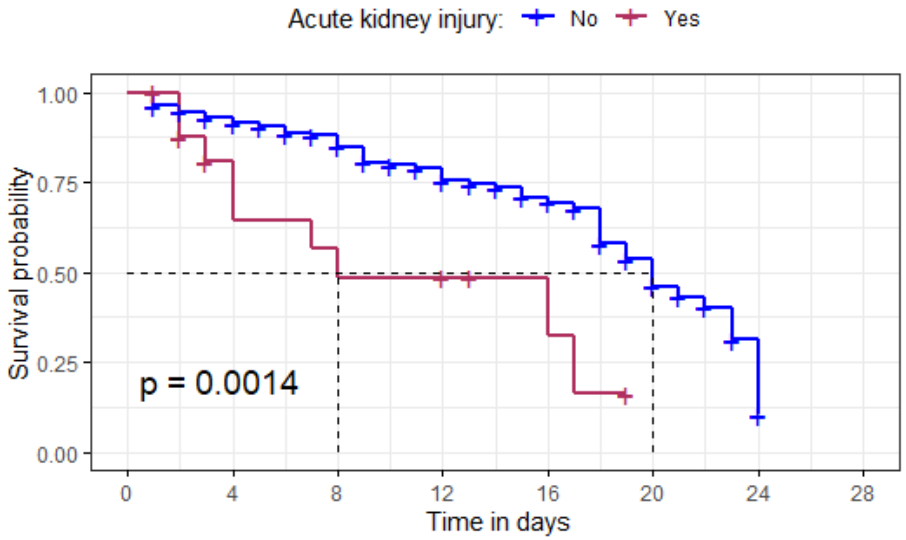

Figure 7: Kaplan-Meier survival plot of acute kidney injury among asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Furthermore, there was a statistically significant difference in the median survival times for neonates with and without stress ulcers, which were 12 and 20 days, respectively, with a log-rank test p-value ≤ 0.05.

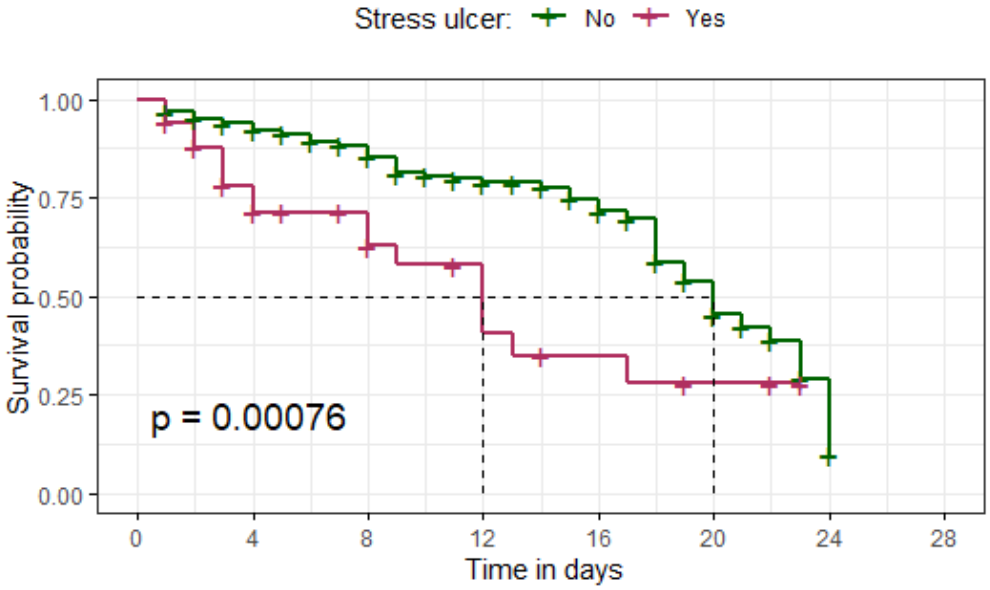

Figure 8: Kaplan-Meier survival plot of stress ulcers for asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

5.6.2. Log-rank test

According to a category of antepartum hemorrhage, hyaline membrane disease, stress ulcers, acute kidney injury, and stages of HIE, a log-rank test indicated a statistically significant median survival time difference among asphyxiated neonates(Table 7 below).

Table 7: Log-rank test of median survival time difference among asphyxiated neonates admitted to Jimma University Medical center, SW Ethiopia, April 12/2019 to May 5 /2022

Variables	Category	Median survival time	X^2	P-value
Sex of neonate	Male	20	0	0.9
	Female	22		
Gestational age	<37 week	16	4.5	0.1
	37-40 week	20		
	>40 week	Not available (NA)		
Birth weight	<1500g	15	2	0.4
	1500-2499g	18		
	2500-3999g	20		
Age of neonates	<1 day	20	4.2	0.1
	2-4 days	18		
	≥5 days	24		
Aspiration pneumonia	Yes	Not available (NA)	0.5	0.5
	No	20		
Number of ANC visit	No visit	Not available (NA)	2.8	0.3
	1-3 visits	19		
	≥4 visits	21		
Preeclampsia	Yes	20	1.8	0.2
	No	20		
Antepartum hemorrhage	Yes	9	7.1	**0.008**
	No	18		
Time of rupture of membrane	<12 hour	19	1.1	0.3
	≥12 hours	24		
Mode of delivery	C/S	20	0.3	0.9
	Instrumental	19		
	SVD	24		
Place of delivery	Inborn	19	1.1	0.3
	Out born	20		
Duration of labor	<4 hour	23	1.3	0.5
	4-12 hour	19		
	>12 hour	20		

Parity	Primipara	21	0.4	0.8
	Multipara	18		
	Grand multipara	16		
Meconium aspiration syndrome	Yes	19	0.7	0.4
	No	20		
Neonatal sepsis	Yes	18	0.3	0.6
	No	21		
Birth injury	Yes	18	1.1	0.3
	No	18		
Acute kidney injury	Yes	8	10.2	**0.001**
	No	20		
Pathologic jaundice	Yes	17	0.1	0.7
	No	20		
Stress ulcers	Yes	8	11.3	**<0.001**
	No	20		
Convulsion	Yes	18	0	0.9
	No	20		
Hyaline membrane disease	Yes	16	6.6	**0.01**
	No	20		
Hypoglycemia	Yes	20	2.5	0.1
	No	20		
Hypothermia	Yes	23	0.4	0.5
	No	19		
HIE stage	Stage I	24	15.8	<**0.001**
	Stage II	20		
	Stage III	14		

5.6.3. Predictors of time to death among asphyxiated neonates

At a p-value <0.25 in bivariable Cox regression, eight variables were selected for the final model: Birth Weight, Gestational Age, Acute Kidney Injury, Hypoglycemia, Stress Ulcers, Hyaline Membrane Disease, Antepartum Hemorrhage, and Stages Of HIE. However, in multivariable Cox regression by considering 95%CI of the adjusted hazard ratio, and a corresponding P-value of ≤0.05, the three independent predictors of time to death were stage III HIE (AHR: 3.46 (95%CI: 1.55,7.70)), acute kidney injury (AHR: 2.82(95%CI: 1.28, 6.23)), and stress ulcers (AHR: 2.24(95%CI: 1.26, 3.97))(Table 8 on the next page).

Table 8: Bivariable and multivariable Cox regression of asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Variable	Categories	CHR(95% CI)	P-value	AHR(95% CI)	P-Value
Birth weight in grams					
	<1500	1.66(0.60,4.61)	0.329	1.03(0.23, 4.64)	.968
	1500-2499	1.36(0.81,2.26)	0.244	1.22(0.66 , 2.25)	.524
	2500-3999	1(Reference)			
Gestational age in weeks					
	<37	1.66(0.93, 2.96)	0.084	0.90(0.29, 2.81)	.859
	37-40	1(Reference)			
	>40	0.33(0.05,2.41)	0.277	0.43(0.06 ,3.12)	.403
Acute kidney injury					
	Yes	2.95(1.47,5.93)	0.002	**2.82(1.28,6.23)**	**0.010**
	No	1(Reference)			
Hypoglycemia					
	Yes	1.78(0.85,3.72)	0.12	1.71(0.79, 3.71)	.173
	No	1(Reference)			
Stress ulcers					
	Yes	2.42(1.42,4.13)	0.001	**2.24(1.26, 3.97)**	**.006**
	No	1(Reference)			
Hyaline membrane disease					
	Yes	2.70(1.24,5.89)	0.012	2.70(0.71, 10.25)	.144
	No	1(Reference)			
Antepartum hemorrhage					
	Yes	2.26(1.22,4.17)	0.009	1.71(0.80,3.64)	.163
	No	1(Reference)			
Stages of hypoxic-ischemic encephalopathy					
	Stage I	1(Reference)			
	Stage II	1.20(0.60,2.41)	0.604	1.17(0.57, 2.38)	.674
	Stage III	3.12(1.43,6.81)	0.004	**3.46 (1.55, 7.70)**	**.002**

CHAPTER SIX: DISCUSSION

This retrospective cohort study aimed to assess time to death, and its predictors among asphyxiated neonates admitted to Jimma University Medical Center from April 12/2019 to May 5/2022 G.C, with data extracted from May 18 to June 3/2022. We identified, an incidence rate of 29.09 per 1000 neonatal days. The median survival time was 20 days, and the three predictors of time to death of the neonates were stage III HIE, acute kidney injury, and stress ulcers.

The present study showed 22.52% of neonatal death, which is comparable to the proportion reported in Nigeria(46). However, it is higher than the proportion in southern Ethiopia(45), which might be due to the differences in clinical conditions of the study participants; the current study was conducted at a referral hospital, where neonates need critical care referred from various public and private health institutions are treated, decreasing the likelihood that they will survive, whereas, a study in southern Ethiopia was at general and district hospitals.

The survival probability on the first, second, and third follow-up dates were 96.5%, 94.4%, and 92.3%, respectively, which is almost identical to the probability reported in southern Ethiopia(45). However, it is longer than the probability reported in Nigeria(46), which might be due to a difference in the proportion of stage III HIE, which was 13.14% in the current study and 24% in the study in Nigeria, which might be reduced the survival time.

Furthermore, the incidence rate of neonatal mortality in the current study was 29.09 per 1000 person-days, which is almost similar to the incidence reported in Nigeria(46).

At a given instant in time, neonates in stage III HIE were 3.46 as likely to die as those in stage I adjusting for other factors; this finding is supported by studies done in India(AOR=1.60(1.04-2.46)), Nigeria(AHR=4.3 (1.8–10.4)) and Congo(46,48,49). The probability that stage III HIE increases the hazard of mortality might be because of being usually lethargic, having an absent sucking reflex, and having persistent feeding difficulty. Furthermore, irregularities in heart rate and blood pressure are common during perfusion injury, the primary cause of death is mainly cardiorespiratory failure(6). This implies that they need close follow-up as compared to other neonates.

At a given instant of time during the follow-up period, neonates who had Acute kidney injury were 2.82 times more likely to die compared to those who do not have it, adjusting for other covariates. This finding is consistent with a study conducted in Kenya(where acute

kidney injury increased the risk of mortality 24 folds) and Tanzania(56,57). The death rate of neonates with acute kidney injury might be increased by hypotension, the need for mechanical ventilation, hemodynamic instability, and multi-organ failure(4). Although the current recommendations and evidence suggest a single dose of prophylactic theophylline to reduce the risk of acute kidney injury in asphyxiated neonates(4,35), the drug was not given in the study area. This could be due to the absence of the medication or lack of utilization. This might imply the requirement for further research on the quality of neonatal care.

Neonates with a history of stress ulcers died at a hazard of 2.24 times at all follow-up periods as compared to those who did not have. To the level of knowledge of the researcher, no previous study was found to support this finding. However, perinatal asphyxia and prolonged labor were found to be risk factors for stress ulcers in neonates(60). In general, neonates might die from anemia and shock secondary to bleeding caused by stress ulcers. This finding might indicate a lack of early diagnosis or prevention of stress ulcers, which might necessitate further quality of care research.

Strengths and limitations of the study

Strengths of the study

- Although the estimated sample size was 219, this study included all eligible 373 asphyxiated neonates available at the neonatal intensive care unit of Jimma University Medical Center during the study period. However, this does not imply that always taking the entire population yields more accurate estimates than sampling; thus, we took all eligible populations because it was manageable.
- Because potential predictors were measured before the outcome occurs, the study showed that predictors preceded the outcome; this sequence of time strengthens the inference that predictors might be a cause of the outcome(death of neonates).

Limitations of the study

- Due to the nature of the study design, some covariates such as educational status, occupational status, nutritional status of mothers, and birth interval were missed. However, it might not be a possible alternative explanation of the finding of the present study because a previous study that included it found no significant effect on neonatal mortality(45).
- Lost and incomplete records were excluded and might have caused the study finding to be under or over-estimated. This is to imply that there were 23 records lost from the hospital's record center and 12 incomplete records.

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATION

7.1. Conclusion

The incidence of neonatal mortality rate was higher in the study area when compared to the previous study conducted in Ethiopia. However, the cumulative survival probabilities at the first, second, and third follow-up dates were almost similar to the previous study.

Almost half of the death of neonates have occurred during the first 7 days of admission with a median survival time of 20 days. There was a statistically significant median survival time difference in the category of antepartum hemorrhage, hyaline membrane disease, stress ulcers, acute kidney injury, and stages of HIE. Independent predictors of time to death of asphyxiated neonates in the study area were stage III HIE, Acute kidney injury, and stress ulcers.

7.2. Recommendation

To Jimma University Medical Center

In addition to the care provided to asphyxiated neonates in the JUMC NICU unit, we recommend that the care of neonates with stage III HIE, acute kidney injury, and stress ulcers should be improved. We also suggest close follow-up of asphyxiated neonates for early detection and prompt management of stress ulcers and acute kidney injury.

To health facilities in Jimma zone and labor ward of JUMC

It is recommended that labor should be closely monitored to reduce preventable risks of perinatal asphyxia. Furthermore, a sterile procedure during delivery is recommended to prevent early-onset neonatal sepsis because, neonates with this condition are treated with antibiotics, and prolonged use of some antibiotics, such as gentamycin, was found to increase the risk of acute kidney injury(57,65). Moreover, we suggest they should not delay the referral of high-risk neonates for a better outcome.

To future researchers

Further studies on the long-term neurological complications of perinatal asphyxia beyond 28 days on censored neonates should be conducted. Furthermore, the quality of neonatal care study should be conducted at the JUMC.

To Non-Governmental Organization

Interested Non-Governmental Organizations were suggested to assess and intervene in neurologic abnormalities related to perinatal asphyxia in the community in collaboration with Jimma University Medical Center Psychomotor simulation center.

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APPENDIXES

Annex I: Additional files

Multi-collinearity test

There was no Multicollinearity among independent variables because the mean-variance inflation factor(VIF) of covariates was 1.52 and the maximum VIF was 3.90, which was for gestational age (Table 9 below).

Table 9: Multi-collinearity test of variables final model on time to death and its predictors among asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Variables	VIF
Birth weight in grams	2.89
Gestational age in weeks	3.90
HIE stage	1.12
Acute kidney injury	1.28
Hypoglycemia	1.11
Stress ulcers	1.14
Hyaline membrane disease	2.93
Antepartum haemorrhage	1.52

Proportional hazard assumption test

Schoenfeld residual test results showed that the Cox proportional hazard assumption was not violated for any variable included in the final model and the Global test since it was insignificant at 0.05(table 10 on the next page). A similar result was shown by the graphical representation of the Schoenfeld residual plotted against time (Figure 9 on the next page).

Table 10: Proportional hazard assumption test of a Cox regression on time to death and its predictors among asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Variables	Chi-square	p-value
Birth weight(BW)	1.15	0.56
Gestation age(GA)	1.55	0.46
Acute kidney injury(AKI)	0.21	0.65
Hypoglycemia(hypog)	2.20	0.14
Stress ulcers	2.33	0.13
Hyaline membrane disease(hmd)	0.49	0.49
Antepartum hemorrhage(aph)	2.02	0.16
HIE stage	1.14	0.57
Global test	8.47	0.67

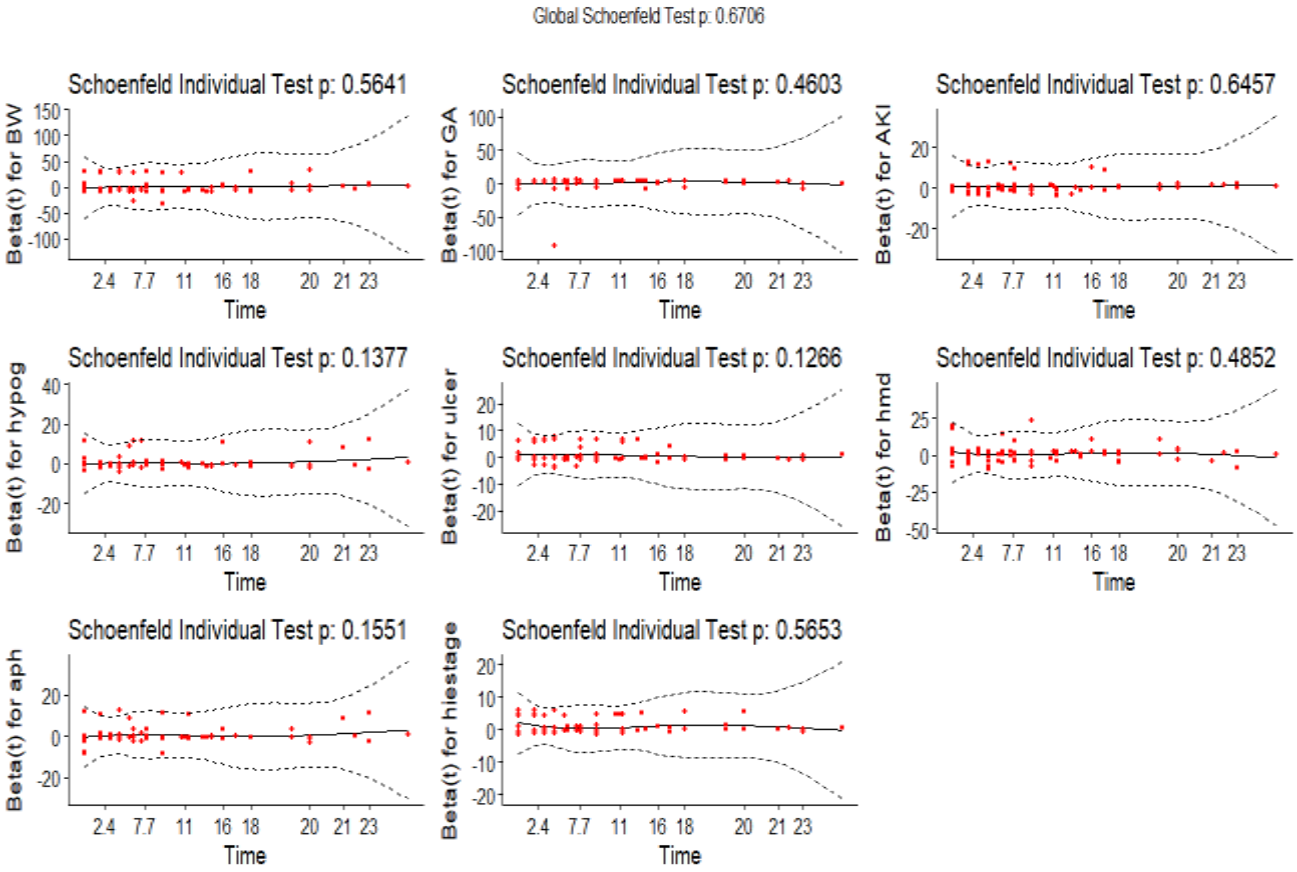

Figure 9: Plot of Schoenfeld residuals against time for asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Potential outliers

There were no potential outliers that the model did not adequately describe because the deviance residuals around the fitted line were found to be distributed roughly symmetrically between -2 and +3(Figure 10 below).

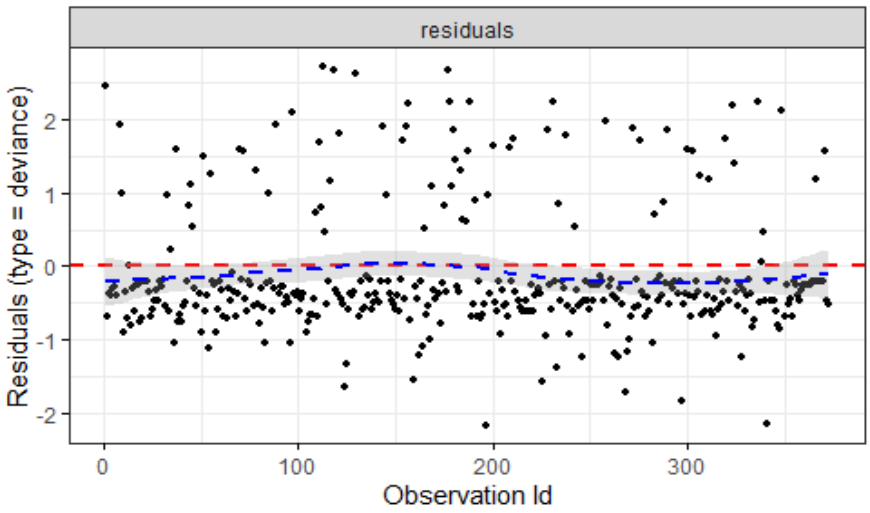

Figure 10: Deviance residual for covariates of time to death among asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, April 12/2019 to May 5 /2022

Overall Goodness of fit test

To assess the overall Goodness of fit test, Cox-Snell residuals were plotted against the cumulative hazard. This showed that the residuals followed an exponential distribution along the 45-degree slope of the fitted line.

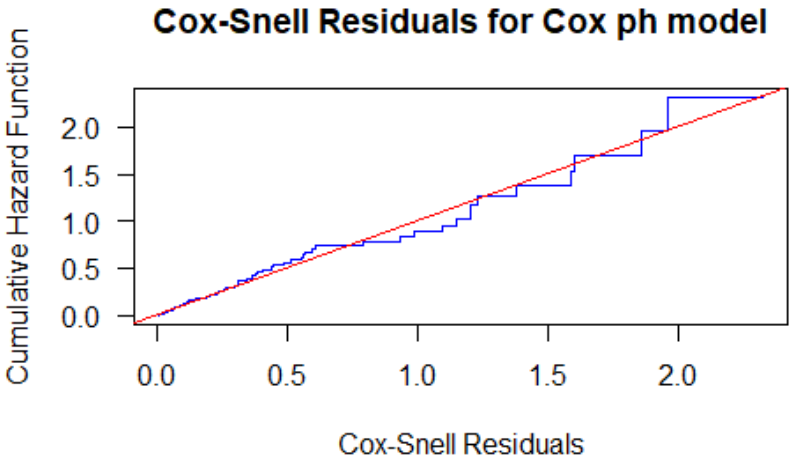

Figure 11: Cox-Snell residual plot to test Cox regression model fitness for asphyxiated neonates admitted to Jimma University Medical Center, SW Ethiopia, 2022

Annex II: Information sheet

My name is _____I am working as a data collector for the research being conducted assessing time to death and its predictors among asphyxiated neonates admitted to Jimma university medical Center by **Lencho Kajela Solbana** who is a candidate for MPH in Epidemiology in Faculty of Public Health, Jimma University.

The study Topic: time to death and its predictors among asphyxiated neonates admitted to Jimma university medical Center, southwest Ethiopia: A retrospective cohort study

Purpose of the study: The main aim of this study is to write a thesis as a partial requirement for the fulfillment of a master's degree in Epidemiology for the principal investigator. Moreover, the result of the study will be used as evidence and input for the health facilities of Jimma Medical Center and other governmental and non-governmental organizations working on neonates.

Procedure and duration: The data collectors will collect the necessary information from patient records (cards) using structured data extraction tools to have pertinent data that is helpful for the study which will stay for about 14 days during the data collection period.

Risk and discomfort: By participating in this research project, no risk comes to the NICU in general and the client whose record was reviewed. Whereas the review is of great importance to the research project which is in turn important for the overall planning of the program.

Benefit: The research has no direct benefit to those who have participated in this project. But the indirect benefit of the research for the participant and all other clients in the program is great. As identifying areas of improvement and taking appropriate decisions helps to improve the service, increase access and overall effectiveness of the program and reduce the incidence of mortality among asphyxiated neonates.

Confidentiality: The information acquired from the patient file will be confidential. There will be no information that identifies in particular. The findings of the study will be general for the study community and will not reflect anything, particularly of individual persons.

The data extraction tools will be coded to exclude showing names and other personal information. No reference will be made in oral or written reports that could link participants to the study.

Rights to refusal or Withdrawal: Permitting this study is fully voluntary. You have the right to permit or not this study. If you decide to permit the study, you have the right to terminate the study at any time if you consider something related to the study is wrong.

Contact address: This research project will be reviewed and approved by the research ethics board of the Institute of Health, Jimma University. If there is any unclear or discomfort you can contact the committees, the advisors, and the principal investigator

Principal investigator: Lencho Kajela Solbana (BSc)

Mobile phone: +2519-13-00-50-24, E-mail: lejch7@gmail.com

Advisors:

Mr. Solomon Berhanu (MPHE, Assistant professor): Jimma University, Faculty of Public Health, Department of Epidemiology

Phone number: +2519-13-45-89-61, Email Address- Solo.berhanu@gmail.com

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Phone number-+2519-11-61-87-66, Email address- juyene@gmail.com

Annex III: Data extraction checklist

Neonate's medical record number: _____

Part I: Socio-demographic and admission baseline data

S/N	Question(variable)	Response category
101	Sex of neonate	1) Male 2) Female 9) not recorded
102	Age of neonate at admission	_____days
103	Birth weight in gram	_____gram
104	Gestational age at birth	_____weeks
105	Residence(district)	_____
106	Admission pulse rate	_____bpm
107	Admission respiratory rate	_____bpm
108	Admission body temperature	_____degree Celsius

Part II: maternal medical diseases during the index pregnancy

No	Question	Response
201	Does the mother have medical health problems during the index pregnancy?	1)Yes 2) No
202	If yes, identify the diagnosis	1) Hypertension 2) Iron deficiency anemia 3) Others (specify)----------

Part III: Maternal obstetric and Gynaecologic conditions

Please circle on the lists or write a response in the space provided for each of the following obstetric and gynaecologic conditions and/or care that affected/given to the mothers during the index pregnancy**.**

No	Question(or variable)	Response
301	Number of parity	_____
302	Total number of ANC visit	1) no visit 2) 1-3times 3) ≥4 times 9) NR
303	Was there a history of Obstetric complications?	1) Yes 2) No
304	If yes for 303, specify it	1) preeclampsia 2) APH 3) Others(specify)--------
305	Place of delivery	1) Inborn 2)Referred_____ 9) NR
306	Duration of labor	_____ hours

307 Time of rupture of membrane _____hours

308 Mode of delivery 1)C/S 2) SVD 3) instrumental 9) NR

309 Was there a history of Cord prolapse? 1) Yes 2) No

Part IV: neonatal comorbid disease and treatment provided:

A: neonatal comorbid disease (clinical condition)

Please read the history note and discharge summary to mark "yes" if the neonate has the indicated comorbid disease, otherwise "no."

No	Questions(variables)	Response(category)		
401	Neonatal sepsis	1) yes	2) no	,if no go to Q403
402	If yes for Q401, specify the type of sepsis			
403	Meconium aspiration syndrome	1) yes	2)no	
404	Respiratory distress syndrome	1) yes	2)no	
405	Hypothermia	1) yes	2)no	
406	Hypoglycemia	1) yes	2)no	
407	Convulsion	1) yes	2)no	
408	Acute kidney injury	1) yes	2)no	
409	Congenital malformation	1) yes	2)no	If no, go to Q411
410	If yes for Q408, identify the diagnsosis_____			
411	What was the neonates' stage of HIE?	1) Stage I	2) Stage II	3) Stage III
412	Any other comorbidities	_____		

B: Treatments provided for the neonates

Please read the history sheet, order sheet, progress note, and discharge summary and mark "yes" if the neonate received the stated treatment below; otherwise, circle "no."

S/N	Treatments	Response	
411	Resuscitation	1) Yes	2) no
412	CPAP	1) Yes	2) no
413	Oxygen therapy	1) Yes	2) no
414	Antibiotics	1) Yes	2) no
415	Blood transfusion	1) Yes	2) no
416	Anticonvulsant	1) Yes	2) no
417	Phototherapy	1) Yes	2) no
418	KMC	1) Yes	2) no

419 Thermal care 1) Yes 2) no

420 Any other treatment privided_____

Part V: Summary of survival status

Please read the history note, discharge summary, or death summary before filling out this general summary of the discharge status of the asphyxiated neonate

501 Date of admission(DD/MM/YY)_____

502 Date of discharge (DD/MM/YY)_____

503 Length of hospital stay in days_____

504 Discharge status: 1) Died 2) Survived 3) LAMA 4) Referred **9**) NR

505 If died, what was the cause of death?

1) Cardiorespiratory failure 2) Multi-organ failure

3) Other_____ **9**) NR

Name and signature of data collector:

_____

_____

Name and signature of supervisor

_____

_____

Annex IV: Declaration

I, the undersigned, declare that this thesis is my original work, has not been presented for a degree in this or any other university, and that all sources of materials used for the thesis have been fully acknowledged.

Name: **Lencho Kajela Solbana**

Signature_____Date_____

Name of the institution: Jimma University

Date of submission: September 12/2022

This thesis has been submitted for submission with our approval as University advisors Name and Signature of the advisors

Name and Signature of the first advisor**:**

Mr. Solomon Berhanu

Signature_____Date_____

Name and Signature of the second advisor

Mrs. Yenealem Gezehagn

Signature_____Date_____

Name and Signature of internal examiner:

Mr. Masrie Getnet

Signature_____Date_____