Incidence and Predictors of Mortality Among Neonates with Perinatal Asphyxia, Northwest Ethiopia, 2021: An Institution Based Retrospective Cohort Study.

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Abstract

Background: - Perinatal asphyxia is the third leading cause of neonatal mortality globally, which usually happens within the first week of life. Therefore, evidence-based estimation of neonatal mortality is a cornerstone for tracking progress towards child survival goal and identifying priority areas to improve progress towards eliminating preventable deaths due to perinatal asphyxia.

Objective: To assess incidence and predictors of mortality among neonates with perinatal asphyxia admitted to the neonatal intensive care unit of Debre Markos Comprehensive Specialized Hospital, 2021.

Methods: An institutional-based retrospective follow-up study was conducted among 402 neonates with perinatal asphyxia (PNA) admitted to the neonatal intensive care unit (NICU) of Debre Markos Comprehensive Specialized Hospital from January 1st, 2018 to the 30th of December, 2020. A simple random sampling technique was used to select the estimated sample. Data were entered using Epi data Version 4.6.0.0 and analyzed using Stata Version 14. The Kaplan–Meier and log-rank test were used to estimate and compare the survival time. Both the bi-variable and multivariable Weibull regression models were fitted to identify predictors of mortality. Finally, the Hazard ratio with a 95%CI was computed, and variables with p-values <0.05 were considered as statistically significant predictors of mortality.

Results: A total of 125 (31.09%) neonates died during the follow-up period. The overall incidence rate of mortality was found to be 53.49 per 1000 neonate-days of observations (95%CI: 44.89-63.74). Neonatal sepsis (AHR=2.13;95%CI: 1.38-3.27), preterm birth (AHR= 3.42 95%CI; 2.13- 5.48), Hypoxic Ischemic Encephalopathy stage II (AHR=6.65 95%CI: 2.57-17.26), and III (AHR=16.8 95%CI; 6.28- 44.9), Antepartum hemorrhage (AHR=2;95%CI: 1.13-3.92), the induced onset of labor (AHR=3.90;95%CI; 1.83-8.27), and post-partum hemorrhage (AHR=2.12;95%CI: 1.32-3.38) were significant predictors of mortality among neonates with perinatal asphyxia.

Conclusion: The study found that the overall incidence rate of mortality among neonates with PNA remains high. Neonatal sepsis, Hypoxic-ischemic encephalopathy stage II and III, preterm birth, antepartum hemorrhage, postpartum hemorrhage and induced onset of labor were independent predictors of mortality. Therefore, early anticipating high-risk pregnancies and newborns with the respective intervention could reduce neonatal due to perinatal asphyxia.

Background

According to the World Health Organization (WHO), Perinatal asphyxia is defined as the failure to initiate and sustain breathing at birth (1). It results in progressively marked impairment of gas exchange and subsequently leads to metabolic acidosis, and multi-organ system dysfunction (brain damage, heart, lungs, gut, kidneys (2–4). Appearance Pulse Grimacing Activity and Respiration (APGAR) score is still an important universally accepted tool for prenatal asphyxia diagnosis and its severity and is assessed mostly in the 1st and 5th minutes of life with scores eight to ten: normal, four to seven: moderate, and between zero and three: severe perinatal asphyxia (5).

Globally, perinatal asphyxia is the major cause of neonatal mortality and morbidity. According to 2014, WHO report, between 4 and 9 million newborns develop birth asphyxia each year. Among these, around 1.2 million newborns died during the neonatal period. Moreover, at least a similar number of neonates develop severe consequences, such as developmental delay, epilepsy, cerebral palsy, and 42 million disability-adjusted life years (6–8). Indeed, it is a responsible factor for 24% of all neonatal deaths and 11% of deaths of children under 5 years of age (4, 9). Approximately, three-fourths (75%) of such deaths happen on the first day and less than 2% after 72 hours of birth (10).

The impact of perinatal asphyxia is not restricted at neonatal age but also results in the long-term and short-term neurodevelopmental sequelae, counting cognitive and engine incapacities which are mostly untreatable (11, 12). Nearly a quarter of newborns who survived with perinatal asphyxia faced neurological disorders, such as cerebral palsy, certain neurodevelopment learning disabilities (13), and post-traumatic stress disorders (14). Moreover, medical-related costs for the treatment of perinatal asphyxia were high, spent 9.1% of their annual income on acute care (15).

Perinatal asphyxia causes 40% of all early neonatal deaths in Brazil, (16), 20-40% in South Asia (17, 18), and 4.8-40.6% (19–23) in Indian. In sub-Saharan Africa, the PNA case fatality rate was still high, accounts for 31 per 1000 live births.

In Ethiopia, neonatal mortality is 30/1000 live birth, depicting an upward trend (24) and Perinatal asphyxia is the third leading cause of neonatal mortality that accounts for 12.5-35%, followed by preterm (21.8%), and neonatal sepsis (18.5%) of all mortalities (18.5%) (25–28).

Previous studies conducted on predictors of mortality found maternal age less than 20 years (29, 30), mothers who did not attend ANC (20, 21, 31), primipara (20, 32), maternal anemia (21), pregnancy-induced hypertension (30), delivered out of the hospital (33–35), premature rupture of the membrane (PROM) (20, 30, 32), spontaneous vaginal delivery (29, 33–35), instrumental delivery (23), multiple births (32), prolonged labour (23, 32), Obstructed labour (30), meconium-stained amniotic (20), preterm birth (32, 35, 36), low birth weight (35–39), Hypoxic-ischemic encephalopathy (HIE) stage II and III (20, 21, 23, 40), respiratory distress at admission (21, 39), neonatal sepsis (32, 40, 41), hypoglycemia (20), neonatal anemia (21) and hypothermia (20) were independent predictors of mortality among neonates with perinatal asphyxia.

Sustainable development goal (SDG) 3 sets a target of reducing neonatal mortality to 12 deaths or less per 1000 live births and to end all preventable neonatal deaths including PNA (42–44). Despite this, neonatal mortality increases from time to time in Ethiopia since 2016 (24, 45). Moreover, limited studies were conducted in the study area to emphasize mortality and its predictor among newborns with perinatal asphyxia.

Therefore, estimating the incidence and identifying predictors of mortality are cornerstone for tracking progress towards child survival goal and identifying priority areas to improve progress towards eliminating preventable deaths due to perinatal asphyxia. Improvement of neonatal survival is a good

indicator of quality care. Hence, it is important for the health care providers and health care commissioners to early detection, diagnosis, management and have follow-up care and have also practical vital value for patients, health care providers, researchers and policy-makers in the Ministry of Health.

Hence, this study aimed to determine mortality and its predictors among neonates with perinatal asphyxia admitted in the neonatal intensive care unit of Debre Markos Comprehensive Specialized Hospital.

Methods

Study design, period and population

A retrospective follow-up study was carried out from April to May, 2021 at Debre Markos compressive specialized hospital which serves more than 5 million people in its catchment area. Currently, about 100 health centers and 9 district hospitals are available in the catchment area of the referral hospital. The hospital has a total of 489(282 male, 207 female) clinical staffs. Furthermore, it provides neonatal intensive care services for critically ill neonates and those who need neonatal care. The NICU has 27 nurses, one pediatrician, and two general practitioners. In addition, the neonatal intensive unit has 28 neonatal beds and 27 maternal beds(46). The source population was all neonates with perinatal asphyxia admitted to the NICU of Debre Markos comprehensive specialized hospital. The study population included randomly selected eligible neonates with perinatal asphyxia admitted to NICU of Debre Markos comprehensive specialized hospital from January 1, 2018, to December 30, 2020.

Inclusion and exclusion criteria

All neonates with perinatal asphyxia admitted to the NICU of Debre Markos comprehensive specialized hospital from January 1, 2018, to December 30, 2020, who had registration were included. While records of children whose admission date and discharge date were not recorded, missing of outcome variable and neonates with major congenital malformation were excluded in the study.

Sample size and sampling technique

Sample size was computed using single proportion formula with the following assumptions: death rate= 38.7% ($p=0.387$ and $q=0.613$) (35), 95% confidence level, 5% margin of error. A total of 789 neonates were admitted to the hospital from January 1/2018 to December 30/ 2020. A sample of 402 neonates with asphyxia were selected from 789 neonates using random number computer generated method, the subsequent unique chart numbers from the registration file were extracted.

Data collection procedure

A data extraction format was developed from standardized management protocol for neonates and reviewing applicable articles to assemble the required individual information. The data extraction format consists of socio-demographic characteristics of the mother and the newborn (age, religion, residence,

sex of the newborn, and age at admission), antepartum related variables (ANC follow-up, pregnancy induced hypertension, Antepartum hemorrhage, Anemia during pregnancy, gestational diabetic mellitus, Parity, Gestational Hypertension, diabetic mellites, tetanus vaccination, pregnancy screening test (Rh factor, syphilis screening test, HIV, and Hepatitis), Intra-partum related variables (mode of delivery, place of delivery, premature rupture of membrane, Malpresentation, postpartum hemorrhage, prolonged labor, obstructed labor, types of pregnancy, and onset of labor) and neonatal related variables (gestational age, birth weight, Meconium aspiration syndrome, anemia, clinically diagnosis neonatal sepsis, Hypoxic ischemic encephalopathy, birth injury, hypothermia, respiratory distress syndrome, Jaundice, phototherapy, and Random blood sugar). Three experienced nurses were recruited for data collection and supervision, and two days training was given for them to standardize and agree on the way to review medical records. The data extraction tool was checked for completeness and consistency using 5% preliminary reviewed randomly selected charts to maintain data quality assurance.

Data processing and analysis

Data were entered into Epi data Version 4.6 and exported to Stata version 14 statistical software for further analysis. Descriptive statistics of numeric variables presented in medians with interquartile range (IQR), categorical variables were presented using frequency tables and percentages. Multicollinearity was checked between independent variables. The incidence rate of mortality was also calculated for the entire follow-up by dividing the total number of new cases of PNA to the total person-days of follow-up. The Kaplan-Meier failure curve was used to estimate survival time. The Log-rank test was used to compare Survival experiences between independent groups. Proportional hazard assumption was checked by graphically using the plot of $\log[-\log(\text{survival probability})]$ versus the log of survival time, by interacting each covariate with time. The Schoenfeld residual global test for the proportionality assumption was checked, and (**p-value =0.7554**) finding was used as a suggestive of satisfying assumption. The log-likelihood and Akaike Information Criteria (AIC) were applied to select the best fitted model, and a model with minimum AIC value was considered as the best fitted model. As a result Weibull regression model was selected with **AIC=586.39**. The goodness of model fitness was also checked using the Cox-Snell residual test. Variables with $P < 0.2$ in the bi-variable analyses were potential candidate variables for the multivariable analysis, and stepwise forward variable selection was done so as to identify eligible variables using Weibull regression. Variables having p-value ≤ 0.05 in the multivariable model were considered to be significantly associated with the outcome. Finally, the crude and adjusted hazard ratio (HR) with 95% CI was calculated to determine statistical significance level.

Operational definitions

Perinatal asphyxia:- is considered when the 5th minute APGAR score is <7 (21, 47).

Event(death):- Neonate died in the hospital and death summary written on a chart due to PNA (48).

Censored

newborns with PNA who did not develop the outcome of interest (death) until the end of follow-up period or lost to follow-up, recovery from illness, discharged against medical advice or transfer out to other health institutions without knowing the outcome

Survival time

The time in days from admission to the development of outcome variable (Death) within 28 days follow-up time.

Defaulted- PNA cases that are signed (parents on behalf of their child) against treatment to leave treatment before cure.

Results

Socio-demographic and admission characteristics

A total of 402 newborns were enrolled into the study. Nearly two-thirds, 260(64.68 %) of neonates were males. About 340 (84.58%) of neonates were admitted within the first 24 hours immediately after birth. The median age of mothers was 25 (IQR: 23, 30) years old, and 37.81% were belonged to the age group of 20-24 years old. Majority, 348 (86.57%) of the respondents were Orthodox Christianity followers, and nearly two- thirds, 252(62.69) of them were rural resident (Table 1).

Table 1
Socio-demographic characteristics of the mother and the newborn admitted
DMCSH from January, 2018 to 30th of December, 2020, Northwest, Ethiopia,
(N=402)

Variables	Category	Frequency	Percent
Sex of the newborn	Male	260	64.68
	Female	142	35.32
Admission age of the newborn (hr)	≤24hr	340	84.58
	>24hr	62	15.42
Maternal Age in years	15-19	16	3.98
	20-24	152	37.81
	25-29	132	32.84
	30-34	54	13.43
	35-49	48	11.94
Religion	Orthodox	348	86.57
	Protestant	31	7.71
	Muslim	23	5.72
Residence	Rural	252	62.69
	Urban	150	37.31

Antepartum characteristics of the mother

Nearly two-thirds, 262(65.17%) of the participants were primipara and almost all, 387(96.27%) were attending ANC follow-up. Among these who attend ANC nearly two third 253 (65.37%) had four and above ANC visit (Table 2).

Table 2
Medical and antenatal obstetric characteristics of the mother at
DMCSH from January 1/2018 to December 30/2020, Northwest,
Ethiopia, (N=402)

Variables	Category	Frequency	Percent
Antenatal care	Yes	387	96.27
	No	15	3.73
No of ANC follow up	1-3	134	34.63
	4 and above	253	65.37
Parity	Primipara	262	65.17
	Multipara	140	33.83
Anemia	Yes	92	22.89
	No	310	77.11
Hypertension	Yes	18	4.48
	No	384	95.52
Diabetic mellites	Yes	20	5.00
	No	382	95.00
Antepartum hemorrhage	Yes	32	7.96
	No	370	92.04
Postpartum hemorrhage	Yes	43	10.70
	No	359	89.30
Preeclampsia/eclampsia	Yes	53	13.18
	No	349	86.82
Gestational diabetes	Yes	22	5.47
	No	380	94.53
Rh factor	Positive	382	95.02
	Negative	20	4.98
HIV status	Positive	9	2.24
	Negative	393	97.76
Hepatitis	Positive	5	1.24
	Negative	397	98.76

Variables	Category	Frequency	Percent
VDRL	Positive	8	1.99
	Negative	394	98.01
TT vaccination	Yes	371	92.79
	No	31	7.71

Intrapartum obstetric factors of the mother

As shown on the **(Table 3)** more than half, 216 (53.73%) of the respondents delivered through spontaneous vaginal delivery and nearly one-fifths, 79 (19.65) delivered above 18 hrs duration of labor. Of all 376 (93.53%) labor started with spontaneously.

Table 3: Intrapartum obstetric characteristics of the mother at DMCSH from January 1/2018 to December 31/2020, Northwest, Ethiopia (N=402)

Variables	Category	Frequency	Percent
Mode of delivery	SVD	216	53.73
	CS	91	22.64
	Instrumental	95	23.63
Duration of labor	≤18hr	323	80.35
	>18hr	79	19.65
Onset of labor	Spontaneous	376	93.53
	Induced	26	4.73
Types of pregnancy	Single	385	95.77
	Multiple	17	4.23
Presentation of the fetus	Vertex	367	91.29
	Non vertex	35	8.71
PROM	Yes	71	17.66
	No	331	82.34
Obstructed labor	Yes	40	9.95
	No	362	90.05
Place of delivery	Health center	97	24.13
	Hospital	305	75.87
PROM= premature rupture of membrane SVD= spontaneous vaginal delivery CS= caesarean section			

Clinical characteristics of neonates. The mean gestational age of the newborn was 38.5(±2.6 SD) weeks and most, 284 (70.65%) neonates' gestational age belonged to the age group of 37-42 weeks. Nearly two-thirds, 268(66.67%) of the newborns were had normal birth weight (**Table 4**).

Table 4
Clinical characteristics of the newborn admitted in the NICU of DMCSH from
January 1/2018 to December 31/2020, North West, Ethiopia, (N=402)

Variables	Category	Frequency	Percent
Gestational age	Preterm	92	22.89
	Term	284	70.65
	Post term	26	6.47
Birth weight	<2.5kg	134	33.33
	≥2.5-2.99kg	260	66.67
	4 & above kg	8	2.00
Neonatal sepsis	Yes	159	39.55
	No	243	60.45
RDS	Yes	70	17.41
	No	332	82.59
MAS	Yes	128	31.84
	No	274	68.16
Resuscitation	Yes	362	90.05
	No	40	9.95
HIE stages	I	124	30.85
	II	191	47.51
	III	87	21.61
Neonatal jaundice	Yes	15	3.73
	No	387	96.27
Phototherapy	Yes	18	4.48
	No	384	95.52
Hypothermia	Yes	301	74.88
	No	101	25.12
Birth injury	Yes	62	15.42
	No	340	84.58

RDS=Respiratory distress syndrome, MAS= meconium aspiration syndrome

Variables	Category	Frequency	Percent
Neonatal anemia	Yes	101	25.12
	No	301	74.88
Hypoglycemia	Yes	5	1.24
	No	397	98.76
RDS=Respiratory distress syndrome, MAS= meconium aspiration syndrome			

Incidence of mortality

From the total of 402 neonates who were admitted with perinatal asphyxia (PNA) 125(31.09%) (95% CI: 26.74- 35.81) of them developed the event of interest (death). The total neonate-days observation for the entire follow-up time was 2337 person-days with minimum and maximum follow up time were 1 and 22 days respectively. The overall incidence of mortality was 53.49 per 1000 neonate- days observation (95%CI: 44.89- 63.74) during the entire follow-up time. The incidence of death at the beginning of 5, 10, 15 and 20 days was 67, 35, 5.84 and 21.7% per 1000-neonate days observation, respectively.

Overall failure Function (survivorship function)

The overall Kaplan- Meier failure function showed that the probability of death among neonates with PNA was increased during the follow-up period. During the first day of admission 13% probability of death was observed. The cumulative probability of death at the end of 5, 10, 15 and 20 days was 0.27, 0.38, 0.39, and 0.44 respectively and the least probability death 0.44 was observed at the end of 28 days follow-up time (Figure 2)

Comparison of Survivorship Functions for different categorical variables

The test of equality for survival distribution for different categories of variables were performed with Kaplan-Meier and the log-rank test. In general, the pattern that one group survivorship function lying above another group showed that the upper curve had a better probability of survival compared to the lower curve. On the other hand, the probability of death was high among the lower groups described by Kaplan-Meier survival curve. Furthermore, the log-rank test confirmed the observed difference seen on the KM graph statistical difference or not.

In the current study, newborns who faced HIE stage III has lower survival time compared with stage II and I, and newborns who developed HIE stage II were lower survival time compared to stage I. Moreover, neonates without sepsis have favorable survival probability than those neonates with sepsis. This study also revealed that neonates born from mothers who hadn't PPH at admission had better probability of survival compared with those mothers faced PPH.. Furthermore, neonates born from mothers who had

antepartum hemorrhage (APH) had better probability of survival compared with newborns born from mothers who did not face APH among neonates admitted with PNA. These differences were statistically significant with p value < 0.001 in log rank test (Figure 3)

Model comparison

After the proportional hazard assumption was checked, both semi-parametric and parametric proportional hazard models were fitted to estimate the survival time to death and identify its predictors among neonates with perinatal asphyxia. As shown in figure 3 model Comparison was checked graphically.

Besides, Model Comparison was checked statistically by using information criteria (AIC, BIC) and log-likelihood to select the most parsimonious models for the data set. Based on this, the Weibull regression with the **AIC= 586.39** model was best fitted model (Table 5).

Table 5
Summary of model comparison among the Cox proportional hazard model, parametric Cox- Regression models using AIC and LR criteria

Model	Baseline Hazard	Log-likelihood	AIC
Cox regression	Unspecific	-602.86	1257.72
Weibull regression	Weibull	-265.19	586.39
Exponential	Exponential	-266.64	587.29
Gompertz	Gompertz	-265.66	587.32

Predictors of mortality among neonates with perinatal asphyxia

In the Bi-variable Weibull regression analysis, age of the mother, parity, postpartum hemorrhage, preeclampsia or eclampsia, antepartum hemorrhage, chronic diabetes mellites, chronic hypertension, maternal anemia, other pregnancy related complications like (abortion, placenta previa...), duration of labor, presentation, onset of labor number of pregnancy, onset of labor ,birth weight, gestational age, neonatal sepsis, respiratory distress syndrome, Meconium aspiration syndrome, phototherapy, birth injury, neonatal anemia, hypothermia and HIE status were significant predictors of mortality with P- value less 0.2. However, in the multivariable Weibull regression analysis, prematurity, neonatal sepsis, Antepartum hemorrhage, induced onset of labor, postpartum hemorrhage and HIE stage II and III were significant predictors of mortality among neonates admitted with PNA with p value <0.005.

After adjusting for other variables neonates born from mothers who faced postpartum hemorrhage (PPH) during delivery increased the hazard of death by two times than mothers without PPH (AHR=2.12; 95%CI: 1.32-3.38). Induced onset of labor was also independent predictor of mortality among neonates with

PNA, which increased the hazard of death nearly four times more likely compared with spontaneous onset (AHR=3.90; 95%CI: 1.83- 8.27) by keeping other variables constant. In addition to this neonate born from mothers with current pregnancy complicated with antepartum hemorrhage (APH) increased the hazard of death by two folds (AHR=2.10; 95%CI: 1.13-3.92) among neonates with PNA compared with newborns born from mothers without APH. Moreover, neonatal sepsis was independent predictor of death, which increased the hazard of death among newborns with PNA two times (AHR=2.13; 95%CI: 1.38-3.27) compared with newborns without neonatal sepsis holding other variables constant. Preterm birth increases the hazard of death by more than three times than neonates delivered within 37-42 weeks of gestational age (AHR= 3.42; 95%CI: 2.13-5.48) by keeping other variables constant. Besides, HIE stage II and stage III were strong predictors of death, which increased the hazard of death by seven and nearly 17- times more likely with (AHR=6.65; 95%CI: 2.57-7.26), and (AHR=16.8; 95%CI: 6.28 -44.9) compared to HIE stage I respectively holding other variables constant (Table 6).

Table 6

Bivariable and multivariable Weibull regression analysis for predictors death among neonates with perinatal asphyxia admitted at DMCSH from 2018-2020, North West, Ethiopia, December January 1/2018 to December 31/2020 (N=402)

Variables	Category	Status		CHR;(95%CI)	AHR;(95%CI)
		Event	Censored		
Phototherapy	Yes	9	9	1.58(0.80- 3.11)	0.66(0.30-1.43)
	No	116	268	1	1
Age of the mother	15-19	7	9	1.54 (0 .69 3.41)	0.58(0 .21-1.61)
	20-24	45	107	1	1
	25-29	34	98	0.76 (0.49-1.19)	0.70(0.40-1.23)
	30-34	15	39	1.02(0.57- 1.84)	1.73(0 .80- 3.75)
	above 35	24	24	2.12(1.29-3.48)	1.61(0 .77- 3.38)
Parity	Multipara	51	89	1.44 (1.01-2.05)	0.84 (0.48-1.48)
	Primi para	74	188	1	1
Maternal anemia	Yes	38	54	1.70(1.16- 2.49)	1.05 (0 .64-1.72)
	No	87	223	1	1
Hypertension	Yes	13	5	4.00 (2.26-7.17)	1.27 (0 .62- 2.62)
	No	112	272	1	1
PPH	Yes	30	13	3.49(2.31- 5.26)	2.12(1.32-3.38) **
	NO	95	264		
APH	Yes	19	13	2.64(1.62- 4.30)	2.10 (1.23-3.92) *
	No	106	264	1	1
Pre/eclampsia	Yes	25	28	1.62(1.04-2.51)	0.73 (0.42-1.26)
	No	100	249	1	1
Diabetes mellites	Yes	12	8	3.47 (1.90- 6.31)	1.25 (0.60-2.60)
	No	113	269	1	1
Duration of labor	>18hr	35	44	1.82(1.23- 2.69)	1.35 (0.86-2.14)
	≤18hr	90	233	1	1

APH= Antepartum hemorrhage, PPH= Postpartum hemorrhage, RDS= respiratory distress syndrome, HIE= hypoxia ischemic encephalopathy and MAS= Meconium Aspiration Syndrome

Types of	Multiple	9	8	2.51(1.27- 4.97)	1.41 (0.61-3.27)
Pregnancy	Single	116	269	1	1
Onset of labor	Induced	11	15	1.72(0.93- 3.20)	3.90 (1.83-8.27) ***
	Spontaneous	114	262	1	1
Presentation	Non- Vertex	14	21	1.65(0.95-2.88)	1.78 (0.93-3.42)
	Vertex	111	256	1	1
Gestational Age(week)	Preterm	73	19	7.86(5.44-11.37)	3.42 (2.13-5.48) ***
	Term	48	236	1	1
	Post term	4	22	0.82(0.30- 2.28)	0.52 (0.17-1.56)
	Term	44	240	1	1
Sepsis	Yes	87	72	4.17(2.85-6.11)	2.13 (1.38-3.27) **
	No	38	205		1
MAS	Yes	49	79	1.33(0 .93- 1.90)	1.22 (0.80-1.84)
	No	76	198	1	1
RDS	Yes	38	32	2.40 (1.64- 3.50)	1.07 (0.68-1.68)
	No	87	245	1	1
Neonatal Anemia	Yes	51	50	2.45(1.71- 3.50)	1.26 (0.82-1.93)
	No	74	227	1	1
HIE	I	5	119	1	1
	II	47	144	5.9(2.35-14.85)	6.65 (2.57-17.26) ***
	III	73	14	34.5(13.9-85.44)	16.8(6.28 -44.9) ***
Birth injury	Yes	24	38	1.46(0 .93-2.27)	1.06 (0.62-1.80)
	No	101	239	1	1
Hypothermia	Yes	103	198	1.55(0.98- 2.46)	0.63 (0.37-1.05)
	No	22	79	1	1
APH= Antepartum hemorrhage, PPH= Postpartum hemorrhage, RDS= respiratory distress syndrome, HIE= hypoxia ischemic encephalopathy and MAS= Meconium Aspiration Syndrome					

NB: *** Significant (P-value < 0.001), ** significant (p-value<0.005), * significant (p<0.05)

Discussion

Among 402 neonates under the follow up, 125 (31.09%) died during the follow-up period. The overall incidence of mortality was 53.5 deaths per 1000 neonate-days observation with (95%CI: 44.89- 63.74). This finding is higher than a study conducted in Brazil 0.95-1.38/1000 live birth (29), 0.65-0.81/1000 live birth in 2017 (16), and 9.7/1000 live birth in Southern Nepal (32). This marked difference might be attributed to a number of factors such as source population of the study participants was live birth, while the current study was PNA, another possible justifying may be due to a study area was population based. On the other hand, the current study was intuitional based.

The proportion 31.09% was relatively comparable with studies reported from Nigeria 31% (31), Congo 28.5% (49), India 26%(23). The finding of this study was higher than the studies reported in Nigeria 18% (34), 14.7% (39), and 23% (30),Tanzania 23% (50), South Africa 13.3%(33), India 4.8%(19) and 10% (20). On the other hand, this finding was lower than the studies conducted at India 40.6(21) and Nigeria 38.7% (35). This may be due to the fact that other studies included only outborn newborns; while in this study participants were both inborn and outborn newborns. Therefore, including outborn overestimated death rate. Moreover, The discrepancy might be variation in different studies was due to different operational definitions for birth asphyxia and adopted by different researchers (30, 33, 34, 39, 50). Moreover, this high death emanated from the poor neonatal resuscitation skills, the lack of resuscitative equipment, lack of skilled manpower in neonatal resuscitation at birth and delay in transporting the asphyxiated newborn to a higher health facilities (51, 52).

Neonatal sepsis at the time of admission significantly increased the hazard of death among neonates with PNA. This finding was supported by the studies conducted in developed and developing countries (32, 38, 40, 41, 50). The possible reason might be associated with neonatal sepsis causes hypothermia/fever, poor feeding, hypotension respiratory distress, shock, multi-organ failure, and meningitis. Besides, poor quality of care and treatment delay also the major gaps of developing counties including Ethiopia. Moreover, the unnecessary overuse of antibiotics can increase the chances of severe candidiasis and multi-drug resistant organisms (53–56). These collectively resulted to have high mortality due to sepsis among neonates with PNA. This study implied that there is a clear gap in the management and prevention of sepsis. This finding emphasizes the need to improve the quality of care in health facilities, in particular, we strongly believe that achieving a high-quality intrapartum and postnatal care is required to improve neonatal health.

Preterm neonates with PNA increased the hazard of death compared to full-term births. This was in accordance with the studies conducted in Nigeria and South Asian (30, 32, 35). Higher risk of mortality among premature neonates could be explained by different factors, like newborns with GA less than 37 weeks (preterm) were higher risk to develop complications, such as, infections, hypothermia, and hypoglycemia due to limited number of immunoglobulins at birth. Another possible explanation may be due to lack of feasible, cost-effective care, such as breastfeeding support, basic care for infections and breathing difficulties were practiced in developing counties like Ethiopia (57, 58). Given these factors are the most common causes of morbidity and mortality in neonates with PNA (59–61). This implies that

anticipating high-risk newborn babies and taking combined approaches to reduce the death of such physiologically and anatomically vulnerable neonates are needed (62, 63)

In the current study, hypoxic ischemic encephalopathy (HIE) stage II and III were strong (leading) independent predictors of death, that stage II and III increase the hazard of death by seven times and 17-fold respectively compared with stage I by holding another variables constant. This finding is supported by the studies conducted in Nigeria (22, 31, 34, 39), South Africa (33) and India (20, 21, 23). The possible reason might be once HIE stage II and III occur, they result in poor feeding, seizure, brain damage, and multiorgan dysfunction. In addition, due to lack of feasible, cost-effective care like therapeutic hypothermia, supportive management of seizure and adequate resuscitation in developing countries including Ethiopia (51, 64). Besides, the probability that infants with the greatest hypoxic-ischemic brain damage will benefit least by any specific intervention (65, 66).

The collectively increased death among neonates with PNA who faced HIE Stage II and III during admission. This study implies that more attention should be focused on the early assessment of high-risk mothers and newborns and timely referral to the tertiary care center. Moreover, adequate resuscitation, therapeutic hypothermia, supportive management of seizure and fluid balance is essential in ensuring optimal outcomes (67).

In the current study, induced onset of labor increases the hazard of death by nearly four times compared with spontaneous onset by adjusting effects of other variables. This may be associated with induced labor was indicted for high-risk mothers like (Preeclampsia, eclampsia, gestational hypertension...), intrauterine growth restriction, and post-term pregnancy (68–71). As well, induction increases the greater risk for instrumental birth, postpartum hemorrhage, affects the natural process of pregnancy and labour and increases hospitalization for maternal as well as newborn. These collectively increase the risk of death among newborns with PNA (72–75).

Antepartum hemorrhage (APH) was increasing the hazard of death among neonates with PNA. This may be associated with APH increases premature delivery, low birth weight, and fetal growth retardation (76). Moreover, APH leads neonatal anemia and decreases placental perfusion as well as hypoxia then which leads to bradycardia, and multiorgan failure (76–79).

Postpartum hemorrhage (PPH) was also independent predictor of neonatal mortality among neonates admitted with PNA, which increases the hazard of death by two times compared with mother who were not faced for PPH during delivery. This may be associated with PPH management delays the time for essential newborn care as well as neonatal resuscitations. Moreover, postpartum hemorrhage is the leading cause of maternal mortality (80, 81), which also resulted neonatal death. since the survival of the mother was vital for their child survival (82, 83). This study implies that regular antenatal care, early detection of high-risk mothers, allowing them to be timely admitted for schedule, availability of blood banks, and early referral to a higher center to reduce APH and PPH related neonatal death (79, 84, 85).

Limitation

As the study was based on secondary data, the main limitation could be incomplete medical records. In this regard, some important predictors, such as maternal nutritional status, mothers' educational level, birth interval, and monthly household income were not available from medical recorded data. In addition, the exact causes of death were not recorded. Thus, we assumed that all causes of the deaths were related to admission diagnosis. Furthermore, as the study was conducted at hospital, neonatal mortality might be underestimated because neonates delivered and died at home could be underreported. On the other hand, since the study included sick neonates, the mortality could be overestimated

Conclusion

The study found that the overall incidence rate of mortality among neonates with PNA remains high. Neonatal sepsis, HIE II and III, prematurity, postpartum hemorrhage, antepartum hemorrhage, and induced onset of labor were significant predictors of mortality.

Abbreviations

AHR	Adjusted Hazard Ratio
AIC	Akaike Information Criteria
APGAR	Appearance Pulse Grimacing Activity and Respiration
APH	Antepartum Hemorrhage
CI	Confidence Interval
CPAP	Continuous positive airway pressure
DM	Diabetic Mellites
DMCSH	Debre Markos Comprehensive Specialized Hospital
EDHS	Ethiopian Demographic Health Survey
EMDHS	Ethiopian Mini Demographic Health Survey
GDM	Gestational Diabetic Mellites
HIE	Hypoxic Ischemic Encephalopathy
LBW	Low Birth Weight
LL	Log Likely hood
MAS	Meconium Aspiration Syndrome
MUAC	Mid Upper Arm Circumference
PNA	Perinatal Asphyxia
PPH	Postpartum Hemorrhage
PROM	Premature Rapture of Membrane
RDS	Respiratory Distress Syndrome
VIF	Variance Inflation Factor
WHO	World Health Organization

Declarations

Ethics approval and consent to participate

The study was carried out after getting approval from the university of Gondar institutional review board (IRB). Then, data were collected after getting consent from the hospital manager. This study didn't inflict or exposes children to unnecessary risk as a result of reviewing their medical records. To maintain confidentiality, each and every one collected data were coded and locked in a separate room prior to enter

into the computer. Following entered into the computer all data were protected by password. Names and unique medical registered numbers (MRN) were not incorporated in the data collection set-up.

Consent for publication

Not applicable

Availability of data and material

Additional file: Data abstraction tool

Data set: The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have declared that they have no competing interest.

Authors' contribution

AT: the conception of the research idea, study design, data collection, analysis and interpretation, and manuscript write-up. GMB, BKD, AML and FWS: data analysis and interpretation and supervision. All authors have read and approved the final manuscript.

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Figures

Figure 1

Kaplan Meier failure function death among neonates with perinatal asphyxia admitted in the NICU of DMCSH from January 2018 to December 2020, North, West, Ethiopia, (N=402)

Figure 2

Kaplan- meier survival function among groups of neonatal sepsis (A), stages of HIE (B), PPH(C) and APH (D) for neonates with perinatal asphyxia admitted the NICU of DMCSH from 2018-2020, North West, Ethiopia ,2021.

Figure 3

Graph of Nelsen -Aalen cumulative hazard function against Cox-Snell residual obtained by fitting (A) Weibull, (B) Cox, (C) Exponential and (D) Gompertz models for mortality among neonates with perinatal asphyxia admitted at the NICU of DMCSH from 2018-2020, North West Ethiopia,2021