

Mortality of preterm neonates and its predictors in the Northwest part of Ethiopia: A retrospective cohort study

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Abstract

Abstract Background: Preterm birth is highly reported in some countries and disparities on survival rates of preterm neonate are escalating across countries. Providing adequate medical care during pregnancy and childbirth has been endorsed. However, neonatal mortality is continuing to be one of the sustainable development goals. To achieve this aim, data from the different geographical area is suggested.

Objective: This study was aimed to assess mortality of preterm neonates and its predictors in the Northwest part of Ethiopia. **Methods:** Institution based retrospective cohort study was conducted among 535 preterm neonates. Data was entered into Epi-data 4.2.0.0 and transferred to STATA version 14 statistical software for analysis. Kaplan-Meier survival analysis and Log-rank test were used to see statistical differences between categories of variables. Cox proportional hazard model was used to identify independent predictors of preterm neonatal mortality. The proportional assumption test had been checked using the Schoenfeld residual test. Variables with p -value ≤ 0.05 were considered as predictors of preterm neonatal mortality. **Results:** In this study, 31.2% (95% CI: 27.3, 35.1) of preterm neonate were died. Preterm neonates with a gestational age of less than 32 weeks (AHR=1.74; 95%CI: 1.24, 2.46), being male sex (AHR=1.38; 95%CI: 1.01, 1.90), born from preeclampsia/ eclampsia mothers (AHR=1.95; 95%CI: 1.13, 3.36), being extremely very low birth weight (AHR=2.94; 95%CI: 1.05, 8.24), diagnosed with respiratory distress syndrome (AHR=1.70; 95%CI: 1.20, 2.41) were predictors of preterm death. **Conclusion and Recommendations:** Preterm neonatal mortality found to be high. Four neonatal and one maternal-related variable were recognized predictors of mortality in preterm neonates. The study suggests preventing and controlling preeclampsia/ eclampsia, especial care for neonates born with very low birth weight, born before 32 weeks of gestation, and diagnosed with respiratory distress syndrome are imperative. **Keywords:** Preterm, Neonate, Mortality, Ethiopia

Background

Preterm neonate is babies born alive before 37 completed weeks of gestation (1). It is one of the main problems and inconsistencies on mortality of preterm neonate are escalating across countries (2). Globally, 15 million preterm neonates are born each year. Of which, more than 60% of preterm neonates are found in Africa and South Asia (3, 4).

An estimated three-quarter of preterm babies could survive by receiving inexpensive care (5). Subsequently, to prevent mortality of preterm neonate, World Health Organization's (WHO) proposed interventions to decrease mortality of preterm neonate. For instance, antenatal corticosteroids, magnesium sulfate, and antibiotic prophylaxis for mothers and Kangaroo mother care, plastic wraps, continuous positive airway pressure therapy, surfactant, and oxygen therapy for neonates are some of them (6).

Despite these interventions, preterm birth is one of the common causes of death in different countries (7). At different time, mortality of preterm neonates reported as 69% in Cameron (8), 52% in East Africa (9), and 21.8% to 34% in Ethiopia (10-13).

The causes of mortality in preterm neonates are multi-factorial and affected by biological, genetic, social, psychological, geographic, and demographic characteristics of the population. Based on the previous studies, very extreme preterm, maternal medical problems, male sex neonate, neonate diagnosed for hypothermia and hyaline membrane disease, and babies born with short birth interval have excessive mortality compared to their counterparts (14-19) were determinants of mortality in preterm neonates. Besides, clinical, behavioral, and health system-related interventions have a potential impact on mortality of preterm neonates (20).

To achieve sustainable development goal (SDG) in reducing child mortality, investigated data from the different geographical area of Ethiopia is necessary. Afterward, recognize the burden of preterm neonatal mortality is essential. Thus, the current study was intended to fill the information gap on preterm neonatal mortality and its predictors in the Northwest part of Ethiopia.

Methods And Materials

Study, design, period, setting, and population

The study was conducted through retrospective cohort study from January 22-February 5/2018 at Debretabor General Hospital, Northwest Ethiopia. Debretabor town is found 666 km far from Addis Ababa and 105 km from Bahirdar, Ethiopia. Debretabor General Hospital is the largest hospital in South Gondar Zone which was established in 1931. The hospital has been provided health care service for more than 2.4 million populations in its catchment area in the Northwest part of Ethiopia. It has a neonatal Intensive Care Unit (NICU) with a total of 21 neonatal beds and approximately 1,159 neonatal admissions per year. Most of the admissions were associated with premature delivery (21). All preterm neonates (<37 weeks of gestational age) in Debretabor General Hospital, Northwest Ethiopia were the study population. Gestational age was assessed using LNMP (last normal menstruation period) or ultrasound whenever mothers couldn't remember LNMP.

Sample size determination and sampling procedure

The sample size was determined using Open Epi Info 7 Statcalc through double population proportion formula with the assumptions of 95% CI, 5% margin of error, 80% power and exposed to unexposed ratio 1:1 by double population proportion formula by considering perinatal asphyxia (PNA), weight at birth, and sex of neonate (22-24) from previous studies, the estimated sample size was 86, 114, and 524 respectively. However, the number 524 is selected because of its largest sample size. By adding 10% non-response rate, the final sample size was 576. A study participant selection process illustrated (Figure 1).

Data collection methods

Data were collected based on a structured data abstraction sheet from preterm neonate medical records. The abstraction sheet includes maternal socio-demographic, obstetric and gynecological, prenatal, intranatal, and neonatal-related variables with considering mortality of preterm neonate as an outcome

variable. The data was collected by six BSc nurses and with the involvement of two MSc nurse supervisors. Completeness of each recorded tool was checked soon after collecting the data.

Operational definitions

The death of a preterm neonate time variable (admission to death time) was recorded. Besides, survival time was measured considered the follow-up time (from date of admission to the occurrence of a death). Preterm neonates referred to another institutions, discharged, and alive at the end of the follow-up period were considered censored.

Data quality control

A pretest was done on 5% of the sample size. Training was given for data collectors and supervisors about data collection tools and procedure. Supervisors closely monitored data collection process. The principal investigator and supervisors checked the completeness of each abstraction sheet on a daily base. Two data clerks entered data and consistency of the entered data was cross-checked.

Statistical analysis

Data were entered, coded, cleaned and checked by Epi Data version 4.2.0.0 and analysis was done using STATA Version 14 statistical software. Descriptive statistics of included variables had been presented by tables and pie chart. Kaplan Meier curves were used to estimate survival time and to depict the pattern of death. The log-rank test was used to look at statistical differences between categories of variables. Bivariable analysis of the individual variables with preterm neonatal survival mortality was carried out to include in the Cox-proportional hazard model. P-value <0.2 in the log-rank test was entered into multivariable analysis. Then, the proportional assumption test had been checked using the Schoenfeld residual test. The assumption met with a p-value in the global test (P= 0.35). Adjusted Hazard ratio (AHR) with 95% confidence interval (CI) had been generated from multivariable analysis and a statistical significance had been accepted at $p\text{-value} \leq 0.05$.

Ethical considerations

Ethical clearance was obtained from Haramaya University, College of Health and Medical Sciences, Institutional Health Research Ethics Review Committee. Then, official letter had been written to Debretabor General Hospital for permission and support. The neonate's name and medical record identification information had not been collected and confidentiality was maintained. All data collected from the chart were kept strictly confidential and used only for the study purpose.

Results

Socio-demographic characteristics of the mother and neonates

A total of six hundred fourteen preterm neonates were admitted during the study period. Of these, five hundred eighty-nine charts were reviewed and only five hundred thirty-five study participants were involved with a response rate of 90.8%. The mean (\pm SD) age of the mother was 27.56 (\pm 6.54) years. Fort-

seven percent (47.3%) of mothers were in the age group of 20-29 years. The majority (72.71%) of them were from the rural area. Most (92.5%) of the neonates were admitted within the first day of birth. More than half (51.6%) were males (Table 1).

Obstetrics/gynecological characteristics

Seventy-seven percent (77.1%) of mothers had ante-natal care (ANC) follow-up. Out of which, 15.1% had four and above ANC contact and 34.9% of mothers had encountered maternal complication during the current pregnancy, labor and delivery, such as pregnancy induced hypertension (PIH)/preeclampsia/eclampsia, premature rupture of membrane (PROM), antepartum hemorrhage (APH), and chorioamnionitis. Majority (60.2%) of preterm neonate was born at Debretabor General Hospital (Table 2).

Neonatal characteristics

Sixty-nine percent (69.2%) of neonates were born with the gestational age of greater than or equal to thirty-two weeks. Sixty-eight percent (67.8%) of preterm neonate were low birth weight and 90.1% were hypothermic during admission time. From all neonates, 86.2% of preterm neonates had neonatal complications during admissions, such as sepsis, respiratory distress syndrome (RDS), PNA, and meconium aspiration syndrome (MAS) (Table 3).

Kaplan-Meier survival curve

Five hundred thirty-five participants were followed for a different time ranging from one day to 40 days, which provided 4985.86 days total time at risk. The median survival time was 27 days. Preterm neonatal survival probability by the end of follow-up was 0.50 (95%CI: 0.42, 0.58). The graph shows the proportion of neonates who survived during the follow-up time (Figure 2). Of all study participants, 31.2 % (95% CI: 27.3, 35.1) preterm neonates were died; 326 (60.9%) improved, 7 (1.3%) referred to other institution for further management, absconded 1 (0.2%), and left against medical advice were 34 (6.4%).

Predictors of mortality of preterm neonate

In multivariable Cox regression analysis, gestational age <32 weeks, male sex, mothers diagnosed with preeclampsia/eclampsia, very extreme birth weight, and neonatal respiratory distress syndrome were found to be significant predictors.

Preterm neonates who were born with a gestational age of less than 32 weeks of gestation had 1.74 (95%CI: 1.24, 2.46) times more hazard of death than neonate born with a gestational age of greater than or equal to 32 weeks of gestation. Preterm neonates born from preeclampsia/eclampsia mother were 1.95 (95%CI: 1.13, 3.36) times more hazard of death than preterm neonate born from non-preeclampsia/eclampsia mothers. Male preterm neonates were 1.38 (95%CI: 1.01, 1.90) times more hazard of death than female preterm neonates. Extremely low birth weight preterm neonates were 2.94 (95%CI: 1.05, 8.24) times more hazard of death than normal birth weight preterm neonates. A preterm

neonate who had respiratory distress syndrome was 1.70 (95%CI: 1.20, 2.41) times more hazard of death as compared to their counter parts (Table 4).

Discussion

Preterm mortality is the major causes of neonatal mortality in low and middle-income countries (25). Similarly, this study revealed that the proportion of preterm mortality was found to be 31.2 % (95% CI: 27.3, 35.1). This finding is comparable with studies conducted in Addis Ababa, Ethiopia 30.7% (23), Jimma Ethiopia 34.9% (22) and Nigeria 27.7% (26). Though low cost interventions are critical to reduce neonatal mortality, the problem is still high as evidenced from these studies. This similarity might be due to in developing world, the services provided for maternal and neonatal health are not sufficient. Social exclusion, caste, maternal literacy, lack of basic prenatal, natal, and postnatal care might be the problem in developing countries.

On the other hand, the finding of the current study is higher than studies conducted in Iran 9.1% (27) and China 8.8% (28). This difference might be due to the high quality of service provided in Iran and China. Studies in Iran and China were conducted in the hospital with level III NICU while this study was conducted in General hospital with level II NICU. Moreover, the low proportion of mortality Iran and China is due to infants born preterm have received improved care during pre-pregnancy, antenatal, intrapartum, and post-natal periods (29, 30). Besides, preventive and control measures of infections in developed countries are strictly implemented.

Predictors of the high mortality of preterm neonate are also identified in the current study. Accordingly, gestational age of less than 32 weeks, male neonate, neonate born from preeclampsia/eclampsia women, very extreme low birth weight neonate, and neonate with respiratory distress syndrome were identified predictors of mortality of preterm neonate.

This study showed that preterm neonates who were born with a gestational age of less than 32 weeks of gestation were more hazard of death than neonate born with a gestational age of greater than or equal to 32 weeks of gestation. This finding was consistent with studies conducted in Jimma, Ethiopia (22) and Nigeria (26). The possible explanation could be the effect of gestational age was partially explained by the heterogeneity of mechanisms leading to physiological immaturity and biological determinants of preterm birth acting through gestational age. Moreover, placental ischemia and other hypoxia exacerbated the effect of gestational age to poor outcomes (31, 32). The frequency of preterm neonatal morbidities decreased above 32 weeks of gestation and each additional week for gestation has survival benefit while reducing the length of hospitalization (33).

Preterm neonates born from preeclampsia/eclampsia mother were more hazard of death than preterm neonate born from non-preeclampsia/eclampsia mothers. This finding is agreeing with studies conducted in Netherland (34) and Australia (35). The reason could be preeclampsia/eclampsia increases the rate of born with small for gestational age and further it increases neonatal complications (34).

Furthermore, preeclampsia could impair fetal growth through reducing uteroplacental perfusion (36), which leads to neonatal morbidity (37) and neonatal mortality as a result. Induction of non-spontaneous labour, high oxidative stress, and free radicals from preeclampsia/eclampsia mother might lead to neonatal mortality.

Male preterm neonates were more hazard of death than female preterm neonates. This finding approved results from previous study done in Ethiopia, Tanzania, Pennsylvania, Switzerland, England, California, China (23, 28, 35, 38-40). This could high preterm birth, operative delivery, neonatal death, congenital anomaly, increased rate of respiratory morbidity (41, 42), such as respiratory distress syndrome, bronchopulmonary dysplasia, intra-ventricular hemorrhage, and retinopathy of prematurity (43, 44) are highly observed in male preterm neonates.

Extremely low birth weight preterm neonates were more hazard of death than normal birth weight preterm neonates. This study is consistent with studies conducted in South Africa, Malawi, and China (28, 45, 46). This could be due to extremely low birth weight babies are more likely to born prematurely and suffer from infections (47). In extremely low birth weight neonate, immaturity of physiological and anatomical structures, principally lung deficient in surfactant, lack of subcutaneous tissue, large surface area to body mass ratio and fragile capillaries in their brain may lead to have more medical problems.

In the present study, preterm neonates who had respiratory distress syndrome were more hazard of death than preterm neonates without respiratory distress syndrome. This study is consistent with the study conducted in Gondar and Jimma Ethiopia (22, 48). Tracheoesophageal fistula, bronchopulmonary sequestration, and bronchogenetic cysts might be the underlined causes of respiratory distress syndrome. Failure to diagnose and treat these underlined causes of respiratory distress syndrome could leads to short-and long-term complications including death of neonates.

The finding of the current study will enable health policy and/or decision makers to establish or strengthening already established programs that aimed at reducing neonatal morbidity and mortality. Though a very limitation of resources observed in the study settings, many of contributing factors for neonatal mortality can be preventable. Priority and special attention has to be given for the identified independent predictors to prevent neonatal mortality.

Limitation of the study

Since the study was retrospective follow-up and depends on medical records not designed for research which is prone to data incompleteness. Mode of labour (spontaneous or induced) and level of preeclampsia were not recorded. The time-covariate variables were not handled because the data were collected at baseline.

Conclusions

The preterm neonatal mortality is high. Gestational age, sex of neonates, preeclampsia /eclampsia, birth weight, and respiratory distress syndrome were important predictors of mortality in preterm neonates.

Therefore, a great focus should be given towards addressing universal antenatal care and health institution delivery with much emphasis on the preterm neonate. In addition, managing maternal complications, low birth weight, prematurity and ensuring a continuum of care to decrease mortality of preterm neonates.

List Of Abbreviations:

AHR: Adjusted Hazard Ratio; ANC: Antenatal Care; APH: Antepartum Hemorrhage; CI: Confidence Interval; CHR: Crude Hazard Ratio; NICU: Neonatal Intensive Care Unit; PROM: premature rupture of membrane; PNA: perinatal asphyxia; RDS: Respiratory Distress Syndrome; SDG: Sustainable development goal; WHO: World Health Organization

Declarations

Ethical approval and consent to participate: Ethical clearance was obtained from Haramaya University, College of Health and Medical Sciences, Institutional Health Research Ethics Review Committee.

Consent to publication: Not applicable

Availability of data and materials: Data will be available upon request from the corresponding author.

Competing interests: The authors declare that they have no competing interests.

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Authors' Contribution: BM worked on designing the study, training the data collectors, supervising the data collectors, interpreting the result, preparing the manuscript. BM1, BM, NA, AY, and AE analyzed and interpreted the result and wrote the manuscript. All authors involved starting from design, data interpretation, to critically review the manuscript.

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Tables

Table 1: Socio-demographic characteristics of mothers and preterm Neonates at Debretabor General Hospital NICU, Northwest Ethiopia, from January 1, 2014 -December 30, 2017. (n=535)

Characteristics	Frequency	Percentage (%)
Maternal age		
<20 years	86	16.1
20-29 years	253	47.3
30-39 years	176	32.9
>40 years	20	3.7
Residence		
Urban	146	27.3
Rural	389	72.7
Sex of neonate		
Male	276	51.6
Female	259	48.4
Neonatal age at admission		
0-1days	495	92.5
1-7days	30	5.6
>7days	10	1.9

Table 2:-Obstetric/gynecological characteristics of mothers who had Preterm neonatal admission at Debretabor General Hospital NICU, Northwest Ethiopia, from January 1, 2014 - December 30, 2017(n=535)

Variables	Outcome		Total No. (%)
	Died No. (%)	Censored No. (%)	
Antenatal care visit			
Yes	125(23.7)	287(53.4)	412(77.1)
No	42(7.8)	81(15.1)	123(22.9)
Number of ANC visit (n=412)			
≥4 visit	9(2.2)	53(12.9)	62(15.1)
<4visit	116(28.2)	234(56.7)	350(84.9)
Gravidity			
1	57(10.7)	128(23.9)	185(34.6)
2-4	73(13.6)	139(26.0)	212(39.6)
≥ 5	37(6.9)	101(18.8)	138(25.7)
Parity			
First time pregnant	63(11.8)	148(27.7)	211(39.3)
1-4 births	81(15.1)	161(30.1)	242(45.2)
≥ 5 births	23(4.3)	59(11.0)	82(15.3)
Antenatal corticosteroid(n=502)			
Yes	27(5.3)	31(6.2)	58(11.5)
No	128(23.3)	316(63.0)	444(88.5)
Place of birth			
Inborn	97(18.1)	225(42.1)	322 (60.2)
Out born	70(13.1)	143(26.7)	213(39.8)
Pregnancy status			
Single	127(23.7)	316(59.1)	443(82.8)
Twin	39(7.2)	49(9.2)	88(16.4)
Triplet	1(0.2)	3(0.6)	4(0.8)
Maternal complication			
Yes	76(7.2)	111(20.7)	187(34.9)
No	91(17.0)	257(48.0)	348(65.0)
Maternal complication lists			
Antepartum hemorrhage	12(2.24)	17(3.2)	29(5.42)

Chorioamnionitis	2(0.4)	6(1.1)	8(1.5)
Preeclampsia/eclampsia	40(7.5)	44(8.2)	84(15.7)
Cephalopelvic disproportion	2(0.4)	10(1.87)	12(2.27)
Premature rupture of membrane	27(5.1)	32(6.0)	59(11.1)
Others*	5(0.01)	10(1.9)	15(1.9)

Others: Cord prolapse, Nonreassurance fetal heart pattern, oligohydramnios, polyhydramnios*

Table 3:-Neonatal characteristics of mothers who had Preterm neonatal admission at Debretabor General Hospital NICU, Northwest Ethiopia from January 1, 2014 - December 30, 2017 (n=535)

Variable	Outcome		Total No. (%)
	Died No. (%)	Censored No. (%)	
Maternal Age			
Very preterm	89(16.6)	76(14.2)	165(30.8)
Moderate to late term	78(14.6)	292(54.6)	370(69.2)
Birth Weight			
Extreme low birth weight	18(3.4)	6(1.1)	24(4.4)
Very low birth weight	62(11.8)	49(9.3)	111(21.0)
Low birth weight	80(15.2)	278(52.7)	358(67.8)
Normal birth weight	5(1.0)	31(5.9)	36(6.8)
Temperature at Admission			
Hypothermia	158(29.6)	324(60.5)	482(90.1)
Normal	6(1.1)	32(6.0)	38(7.1)
Hyperthermia	3(0.6)	12(2.2)	15(2.8)
Respiratory Status			
First	59(11.0)	132(24.7)	191(35.7)
Second and above	108(20.2)	236(44.1)	535 (64.3)
APAR Score-5			
≤3	47(12.5)	45(12.0)	92(24.5)
≥4	66(17.5)	218(58.0)	284(75.5)

breastfeeding	47(8.8)	287(53.6)	334(62.4)
formula feeding	3(0.6)	19(3.6)	22(4.2)
Nothing per oral	117(21.9)	62(11.5)	179(33.4)
neonatal complication at admission			
Yes	160(30.0)	301(56.3)	461(86.2)
No	7(1.3)	67(12.5)	74(13.8)
neonatal complication list			
respiratory distress	104(19.4)	108(20.2)	212(39.6)
seizure			
convulsion	5(0.9)	15(2.8)	20(3.7)
respiration syndrome			
apnea	113(21.1)	233(43.8)	346(64.7)
neonatal asphyxia	51(9.5)	46(8.6)	97(18.1)
anemia	7(1.3)	6(1.1)	13(2.4)
jaundice	4(0.75)	9(1.68)	13(2.43)
congenital	7(1.3)	11(2.10)	18(3.4)
others**	18(3.4)	29(5.4)	47(8.7)

Others**: Hypoglycemia, necrotizing enter colitis, lower leg deformity, Meningitis, Neonatal seizure, Ophthalmic neon trim, Transient tachypnea, Cranocentesis

Table 4: Cox-proportional hazard model of predictors of mortality of preterm neonates admitted in NICU, Debreabor General Hospital, from January 1, 2014-December 30, 2017(n=535)

Variable	Died No. (%)	Censored No. (%)	CHR (95%CI)	AHR (95%CI)
Gestational age				
<32wks	89(16.6)	76(14.2)	2.57(1.89,3.49)	1.74(1.24,2.46)*
≥32wks	78(14.6)	292(54.6)	1	1
Antenatal corticosteroid				
Yes	27(5.4)	31(6.2)	1.58(1.05,2.40)	1.15(0.73,1.83)
No	128(25.8)	316(62.9)	1	1
Maternal complication				
Yes	76(7.2)	111(20.7)	1.58(1.167,2.15)	0.88(0.52,1.47)
No	91(17.0)	257(48.0)	1	1
Preeclampsia/Eclampsia				
Yes	40(7.5)	44(8.2)	1.70(1.19,2.4)	1.95(1.13,3.36)*
No	127(23.7)	324(60.6)	1	1
Premature rupture of membrane				
Yes	27(5.0)	32(6.0)	1.63(1.08,2.5)	1.69(0.97,2.97)
No	140(26.1)	336(62.8)	1	1
Sex				
Male	98(18.3)	178(33.3)	1.49(1.09,2.0)	1.38(1.01,1.90) *
Female	69(12.9)	190(35.5)	1	1
Birth Weight				
Extremely LBW	18(3.4)	6(1.1)	5.33(1.9,14.4)	2.94(1.05,8.24) *
Very LBW	62(11.8)	49(9.3)	2.90(1.16,7.3)	1.90(0.74,4.89)
Low birth weight	80(15.2)	278(52.7)	0.97(0.47,2.9)	1.03(0.41,2.59)
	5(1.0)	31(5.9)	1	1

Normal birth weight				
APGAR Score-5				
	47(12.5)	45(12.0)	2.15(1.5,3.01)	1.09(0.64,1.87)
<7	66(17.5)	218(58.0)	1	1
≥7				
Neonatal health problems at admission				
Yes	160(29.9)	301(56.3)	3.42(1.60,7.3)	1.62(0.73,3.59)
No	7(1.3)	67(12.5)	1	1
Respiratory distress syndrome				
Yes	104(19.4)	108(20.2)	2.50(1.83,3.4)	1.70(1.20,2.41)*
No	63(11.8)	260(48.6)	1	1
Perinatal asphyxia				
Yes	51(9.5)	46(8.6)	2.28(1.64,3.2)	1.56(0.92,2.64)
No	116(21.7)	322(60.2)	1	1

*Significant variable

Figures

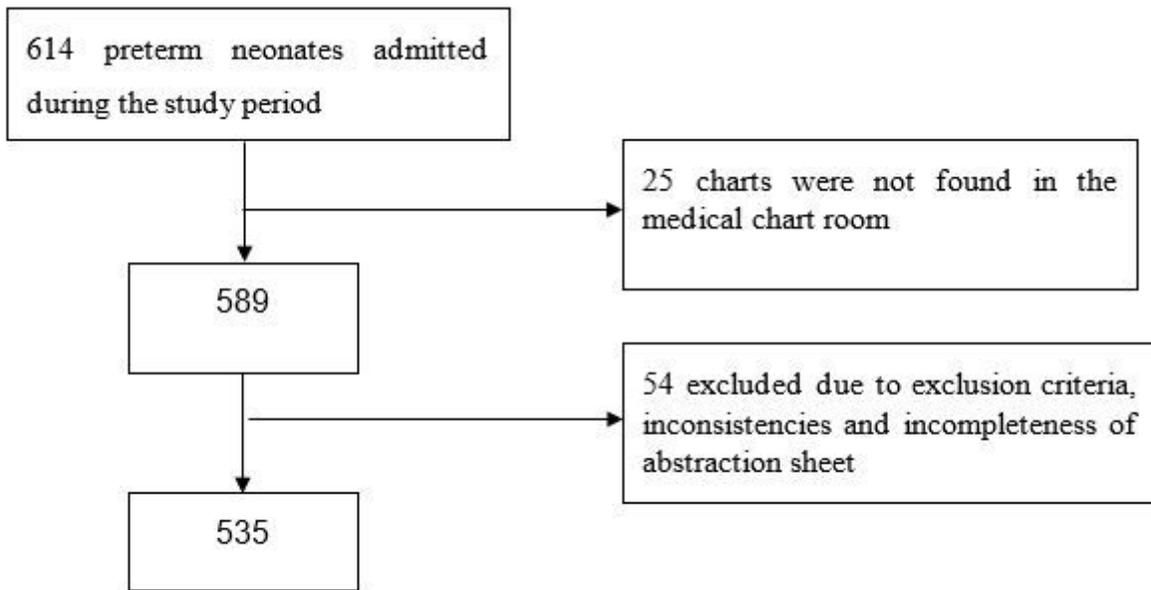


Figure 1

Study participant selection process in Northwest Ethiopia from January 1, 2014-December 30, 2017

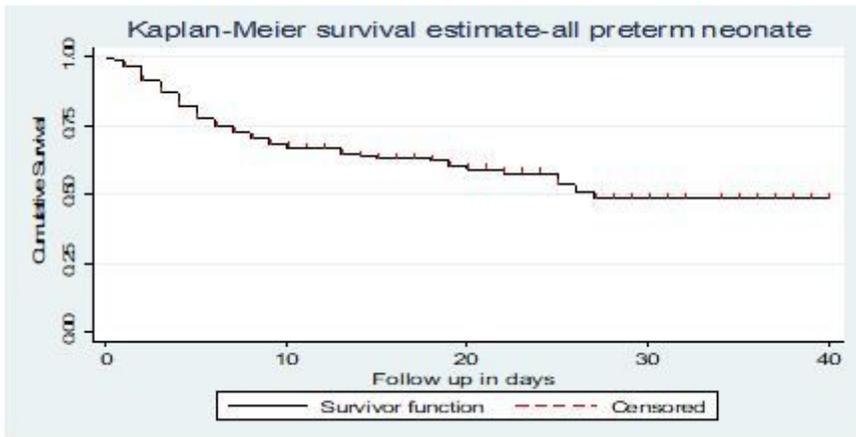


Figure 2

Summary of Kaplan-Meier estimate of survival probability among preterm neonate admitted at Debretabor General Hospital NICU, Northwest Ethiopia, from January 1, 2014-December 30, 2017