**PREDICTORS OF PRETERM NEONATAL MORTALITY IN HAWASSA UNIVERSITY COMPREHENSIVE SPECIALIZED HOSPITAL NEONATAL INTENSIVE CARE UNIT, SOUTHERN ETHIOPIA: A RETROSPECTIVE COHORT STUDY**

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**ABSTRACT**

**BACKGROUND:** The issue of preterm neonate has paramount significance for achieving aims to end all preventable deaths of newborns and children below 5 years by 2030. Globally more than 1 million preterm neonates died out of 15 million babies born preterm every year and the problem is more significant in developing countries like Ethiopia.

OBJECTIVE: The aim of this study was to assess survival status and predictors of mortality among preterm neonates admitted to Neonatal Intensive Care Unit of Hawassa University Comprehensive Specialized Hospital, Hawassa, Ethiopia, 2021

**METHODS:** An Institutional based retrospective cohort study was conducted in Hawassa University Comprehensive Specialized Hospital from May 9–30, 2021 after getting ethical clearance from Institutional Review Board of Hawassa University College of Medicine and Health Sciences. The study population conducted among all preterm neonates admitted to neonatal intensive care units (NICU) at Hawassa University Comprehensive Specialized Hospital (HUCSH) from May 9, 2019 to April 22, 2021. After reviewing different literatures and neonatal national guideline, the data abstraction tool was developed and utilized after making some modification. After collection, data was entered into epidata software version 3.1 and exported to STATA for data cleaning and further analysis. The level of significance was set at p<0.05 with the corresponding confidence intervals at 95% confidence. Cox proportional hazard ratio was used to assess the association between dependent variable and independent variables.

**RESULTS:** The magnitude of preterm neonatal mortality was 33.3%. The final model revealed that early initiation of breast milk (AHR: 0.43 (95% CI: 0.29, 0.62), Early neonatal sepsis at admission (AHR: 1.34(95% CI: 1.003, 1.79), 5th minute Apgar score of less than 7 (AHR: 1.73(95% CI: 1.17, 2.55), perinatal Asphyxia (AHR: 2.25(95% CI: 1.67, 3.02) and recent multiple pregnancy (AHR: 1.66(1.22, 2.26) were significantly associated predictors of preterm neonatal mortality.

**CONCLUSION:** In this study, a total of 241 (33.3%) preterm neonates were died during the follow up/study period**.**  The magnitude of death was found to be high in the first 24 hours of life and all preterm neonates with birth weight of below 1000gm were not survived. Multivariate Cox proportional hazard model showed that the major predictors of the death of preterm neonates admitted to Neonatal Intensive Care Unit were found to be initiations of early breast feeding, having APGAR score of less than 7 in the 5th minutes, prenatal asphyxia, early neonatal sepsis and recent multiple pregnancy.

**KEY WORDS**:Preterm neonatal mortality, Hawassa, Sidama Ethiopia

# **.Introduction**

Preterm neonatal mortality is the death of preterm neonates within the first month (28 days) of life. Those preterm neonates born before reaching maturity are fragile, small, weighing less than full term infants and face a variety of physiologic handicaps which predispose them to many short term and long term complications like respiratory problems, sepsis, seizures, feeding difficulty, altered body temperature and hypoglycemia([1](#_ENREF_1), [2](#_ENREF_2)). Similarly, Antepartum hemorrhage, preeclampsia, eclampsia, multiple pregnancies, premature rupture of membrane, smoking or substance use during pregnancy are the most common factors associated with preterm mortality([3](#_ENREF_3)). Furthermore, those preterm neonates who survive often face a lifetime ill-health including disability, learning difficulties, visual and hearing problems, psychological crises, financial hardships and economic burden for the families and broader society due long term complex health care needs([4](#_ENREF_4), [5](#_ENREF_5)).

Mortality due to preterm neonatal birth complications is supreme; accounting for more than 1 million out of 15 million babies born preterm every year worldwide([5](#_ENREF_5)). This complication is a significant public health problem across the world because of associated morbidity and mortality ([1](#_ENREF_1), [4](#_ENREF_4)). It is a single, direct leading cause of death, accounting for about 18% of all deaths in under five children and the first leading cause of neonatal mortality worldwide ([5](#_ENREF_5), [6](#_ENREF_6)). It accounts for 35% of all neonatal deaths worldwide([4](#_ENREF_4)). Findings in India and Iran indicated lower mortality rates (18.7% and 12% respectively) among preterm infants compared to America and European Countries ([3](#_ENREF_3), [7](#_ENREF_7)). One third of all preterm neonatal deaths occur within the first day after birth, and close to three quarters preterm neonatal death occur within the first week of life worldwide ([2](#_ENREF_2), [4](#_ENREF_4), [5](#_ENREF_5), [9](#_ENREF_9)). Seventy-three percent of deaths occurred within the first week of life in Nigeria([10](#_ENREF_10)). According to the findings of other study conducted in Ethiopia, among preterm neonates admitted to a NICU, 11.4% died in the first 24 hours and 85.27% died in the first 7 days([11](#_ENREF_11)).

Different factors play significant role in preterm neonatal mortality even though the cause is not clear. The most common factors associated with increased risk of preterm neonatal mortality include hypothermia, respiratory distress, Sepsis, low gestational age, low birth weight, being female, feeding problem of the neonate, not received ANC, very low birth weight and length of time on ventilator([1](#_ENREF_1), [11](#_ENREF_11)). Moreover, male sex, congenital anomalies, perinatal asphyxia(PNA), jaundice, hypoglycemia, and timely initiation of breastfeeding upon birth were reported as factors of preterm neonatal death ([11](#_ENREF_11), [12](#_ENREF_12)). The survival rates of preterm babies mainly depends on the economic status of the country they born and the capacity of the health system to respond to their needs ([4](#_ENREF_4)). Preterm neonate born in sub-Saharan Africa is 10 times more likely to die than preterm neonate born in any developed countries ([5](#_ENREF_5), [13](#_ENREF_13)). Furthermore, specifically preterm neonate born in sub-Saharan Africa was 12 times more likely to die than a preterm babies born in Australia and New Zealand ([5](#_ENREF_5), [14](#_ENREF_14)). Additionally, over 90% of extremely preterm babies born in low income countries die within the first few days of life; however less than 10% of extremely preterm babies die in high income countries ([9](#_ENREF_9), [13](#_ENREF_13)). In low income settings half of the preterm babies born at or above 32 weeks were die due to a lack of feasible, cost-effective care, such as warmth, breastfeeding support, and basic care for infections and breathing difficulties ([10](#_ENREF_10), [14](#_ENREF_14)). Although, in the middle income setting suboptimal use of technology causing an increased burden of disability among preterm babies who survive the neonatal period ([13](#_ENREF_13)). In east Africa for instance, 94.6% of preterm neonates born at or after 34 weeks of gestation survive while only 52.6% of those preterm neonates born before 34 weeks survive ([15](#_ENREF_15)). Fifty five percent (55.2%) of preterm neonate survival was achieved at or after 31 weeks of gestation([12](#_ENREF_12)).

World Health Organization sets a target of 50% reduction in preterm deaths by 2025 in countries with a neonatal mortality rate above 5 per 1,000 live births([9](#_ENREF_9)). Similarly reducing the burden of preterm mortality has dominant significance for achieving United Nations Sustainable Development Goal 3 target #3.2 ([16](#_ENREF_16)). More than three-quarter of these preterm neonatal deaths can be averted by feasible and cost-effective interventions like stabilization, prevention and early treatment of infection, preventing hypothermia as well as early introduction of breast milk and further intensive neonatal care ([17](#_ENREF_17)).

Despite varies efforts, mortality due to complication of preterm births is still not reduced as expected and as a result prematurity is first cause of neonatal mortality and the fourth cause of under-five mortality in the country([18](#_ENREF_18), [19](#_ENREF_19)). The purpose of this study was to fill the gap on knowledge of preterm neonatal mortality, lay fertile ground for further studies and indicate other interventional measures. The findings of this study will be helpful especially in southern Ethiopia where there is limited evidence on the status of preterm neonatal mortality and associated factors.

# **METHODS**

## **Study setting, period and population**

Retrospective cohort study was conducted in Hawassa university comprehensive specialized hospital to identify the predictors of preterm mortalities. This Hospital is found in Hawassa City which is 275 Kilometer far to the south from Addis Ababa, the capital city of Ethiopia. It offers both diagnostic and treatment services including delivery and Neonatal Intensive care service for more than 12 million populations per year. It had about 450 beds for medical, gynecological and obstetrics, surgical, pediatrics, emergency, orthopedic and outpatient department (OPD) services. In average, about 4,500 deliveries attended in Hawassa University Comprehensive Specialized delivery room. The Neonatal Intensive Care Unit of the hospital had about 1000-1500 admissions of neonates among which 350-400 were preterm neonates with estimated annual neonatal death of more than 150. The study included all preterm neonates admitted to neonatal intensive care unit of Hawassa University Comprehensive Specialized Hospital from May 9, 2019 to April 22, 2021. Preterm neonate’s charts with incomplete records or missing important variables (baseline characteristics, outcome of preterm neonates and duration of stay) or whose card is not available in the card room at the time of data collection were excluded

**Data Collection Procedure and period**

Data extraction/collection tool was developed after reviewing different literature. Finally, we adopted questionnaire from previous studies conducted in Gondar and Felegahiwot Specialized Hospitals, Amhara region, Ethiopia, 2020. After adaption, pretest was done on 5% of the participants at the same hospital to test for clarity and consistency. The data collectors were professional nurses and were trained in detail and assigned for data collection process. Data collection was conducted from May 9 -30, 2021. The starting point for follow-up time was the first date of admission to NICU and the endpoint was date of death, censored (i.e. date of discharge or alive at the end of the study) until the last neonatal period.

Preterm neonatal chart number was taken from NICU registration logbook. Before collecting the data, the chart was reviewed (both for baseline and follow up records). The record of all study participants was selected according to the eligibility criteria and reviewed by four BSc nurses. The available information on the chart of neonate was extracted by using data abstraction format. The survival status of study participants was obtained from the charts. Death was confirmed by reviewing the medical record and death certificate of the preterm neonates.

Completed checklists were checked on daily bases for completeness and clarity through close supervision by principal investigator. Data collectors reached source documents after getting permission from the concerned bodies of the hospital.

### **Predictor of Preterm Death**

Dependent variable for this study was time to death of preterm neonates. Outcome assessment was based on the data collected from the chart of the mother of each preterm neonate who were eligible for the study.

The independent variables were Sociodemographic characteristics (Age of preterm neonate, gestational age, sex of neonate and birth weight of preterm neonate, age of the mother, place of residence, place of delivery, length of stay), Maternal obstetric related factors (PROM, preeclampsia, early breast feeding initiation, ANC follow up, gravidity, Parity, mode of delivery and twin pregnancies), Maternal medical related factors (DM, HIV/AIDS, anemia, infection, Hypertension), Neonatal related factors (Respiratory distress syndrome, sepsis, jaundice, hypothermia, Apgar score and Prenatal asphyxia). Those Potential risk factors for time to death were selected based on reviewing previous literatures. Then, each variable was dichotomized into and coded by giving 0 to the group hypothesized as having a lower risk and 1 to the group hypothesized as having a higher risk.

## **Data Quality Control**

Data quality was assured by using data abstraction format that was adapted from other studies ([15](#_ENREF_15), [17](#_ENREF_17)). Pretest was done on 5% (36 premature neonate’s card) of the study participants one week prior to the actual study to check consistency of recorded variables on the patient's medical record. This pretest was done in the same hospital by using charts of preterm neonates that has Modification was made after pretest accordingly. The data was collected by four experienced BSc nurses after one day training about the data abstraction tool and data collection process for both data collectors and supervisor. During the data collection time, intensive supervision was done by the principal investigator and supervisor during the whole period of data collection. Daily evaluation of the data for completeness and encountered difficulties on the time of data collection was attended accordingly.

All the collected data was checked for its completeness and consistency during the data collection, storage and analysis process. Consistency was daily examined through random selection of cards by the principal investigator.

## **Statistical Analysis**

Data were entered into Epi-Data version 3.1 and then exported and analyzed using STATA statistical software version 14. Descriptive exploratory analysis was run to assess missing values and presence of outliers. The mean, standard deviation, median, and percentages were used to describe the baseline demographics and follow up characteristics of preterm neonates. Before analysis, data were cleaned, edited and coded. Any errors were identified and corrected after the review of the original data using the code numbers. Depending on the distribution of data, descriptive statistics such as Mean with standard deviation or median with Inter Quartile Range was used for continuous and frequency distribution was used for categorical data.

The outcome of each participant was dichotomized into censored or death. Incidence rate was calculated. Survival status of preterm neonates were calculated as the time between the dates of delivery to the date of death, censored or the end of study. Kaplan Meir was used to estimate mean survival time and cumulative probability of survival and log-rank tests was used to compare group’s survival curves after admission to NICU.

Before running the Cox Proportional Hazard regression model multi-collinearity test was carried to see the correlation between the independent variables. Cox Snell residuals were used to test goodness-of fit of the model. The Cox-proportional hazard regression model assumption was also checked using Schoenfeld residual test and variables having P-value >0.05 will be considered as fulfilling the assumption. Bivariate Cox-proportional hazards regression model was fitted for each explanatory variables to identify the predictors.

Those variables with p-value ≤ 0.25 in the bivariate analysis were fitted to the multivariable cox-proportional hazards regression model with 95% confidence interval and finally P-value < 0.05 was considered as statistically significant. The crude and adjusted hazard ratios together with their corresponding 95% confidence intervals were interpreted accordingly

## **Ethical Considerations**

Ethical clearance was obtained from institutional review board of Hawassa University, College of medicine and health science. Then letters of cooperation was written to concerned bodies of Hawassa University Comprehensive Specialized Hospital. Permission was obtained from clinical director and subsequent department heads of the hospital. Following these, searching and obtaining of the selected sample medical records were done with the assigned data collectors. Care was taken from disclosing confidentiality of patient’s records. All collected data was coded and locked in a separate room before entered into the computer and names were not included in the data collection format.

**Operational Definitions**

**Preterm birth**: live birth before 37 completed weeks of gestational age. Preterm neonatal Mortality: The death of preterm neonates with gestational age **Censored:** Premature neonate still alive at the end of the study or discharged before end of follow up including discharged to home, discharged against medical advice or referred out to other health institutions without knowing their outcome. **Follow up time**: the duration from admission until either an event or censorship occurs. **Event**: Death of preterm neonate within 28 days of birth confirmed by observing death certificate or medical records. **Early breast feeding initiation**: Initiation of breast milk with two hours of birth. **Medical disorders in mother**: Any history of medical diagnosis in the mother as it has been registered on the neonate’s medical records. **Medical disorders in the neonate**: Any recorded medical diagnosis for the preterm neonates on their medical records. **Perinatal Asphyxia**: Lack of oxygen to organ systems due to a hypoxic or ischemic insult that occurs within close temporal proximity to labor and delivery. **Hypothermia**: An abnormal thermal state in which the newborn's body temperature drops below 36.5 °C (97.7 °F). **Hypoglycemia**: a plasma glucose level of less than 30 mg/dL (1.65 mmol/L) in the first 24 hours of life and less than 45 mg/dL (2.5 mmol/L) thereafter, registered.

## **Dissemination of the Result**

The result of the study was submitted and presented to Hawassa University, College of Medicine and Health Science, School of Public Health. Similarly, it was submitted to Hawassa University Comprehensive Specialized Hospital where the study was conducted. The study findings will be presented in locally and internationally held workshops, seminars, conferences and various meetings. It will also be published in internationally recognized journal.

# **Results**

**Sociodemographic Characteristics of Preterm neonates and their Mothers**

Among 723 preterm neonates, 375 (51.87%) were females and three fifth 438 (60.7%) of those study participants resides in Urban area. The mean length of hospital stay was 10.4 (95% CI: 9.8, 10.9) and the median was 11 (95% CI: 9.2, 12.81). The mean gestational age of the preterm neonates was 32.76±2.26 SD weeks while their mean age at admission was 1.7 ± 2.1 SD days. Most of the preterm neonates 558 (77.18%) included in the study were belong to the gestational age group of 32-36 weeks. About four fifth 645(89.2%) of the preterm neonates had first minute Apgar score of less than seven and two third 447(61.8%) of them had fifth minute Apgar score of less than seven. Mothers with age equal or below 20 accounts 12.2% and around 61% of them were from urban area (Table 1)

**Obstetric and Medical Related Characteristics of Mother’s**

Of the 779 preterm neonate charts reviewed, 723 (92.8%) records were met enrollment criteria and included, but 56 (7.2%) charts were excluded because of their incompleteness. More than half 397(54.9%) of the mothers had delivered at HU-CSH and only ten (1.4%) of the participants gave birth at home which accounts only 20% of the preterm neonatal death. Most of the mothers 684(94.6%) had ANC follow up. More than half 406 (56.2%) of study participants were delivered through spontaneous vaginal delivery and 305 (42.2%) of them with caesarian section. The mean age of the mothers was 27±5.138 SD years. Majorities of the mothers 466(64.5%) had parity less than or equal to two and about half 354(49%) of the mothers had gravidity of less than or equal to two. Around one third 21(37.8%) of the mothers were anemic and only 7(1%) had kidney problem (Table 2)

## **Preterm Neonatal Related problems**

Of the total study participants, Preterm neonates with birth weight <=1000gm were 20(2.8%). Among the preterm neonates with weight between 1000-1500gm; 82(50.9%) were died. Majority of study participants 645 (89.2%) and 447(61.8 %) of them were with 1st and 5th minute Apgar score of <7 respectively. About 304(37.8%) of preterm neonates initiated breast feeding. From the total study participants 107(14.8%), 236(32.6%) and 418(57.8%) had prenatal asphyxia, neonatal sepsis and hypothermia respectively (Table 3)

**Proportion of Preterm Neonatal death**

The finding of this study showed that 241 (33.3%) preterm neonates were died among which females accounts the majorities 126(52.28%). About three fifth 144 (59.75%) of the overall death were occurred within 2-7 days of their birth. All Preterm neonates with birth weight <=1000gm 20(2.8%) were died and among participants with birth weight between 1000-1500gm; about half 82(50.9%) were died. The rest 482 (66.7%) preterm neonates included in the study were censored (Table 1)

**Incidence of death among Preterm Neonates**

Cohorts of 723 premature neonates were admitted to Neonatal Intensive Care Unit and were followed from admission to 28 days of age. The total risk time contributed by study participants was 7501 person-days. The overall incidence rate was 32.12 (95% CI: 28.31, 36.45) deaths per 1000 preterm neonate-days of observation. The median hospital stay was 11 (95% CI: 9.2, 12.81). Among the censored preterm neonates the majority, 393 (81.5%) were discharged home by cure, 72 (14.9%) of them were discharged against medical advice, 6(1.3%) of them were referred and 11 (2.3%) of them were disappeared. All preterm neonates with extremely low birth weight (<1000gm); were died. Those preterm neonates had hypertension (90%), hypothermia (85%) and respiratory distress (45%).

**Overall Survival Function**

The minimum follow up time was 1 day and the maximum was 28 days with overall median length of hospital stay of 11 (95% CI: 9.2, 12.81) days for preterm neonates included in the study. The probability of survival of preterm neonates during the 1st, 7th and 10th days were 25.6%, 55.6% and 78.4% with standard error of 0.086, 0.074 and 0.068 respectively. The maximum survival was observed at 27th day which was 83.3% with a standard error of 0.15 (Figure 1)

**Predictors of time to death for preterm Neonates**

Both Univariate and multivariable parametric procedures were used for analysis to identify predictors of time to death for preterm neonates from admission to discharge/death in the NICU.

According to the findings of bivariate analysis, birth weight, gestational age, Apgar score first and fifth minutes, Respiratory distress, breast feeding, perinatal asphyxia, hypothermia, early neonatal sepsis, Anemia and Multiple pregnancy were significantly associated with time to death of preterm neonatal mortality.

According to the findings of multivariate analysis; Breastfeeding, early neonatal sepsis, fifth (5th) minute Apgar score of less than 7, perinatal asphyxia and multiple pregnancy were found to be significant predictors of time to death for preterm neonates (Table 4).

Early Initiation of breast feeding for all preterm neonates reduce the risk of death by 57% compared to not early initiating breast feeding (AHR: 0.43 (95% CI: 0.29, 0.62))

The risk of death for preterm neonates whose mother had ANC follow up was reduced by 48% compared to the counterpart (AHR, 0.52(0.30, 0.85)

The hazard of death among preterm neonates diagnosed with early neonatal sepsis was 1.34 times compared to those neonates who had not diagnosed with early neonatal sepsis at admission (AHR: 1.34(95% CI: 1.003, 1.79))

Preterm neonates who had Gestational age of 28 -32 weeks were 1.44 times higher than those who were between 32-37 weeks of GA (AHR=1.44: 95% CI (1.02, 2.03)

The hazard of death for preterm neonates who had 5th minute Apgar score of less than 7 increased by 73% as compared to their counterparts (AHR: 1.73(95% CI: 1.17, 2.55)).

The Hazard of death for preterm neonates diagnosed with perinatal asphyxia was 2.25 times compared to preterm neonates who were not diagnosed with perinatal asphyxia at the time of admission (AHR: 2.25(95% CI: 1.67, 3.02))

The risk of death for a preterm neonates whose mother had recent multiple pregnancy was 1.66 times more compare to those preterm neonates whose mothers had no recent history of multiple pregnancy (AHR: 1.66(1.22, 2.26)) (Table 5)

## **Test of proportionally hazard assumption**

The p value of all covariates independently schoenfold residual test were greater than 0.05 except for one variable which was respiratory distress syndrome with the p-value of 0.0014 (Table 5). Proportional hazard assumption of the model was met. Global test of proportional assumption was done for all covariates together for a variable with residual test p value > 0.05 and observed global test p value was 0.19 it indicates the

**Comparison of survivorship functions for categorical variables**

In this study, the overall survival of preterm neonates having the APGAR score of less than 7 at 5th minute was 40.8 % whereas these preterm neonates with APGAR score of >7 at 5th minute was 77.8% at the end of the follow up period ( p-value = 0.001). The median survival time for preterm neonates having APGAR score of less than 7 at fifth minutes was 21 days (95% CI: 14.1, 27.9) (Figure 2)

Those preterm neonates who had perinatal birth asphyxia had overall survival of 58.8% while these preterm neonates without asphyxia had 78.5% survival at the end of the follow up period. This difference was statistically significant with p-value <0.001. The median survival time for those preterm neonates who had experienced birth asphyxia was 5 days (95% CI: 3.74, 6.25) (Figure 3)

# **Discussion**

The aim of this retrospective follow up study was to assess predictors of mortality among preterm neonates admitted to Neonatal Intensive Care Unit at Hawassa University Comprehensive Specialized Hospital. According to the findings of this study, the proportion of preterm neonatal mortality identified was 33.3%. Seven variables such as ANC visit, Gestational age, multiple pregnancy, early initiation of breast feeding, preterm neonatal sepsis at admission, Birth Asphyxia at admission and fifth minute Apgar score of less than seven were independent significant predictors of preterm neonatal Mortalities.

The proportion of mortality of preterm neonates admitted to Neonatal Intensive Care Unit in Hawassa University Comprehensive Specialized Hospital during the study period was 241 (33.3%). This finding was comparable with the study conducted in Jimma 34.9% ([20](#_ENREF_20)) and Felegehiwot Hospitals 34.1% ([21](#_ENREF_21)) in Ethiopia and findings from other developing countries like Uganda 31.6% ([22](#_ENREF_22)). However, it was slightly higher than the findings from study conducted in University of Gondar, 25.2%([23](#_ENREF_23)), and Tertiary care hospital in Addis Ababa, 23.2%([24](#_ENREF_24)), in Ethiopia; study findings from other developing countries like Nigeria 27.69% ([25](#_ENREF_25)), South Africa Johannesburg Hospital 26.5%([26](#_ENREF_26)), Cameroon 15.7% ([27](#_ENREF_27)) and findings of the studies conducted in developed countries like Iran 27.4%([28](#_ENREF_28)). But, it was lower than the study conducted in low income country 37.5%([29](#_ENREF_29)) and urban Pakistan 47.3%([30](#_ENREF_30)).

This difference in the magnitude of neonatal mortality across different neonatal care Units in various countries might reflect variation in the study settings and quality of services provided in those settings. Differences in NICU standard, the quantity and quality of trained health professionals and health service utilization practices of the community and treatment modalities can explain those differences. Other possible reasons might be methodological differences and the differences in sample size utilized. Generally, the higher proportion of mortality in Hawassa University Comprehensive Specialized Hospital compared to some of the hospitals mentioned earlier needs attention to improve the quality of care provided in the unit.

Proportion of preterm neonates with Apgar score of less 7 at 5th minutes was 61.8%. The Possible causes for this fact might be existence of insufficient equipment, space shortage and workload and knowledge gap which are actually the usual problems in developing countries. Of the preterm neonates participated in this study, 61.3% were hypothermic among which 39.7% died. This indicates inadequate service delivery practices in the delivery room that can be directly linked to workload and insufficient equipment’s.

Having ANC follow up during pregnancy was significantly predicted survival time to death of preterm neonates. Preterm neonates whose mother had have ANC follow up were 48% less likely to die when compared to those preterm neonates whose mother had no ANC follow up (AHR, 0.52(0.30, 0.85) (p<0.05). This study was consistent with the study conducted in University of Gonder Specialized Hospital ([31](#_ENREF_31)) and Felegehiwot Hospital ([21](#_ENREF_21)). The possible reason might be lack of ANC visits which could be resulted from inadequate monitoring of pregnancy and lead to neonatal complications and death during and after delivery.

The Hazard of death for Preterm neonates who had 5th minute APGAR score of less than 7 was 91% compare to their counterparts (AHR: 1.91(95% CI: 1.30,2.81)) (p<0.01). This finding was supported by the findings of studies conducted in china([32](#_ENREF_32)), Brazil([33](#_ENREF_33)), Iran([34](#_ENREF_34)) ,Cameroon ([35](#_ENREF_35)) and in Ethiopia like Mizan Tepi hospital([36](#_ENREF_36)), Tikur Anbesa specialized hospital([37](#_ENREF_37)), University of Gonder specialized Hospital ([31](#_ENREF_31)) and Ghana([17](#_ENREF_17)). Miss diagnosis of the preterm neonates and delay in identification of newborn complications and its management might be among the reasons. Scientific evidences put the decreased Apgar score as one of the major reasons for the death of preterm neonate.

According to this study, the risk of death for preterm neonates with perinatal asphyxia at the time of admission was about 3 times higher than preterm neonates who had no perinatal asphyxia at the time of admission (AHR=2.64(95% CI: 1.93, 3.61)) (p<0.001). This finding was in line with the study findings of tertiary hospital in Addis Ababa ([24](#_ENREF_24)), Mizan Tepi Hospital ([36](#_ENREF_36)) and Felegehiwot hospital in Bahir Dar ([21](#_ENREF_21)). The high rate of mortality because of perinatal asphyxia which accounts 74 (69.8%) compared to the mortality of other neonates who had no birth asphyxia 167 (27.1%)) in this finding is of particular interest. This is because it is a preventable cause of neonatal death and higher mortality in neonatal care unit might be related to the inadequate service quality (i.e. lack of commitment, mechanical ventilation, surfactant administration, and parenteral)

Early initiation of breast feeding decreased the risk of preterm neonatal death by 59% (AHR=0.41: 95% CI (0.28, 0.59)) (p<0.001). This finding was supported by the previous study finding in northwest Ethiopia([38](#_ENREF_38)). From the scientific evidences; the initiation of breast feeding/milk might provide protection against various diseases. Breast milk contains antibacterial, immunologic and other factors that can enhance bactericidal enzymes, complements and macrophages([39](#_ENREF_39)).

Gestational age was found to be a predictor of preterm neonatal mortality. The risk of death for preterm neonates who had gestational age of 28 -32 weeks at time of admission was 44% more compare to preterm neonates who had gestational age between 32-37 weeks at admission (AHR=1.44: 95% CI (1.02, 2.03) (P<0.05). This finding was supported by study conducted in Ethiopia Jimma University specialized hospital([20](#_ENREF_20)),University of Gondar specialized Hospital([23](#_ENREF_23)),Mizan tepi Hospital([36](#_ENREF_36)) and studies conducted in Iran Fatimiah Hospital([34](#_ENREF_34)) ,Uganda Tertiary Hospital([40](#_ENREF_40)) .This may be due to immaturity different organ system of the body which leads them to inability to resist external environment

Preterm neonates diagnosed with early neonatal sepsis during admission had 37% increased hazard rate compared to those preterm neonates with no early preterm neonatal sepsis (AHR=1.37(95% CI: 1.03, 1.83)) (p<0.05). This finding was supported by the various studies conducted in Ethiopia including University of Gonder specialized Hospital([31](#_ENREF_31)), Mizan Tepi specialized hospital([36](#_ENREF_36)), Jimma specialized hospital ([20](#_ENREF_20)), Felegehiwot specialized hospital and Iran Fetemiah Hospital ([34](#_ENREF_34)). Preterm neonates born with immaturity of body self-defense mechanisms and other procedure related factors can also contribute for the existences of those differences might have its own contribution.

Recent multiple pregnancy increased the risk of death for preterm neonates by about two times compare to singleton pregnancy (AHR: 1.82(1.35, 2.46)) (p<0.01). This finding was supported with the study conducted in Iran([34](#_ENREF_34)) and contradicts with the study conducted in Uganda([40](#_ENREF_40))

In this study, some covariates like HIV/AIDs was not significantly associated with preterm neonatal death which was actually not the case in studies conducted in Uganda([22](#_ENREF_22" \o "Egesa, 2020 #7)) and Jordan([41](#_ENREF_41" \o "Razeq, 2017 #14)). It might be because of lower sample size since only 4 preterm neonates that born from the mothers who had HIV/AIDS were died.

**Strengths and Limitations of the study**

**Strength**

The study design was retrospective cohort study that enabled for the comparison of preterm neonatal death with censored. This gives important road map or insight for those researchers who have interest to conduct a research by utilizing a better study design (for instance prospective cohort study). The utilized design helped to establish temporal relationship of preterm neonatal mortality with predictor variables. The result of the study was representative of the preterm neonates born in Hawassa University Comprehensive Specialized Hospital. The use of multivariate Cox proportional regression model had maximum chance of controlling for the possible confounders.

**Limitation of the study**

There was a high chance of missing some important predictors since the data was collected from secondary source. Generalization of the study findings to other health institutions in the country is impossible since this study was conducted only in one hospital (i.e. Hawassa University Comprehensive Specialized Hospital). There was high chance of selection bias due to the exclusion of incomplete records that may lead to under or over estimation of the preterm neonatal mortality

**Conclusion**

The magnitude of preterm neonatal mortality in Hawassa University Comprehensive Specialized Hospital was high (33.3%). Initiations of early breast feeding was protective against preterm neonatal mortality while having 5th minute Apgar score of less than 7, prenatal asphyxia, early neonatal sepsis and recent multiple pregnancy were the cause for preterm neonatal mortality. Availing enough skilled manpower, Improving quality of care at ANC for mothers, equipping NICU with adequate infrastructures and giving special care for neonates focusing on preterm neonates can avoid related complications

**Declarations**

**Abbreviation**

**AHR**: Adjusted Hazard Rate, **ANC:** Ante Natal Care, **CPD:** Cephalo Pelvic Disproportion, **DC:** Data Collectors, **EDHS:** Ethiopian Demographic and Health Survey, **FMOH**: Federal Ministry of Health, **GA**: Gestational Age, **HIV**: Human Immune deficiency Virus, **HMD**: Hyaline Membrane Disease, **HUCSH**: Hawassa University Comprehensive Specialized Hospital, **IUGR:** Intrauterine Growth Retardation, **MCH:** Maternal and Child Health, **MOH:** Ministry of Health, **NICU:** Neonatal Intensive Care Unit, **NMR:** Neonatal Mortality Rate, **PNA:** Prenatal Asphyxia, **PROM**: Premature Rupture of Membrane, **RDS:** Respiratory distress Syndrome, **SPSS:** Statistical Package for Social Science, **WHO:** World Health Organization

**Ethical Approval and Consent to Participate**

This research had been conducted in accordance with the declaration of Helsinki and approved by the appropriate ethics committee. Ethical approval was obtained from the Institutional Review Board (IRB) of the Hawassa University College of Medicine and Health Sciences. Then, Permission letter was written to concerned bodies of Hawassa University Comprehensive Specialized Hospital and secured before data collection. Data was collected retrospectively from the records of the patients (i.e. Data collectors had no any contact with the study participants). All eligible records were accessed after getting consent from Institutional Review Board of the College. Care was taken from disclosing confidentiality of patient’s records. All collected data was coded and locked in a separate room before entered into the computer and names were not included in the data collection format.

**Consent for Publication**

Not applicable

**Availability of data and Material**

Data will be shared up on request and will be obtained through the address of corresponding author (i.e. [feleketihun@gmail.com](mailto:feleketihun@gmail.com))

**Computing Interest**

The authors declare that they have no computing interest

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The authors have also declare that there was no financial support in the research, manuscript development, authorship and publication of this article

**Authors Contribution**

TFH Conceived and design the idea, participated in the data collection and analysis process, wrote the paper and developed manuscript. GKY participated in developing proposal, data analysis and developing manuscript. TGA and DL participated in the proposal, analyze data and wrote paper. All authors approved the final draft of the manuscript

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**Table 1:** Sociodemographic characteristics of preterm neonates and their mothers who were admitted at Neonatal intensive Care Unit of HU-CSH from May 9, 2019 to April 22, 2021 in Hawassa, Sidama Regional State, Ethiopia, 2021.

|  |  |  |  |
| --- | --- | --- | --- |
| Variables(n=723) | Frequency | | Percent |
| Sex |  | |  |
| Female | 375 | | 51.9 |
| Male | 348 | | 48.1 |
| Residence |  | |  |
| Urban | 438 | | 60.6 |
| Rural | 285 | | 39.4 |
| Neonatal age at admission |  | |  |
| <24hrs | 567 | | 78.4 |
| 1-7 days  >7 | 139  17 | | 19.2  2.4 |
| Maternal Age |  | |  |
| <=20 | 88 | | 12.2 |
| 20-34 | 547 | | 75.7 |
| >34 | 88 | | 12.2 |
| Gestational Age |  |  | |
| 28-32  33-34 | 345  215 | | 47.72  29.74 |
| 35-36 | 163 | | 22.54 |
| Place of delivery |  | |  |
| HU-CSH | 397 | | 54.9 |
| Other health institutions | 316 | | 43.7 |
| Home | 10 | | 1.4 |
| Length of hospital stay |  | |  |
| <24hrs | **30** | | **4.1** |
| 1-7 days | 275 | | 38 |
| >7 days | 418 | | 57.8 |

**Table 2:** Medical and obstetric related characteristics of the mothers study participants who were admitted at Neonatal intensive Care Unit of HU-CSH, from May 2019 to April 2021 in Hawassa, Sidama Regional State, Ethiopia, 2021.

|  |  |  |
| --- | --- | --- |
| Variables (n=723) | Frequency | Percent |
| Mode of Delivery | | |
| Spontaneous VD | 406 | 56.2 |
| Cesarean section | 305 | 42.2 |
| Instrumental | 12 | 1.7 |
| Multiple pregnancy | | |
| Yes | 79 | 10.9 |
| No | 644 | 89.1 |
| Number of parity | | |
| ≤2 | 466 | 64.5 |
| >2 | 257 | 35.5 |
| Number of Gravidity | | |
| ≤2 | 354 | 49 |
| >2 | 369 | 51 |
| ANC Follow Up |  |  |
| Yes | 684 | 94.6 |
| No | 39 | 5.4 |
| PROM | | |
| Yes | 96 | 13.9 |
| No | 627 | 86.1 |
| Abruption Placenta | | |
| Yes | 42 | 5.8 |
| No | 681 | 94.2 |
| Anemia | | |
| Yes | 21 | 2.9 |
| No | 702 | 97.1 |
| Hypertension | | |
| Yes | 43 | 5.9 |
| No | 680 | 94.1 |
| Other | | |
| Yes | 29 | 4.01 |
| No | 694 | 95.99 |

**Table 3:** Preterm Neonatal related problems of preterm neonates admitted at Neonatal intensive Care Unit of HU-CSH from May 2019 to April 2021, Hawassa, Ethiopia, 2021

|  |  |  |
| --- | --- | --- |
| Variables (n=723 ) | Frequency | Percent |
|
| Birth Weight | | |
| <=1000gm | 20 | 2.8 |
| 1000-1500gm | 161 | 22.3 |
| 1500-2500gm | 507 | 70.1 |
| >2500gm | 35 | 4.8 |
| APGAR Score 1st Minute |  |  |
| < 7 | 645 | 89.2 |
| >7 | 78 | 10.8 |
| APGAR Score 5th Minute |  |  |
| < 7 | 447 | 61.8 |
| >7 | 276 | 38.2 |
| Breast feeding initiated |  |  |
| Yes | 304 | 37.8 |
| No | 419 | 62.2 |
| Hypoglycemia |  |  |
| Yes | 86 | 11.9 |
| No | 637 | 88.1 |
| Neonatal Sepsis |  |  |
| Yes | 236 | 32.6 |
| No | 487 | 67.4 |
| Perinatal Asphyxia |  |  |
| Yes | 106 | 14.7 |
| No | 617 | 85.3 |
| Jaundice |  |  |
| Yes | 80 | 11.1 |
| No | 643 | 88.9 |
| Hypothermia |  |  |
| Yes | 443 | 61.3 |
| No | 280 | 38.7 |

**Table 4:** Bivariate and multivariable Cox regression analysis results of preterm neonates admitted at NICU, HU-CSH from May 2019 to April 2021, Hawassa, Ethiopia, 2021.

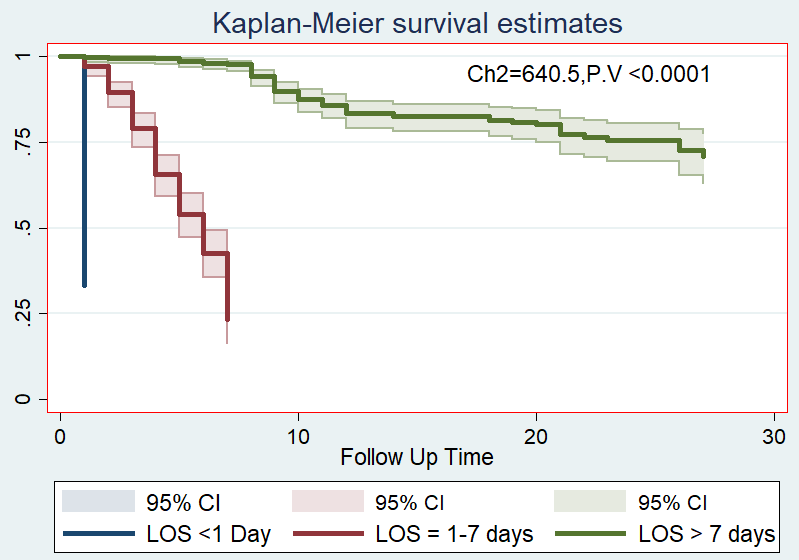
| Variables  (n=723) | Death (%) | Censored (%) | CHR (95% CI) | AHR (95% CI) |
| --- | --- | --- | --- | --- |
| Birth Weight |  |  |  |  |
| <1500gm | 20(100) | 0 (0) | 2.6 (1.26, 5.34) | 2.49(0.58, 2.75) |
| 1500-2500gm | 131(25.8) | 376(74.2) | 1.08(0.53, 2.21) | 1.06(0.51, 2.23) |
| >2500gm | 8(22.9) | 27(77.1) | 1 | 1 |
| APGAR Score  1st Minute |  |  |  |  |
| < 7 | 228(35.3) | 417(64.7) | 2.21(1.27,3.87) | 1.07(0.56, 2.07) |
| >7 | 13(16.7) | 65(83.3) | 1 | 1 |
| APGAR Score  5th Minute |  |  |  |  |
| < 7 | 197(44.1) | 250(55.9) | 3.0(2.17, 4.17) | 1.91(1.30,2.81)\*\* |
| >7 | 44(15.9) | 232(84.1) | 1 | 1 |
| Breast feeding |  |  |  |  |
| Yes | 39 (15.3) | 216(84.7) | 0.29(0.21, 0.41) | 0.41(0.28, 0.59)\*\*\* |
| No | 179(42.7) | 240(57.32) | 1 | 1 |
| Neonatal Sepsis |  |  |  |  |
| Yes | 84 (42.4) | 114 (57.6) | 1.89(1.47, 2.43) | 1.37(1.03, 1.83)\* |
| No | 157(29.9) | 368 (70.1) | 1 | 1 |
| Perinatal Asphyxia |  |  |  |  |
| Yes | 74 (69.8) | 32 (30.2) | 3.72(2.82, 4.91) | 2.64(1.93, 3.61)\*\*\* |
| No | 167(27.1) | 450 (72.9) | 1 | 1 |
| Hypothermia |  |  |  |  |
| Yes | 176(39.7) | 267 (60.3) | 1.86(1.40 ,2.47) | 1.27(0.92,1.77) |
| No | 65 (23.2) | 215 (76.8) | 1 | 1 |
| Multiple pregnancy |  |  |  |  |
| Yes | 24(30.4) | 55 (69.6) | 2.15(1.63, 2.84) | 1.82(1.35, 2.46)\*\*\* |
| No | 217(33.7) | 427 (66.3) | 1 | 1 |
| Maternal anemia |  |  |  |  |
| Yes | 13 (61.9) | 8(38.1) | 1.97(1.12,3.45) | 1.53(0.79, 2.95) |
| No | 8 | 474(67.5) | 1 | 1 |
| ANC follow up |  |  |  |  |
| Yes | 224(32.7) | 460 (67.3) | 0.65(0.34, 1.03) | 0.52(0.30, 0.85)\* |
| No | 17 (43.6) | 22 (56.4) | 1 | 1 |
| GA in weeks |  |  |  |  |
| 28-32 | 89(23.5) | 289(76.5) | 2.01(1.55,2.6) | 1.44(1.02, 2.03)\* |
| 33-36 | 152(44.1) | 193(55.9) | 1 | 1 |
| Abruption placenta |  |  |  |  |
| Yes | 218(32.0) | 463 (68.0) | 1.96(1.28, 3.01) | 1.29( 0.75, 2.21) |
| No | 23 (54.8) | 19(45.2) | 1 | 1 |

NB:

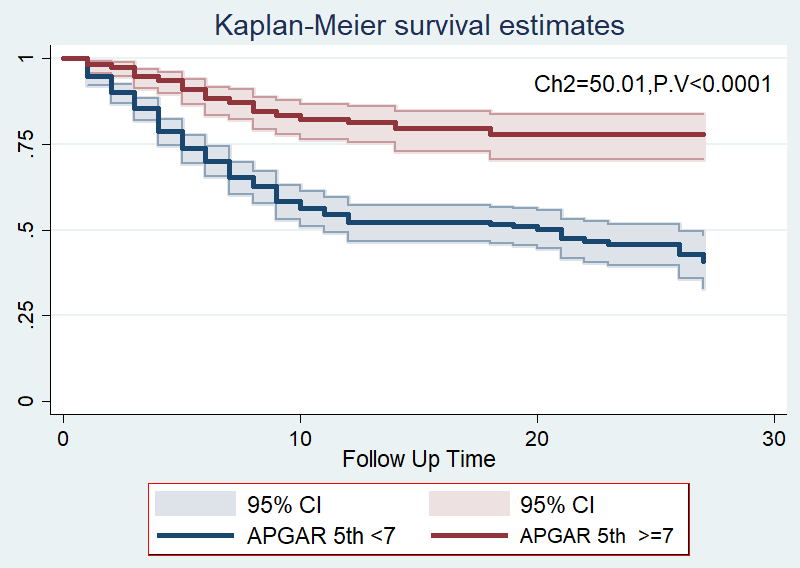
* \*P<0.05, \*\*p<0.0, \*\*\*p<0.001
* Schoenfeld residuals and Global test >0.05(0.27)
* Relatively safe population from scientific point of view were taken as reference category

**Table 5:-** Schoenfold Residuals test for proportionality assumption of covariates and overall model of the stratified Cox Proportional Hazard

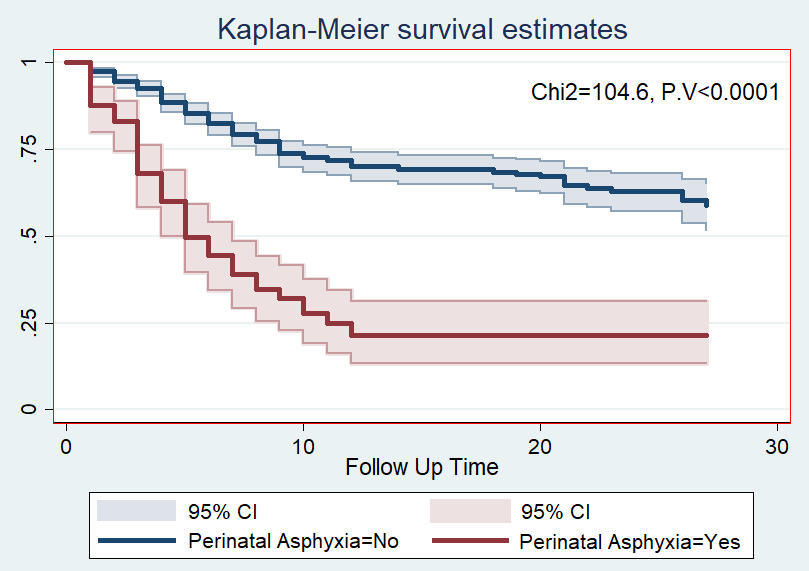
|  |  |  |  |
| --- | --- | --- | --- |
| Covariates |  | X2 | P-value |
| Birth weight |  | 0.07 | 0.79 |
| Gestational Age |  | 1.62 | 0.20 |
| APGAR score 1st minute |  | 0.21 | 0.64 |
| APGAR score 5th minute |  | 0.20 | 0.65 |
| Respiratory Distress |  | 10.2 | 0.0014 |
| Breast Feeding |  | 1.41 | 0.23 |
| ANC |  | 0.65 | 0.41 |
| Perinatal Asphyxia |  | 2.3 | 0.12 |
| Hypothermia |  | 0.2 | 0.65 |
| Neonatal Sepsis |  | 1.68 | 0.19 |
| Anemia |  | 2.34 | 0.12 |
| PROM |  | 1.99 | 0.15 |
| Multiple Pregnancy |  | 0.10 | 0.75 |
| Gravidity |  | 1.8 | 0.17 |
| Placental Abruption |  | 0.10 | 0.75 |
| Hypertension |  | 0.34 | 0.55 |
| Global test |  | 19.54 | 0.19 |



**Figure 1:** The Kaplan-Meier survival curves compare survival time of preterm neonate with categories of Length of hospital stay at NICU of HU-CSH from May 2019 to April 2021, Hawassa, Ethiopia, 2021.



**Figure 2:-** The Kaplan-Meier survival curves compare survival time of preterm neonate with categories of 5th minute Apgar score at NICU, HU-CSH, from May 2019 to April 2021 in Hawassa, Ethiopia, 2021.



**Figure 3:** The Kaplan-Meier survival curves compare survival time of preterm neonate with categories of Preterm neonates with prenatal asphyxia at NICU of HU-CSH from May 2019 to April 2021, Hawassa, Ethiopia, 2021