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Survival status and predictors of mortality among preterm neonates admitted in Bench Sheko Zone, Sheka Zone and Keffa Zone Governmental Hospitals, Southwest Ethiopia (2021): prospective follow-up study

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ABSTRACT

Introduction Prematurity presents a significant challenge to the global community due to the rapid increase in its incidence and its disproportionate contribution to increased infant mortality rates.

Objective To assess the survival status and predictors of mortality among preterm neonates.

Design A multicentre prospective follow-up study was used.

Setting 625 preterm neonates were admitted to hospitals for secondary level of care. The study covers the Bench Maji Zone, Keffa Zone, Sheka Zone, nearby woredas and portions of the Gambella area in Southwest Ethiopia.

Participants 614 preterm neonates with gestational age less than 37 weeks were entered for follow-up and 400 neonates were censored. Neonates with severe fetal malformations and neonates who need urgent referral were excluded from the study.

Results Overall, 200 (32.57%) participants died with an incidence rate of 61.69 deaths per 1000 person-day observations (95% CI: 53.71 to 70.86). Poor kangaroo mother care (KMC) services (adjusted HR (AHR)=0.19, 95% CI: 0.12 to 0.29), sex (AHR=0.66, 95%, CI: 0.47 to 0.94), not initiating breast feeding (HR=2.78, 95% CI: 1.8 to 4.28), hypothermia (AHR=0.63, 95% CI: 0.44 to 0.92), anaemia (AHR=6.2, 95% CI: 2.34 to 16.43) and gestational age less than 28 weeks (AHR=9.28, 95% CI: 1.78 to 48.42) were independent predictors.

Conclusion and recommendation The rate of preterm neonatal mortality was high compared with the Ethiopia Demographic and Health Survey report nationally. Healthcare workers should encourage KMC services and breastfeeding initiation and prevent preterm neonates from being anaemic to increase their chances of survival.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study did address the probable service-related predictors of mortality.
⇒ The study was conducted in a multicentre setting using random sampling and patients were followed for a long duration with a maximum of 28 days, increasing the study's generalisation.
⇒ Data on the site of delivery, home versus the hospital, might be incomplete.
⇒ Possibility of medical record errors and diagnostic subjectivity was not controlled.

INTRODUCTION

Preterm is defined as babies being born alive before 37 weeks of pregnancy are completed. It has subcategories based on gestational age (GA): extremely preterm (less than 28 weeks), very preterm (28–32 weeks) and moderate-to-late preterm (32–37 weeks).[1 2]

In addition, preterm birth is a pervasive disorder that impacts all the functioning of the neonates who survived both in the short and long term, such as neurodevelopment, education, psychosocial, growth and health outcomes. Mortality is also related to GA, and preterm birth continues to be the leading cause of perinatal and postnatal mortality mainly in undeveloped countries where health services are limited and not functioning well.[3]

Prematurity presents a significant challenge to the global community because of the rapid increase in its incidence and disproportionate contribution to increased infant mortality rates.[1] Globally, each year, 15 million babies are born preterm (before 37 completed weeks of gestation), which is estimated to be approximately 11% of all deliveries.[4] Although the burden of under-5 mortality decreased between 2010 (7.6 million)[5] and 2015 (5.942 million),[6] the percentage of mortality caused by preterm-related complications has

increased from 14.1%[5] to 17.8%,[6] and more than 80% of perinatal problems and mortality from preterm deliveries are reported. Among all neonatal deaths globally in 2013, 35% were caused by preterm birth complications alone.[7] The rate of preterm neonatal mortality increased in sub-Saharan Africa from 0.326 million in 2013[8] to 0.356 million in 2015.[6] Survivors experience inferior neurological development, poor academic performance, higher risk of cerebral palsy and metabolic problems in adulthood after surviving the neonatal period.[9]

Preterm labour is the main cause of neonatal deaths in many regions in Ethiopia, and neonates delivered with shorter GAs have demonstrated higher neonatal mortality than term babies.[10] More than two-thirds (76%) of the neonatal deaths in the southwest area of Ethiopia, which accounted for 22.8% of all neonatal deaths, were due to preterm birth.[11] There is a need to identify the causes of preterm mortality given the growing impact of neonatal deaths on overall child mortality.[6 12] To a certain extent, researchers have been more interested in trends concerning the occurrence and subsequent mortality of preterm births over time than in the rates and factors affecting the survival of preterm infants. There is still more research to be conducted on the direct evidence indicating an increased tendency for preterm birth-related mortality. For prenatal care evaluation, parental education, careful selection and development of clinical standards, current estimates of the survival status of preterm neonates admitted to the neonatal intensive care unit (NICU) are required. Thus, the goal of this study was to assess survival status and identify the predictors of mortality among preterm neonates at selected governmental hospitals in Southwest Ethiopia.

METHODS

Study design and setting

Preterm neonates admitted to the NICU wards at Mizan-Tepi University Teaching Hospital, Tepi General Hospital and G/Tsadik Shawo General Hospital located in Bench Sheko, Sheka and Keffa Zones, Southwest Ethiopia were the subjects of this institution-based prospective follow-up study from 10 March to 30 September 2020. They cover the Bench Maji Zone, Keffa Zone, Sheka Zones, nearby woredas and portions of the Gambella area, with a catchment population of more than 2.7 million (Majang Zone). In these three hospitals, more than 665 infants are born each month, with 70 of those admitted to the NICU due to being preterm.

Study population

All preterm neonates who are admitted to the intensive care unit of Bench Sheko Zone, Keffa Zone and Sheka Zone hospitals, Southwest Ethiopia during the study period.

Inclusion criteria

Mothers with their preterm neonates whose GA was less than 37 weeks, who were admitted in the selected hospitals during the study period, were included.

Exclusion criteria

Neonates with severe fetal malformations, mothers who were unable to speak, neonates who need urgent referral and mothers with psychiatric illnesses were excluded from the study.

Sample size and sampling procedure

Sample size was determined by using STATA statistical package (Cox model), V.14 based on the following assumptions: HR of 1.55 for perinatal asphyxia that gives a maximum sample size among covariates,[13] a variability (SD) of 0.5, probability of failure (event) of 0.288, a 5% margin of error, 95% CI and 80% power. The required number of events was 164, and the number of outcomes was 568. The final sample size was 625 after a 10% non-response rate was added.

The total number of preterm neonates admitted to the NICU on a monthly basis in each of the chosen hospitals was assessed before the data collection began. The overall sample size of the study was then proportionally distributed to each chosen hospital depending on the number of preterm neonates admitted to the NICU in the past. Then, at each hospital's corresponding NICU, we included all preterm neonates who had been admitted. Study participants were selected from each hospital using a sequential sampling method. All recruited study subjects were tracked until the desired result (death or censure) manifested itself.

Measurement and variables

Survival status of the preterm neonates was the outcome variable in this study. Sociodemographic-related factors (date of birth, date of admission, sex of the neonate, maternal age, age of the neonate at admission, residency of the mother and place of delivery), neonatal-related factors (birth weight, Apgar score, weight for gestational age at birth, feeding status, breathing condition at birth and kangaroo mother care (KMC)), neonatal preterm-related medical and surgical complications factors (sepsis, necrotising enterocolitis, intraventricular haemorrhage, asphyxia, respiratory distress syndrome (RDS), jaundice, pulmonary haemorrhage, pulmonary hypertension, hypoxic ischaemic encephalopathy, anaemia, congenital anomalies, hypothermia and hypoglycaemia), maternal and obstetric-related factors (maternal chronic disease, obstetric complications, pregnancy-induced hypertension, maternal exposure status to corticosteroids before delivery, presentation at delivery, mode of delivery, antenatal care status, parity of the mother and pregnancy type), and institutional and professional-related factors (place of KMC service provided, level of NICU, hospital level and availability of resuscitation equipment) were the independent variables.

Operational definitions

Survival time: the time from admission to the NICU until the occurrence of an event (death) during the study period.

Event: death of a preterm neonate after admission to the NICU during the hospitalisation period.

Censored: preterm neonates who had survived during the follow-up period (including preterm neonates who were discharged with improvement, lost to follow-up (left against medical advice or transferred to other health institutions), withdrawn (if the mother refused the follow-up due to inconvenience) and still stayed with admission beyond 28 days of neonatal age).

Time scale: the survival time measured in days.

Starting time: the first day of admission of the preterm neonate at the NICU.

End of follow-up time: the last day of an event or censored occurrence in the hospital.

Preterm neonates: neonates who were born less than 37 weeks of GA, irrespective of birth weight.[13]

Data collection tools and procedure

Data were gathered using a pretested interviewer-administered questionnaire based on pertinent literature.[10 13–22] The questionnaire was prepared in English and translated into Amharic and then retranslated into English by senior experts. Sociodemographic, neonatal, medical and surgical complications related to preterm birth, maternal and obstetric-related, and health institution-related variables were included.

Data were gathered using in-person interview for primary data and chart review for secondary data. Secondary data were used to obtain baseline data of mothers that were unable to be collected. After putting aside all baseline information on sociodemographic factors, obstetrics-related factors and neonatal factors related to the date of birth and the first day of enrolment, daily follow-up assessments of factors that could occur beginning on the first day of follow-up (ie, from the time of admission to the neonatal age of 28 days) or until the neonates experienced the event of interest (ie, death or censored) were done. Those neonates who were discharged before experiencing the event of interest were followed through phone calls. Only the first episodes of preterm birth in cases where patients were admitted with more than one episode over the 28 days of the initial trial were considered in the current analysis. Six diploma-holder nurses with experience in newborn critical care and three BSc-trained nurses were hired for the data collection and supervision.

Data quality control

To preserve consistency, the questionnaire was written in English, translated into Amharic and retranslated into English by linguists. Data collectors and supervisors received training in the study's objectives, data collection instruments, techniques and procedures before data collection. 32 (5%) preterm neonates who were admitted to the NICU of the Shenen Gibie Hospital underwent a pretest, and the necessary corrections were performed. By closely monitoring the data collectors and supervisors, lead investigators were able to coordinate the overall data collection. Supervisors assessed the questionnaires, and those with missing information were eliminated. The investigators verified the accuracy of the data before they were entered.

Data processing and analysis

For cleaning and analysis, data were imported into Epi-Data manager V.4.4 and exported to STATA statistical software V.14. Results are presented as descriptive statistics: frequency, graphs, median and range. To further explain the survival status of preterm newborns, non-parametric estimators including life tables, Kaplan-Meier and log-rank tests were used. For preterm newborns, a semi-parametric Cox proportional hazards model was used to determine the important predictors of time to death.

Variables with a p value of less than 0.25 in the bivariate analysis were entered for the multivariable analysis after each variable underwent Cox proportional hazards regression. The Cox proportional hazards regression model assumption was tested graphically using a log–log plot and statically using the Schoenfeld residual test (global test). Before interpreting the results, multicollinearity between the independent variables was evaluated using variance inflation factor (VIF), and a VIF greater than 10 was used to indicate the presence of multicollinearity. A statistically significant predictor of time to death for preterm neonates was found through the multivariate analysis, with an HR, p value of 0.05 and 95% CI. Finally, the Cox-Snell residual graph and log-likelihood test were used to evaluate the model's fitness.

Patient and public involvement

Patients or the public were not involved in the study design, conduct, reporting or distribution strategies of the research.

RESULTS

Neonatal and maternal sociodemographic characteristics

The analysis comprised of 614 preterm neonates in total, with a response rate of 98.24%. 378 (61.56%) participants were male. The majority of neonates (607, 98.86%) were in the age category of ≤7 days and their median age was 0.68 days. 534 (86.97%) mothers belonged to the age category of 20–34 years, with a median age of 25 years. Two-thirds (66.61%) of the neonates were born to mothers who lived in rural areas. The median follow-up duration for preterm neonates was 5.28 days, and the follow-up period ranged from 1 to 28 days, totalling 3242 person-days (table 1).

Neonatal-related characteristics

The majority of neonates (586, 95.44%) were born in hospitals, and 470 (76.55%) of them cried immediately

Table 1 Sociodemographic characteristics of preterm neonates and their mothers admitted to the intensive care unit of Bench Sheko Zone, Keffa Zone and Sheka Zone Hospitals, Southwest Ethiopia, 2021

Characteristics	Category	Total, N (%) N=614	Survival status of the neonate	
			Censored, N (%) N=414	Died, N (%) N=200
Sex	Female	236 (38.44)	148 (62.71)	88 (37.29)
	Male	378 (61.56)	266 (70.37)	112 (29.63)
Age of neonate	≤7 days	607 (98.86)	407 (67.05)	200 (32.95)
	8–28 days	7 (1.14)	7 (100.00)	–
Maternal age	<20 years	57 (9.28)	38 (66.67)	19 (33.33)
	20–34 years	534 (86.97	364 (68.16)	170 (31.84)
	≥35 years	23 (3.75)	12 (52.17)	11 (47.83)
Residency	Urban	205 (33.39)	125 (60.98)	80 (39.02)
	Rural	409 (66.61)	289 (70.66)	120 (29.34)

after birth. With a mean GA of 32.96, about 368 (59.93%) newborns were born prematurely. With a mean weight of 1560.48, more neonates (54.07%) were born with low birth weight. The 1-minute Apgar scores for 419 of the preterm newborns (71.50%) were less than 7, with an overall median Apgar score of 5.64 and 7.10 for 1-minute and 5-minute scores, respectively. Regarding the type and status of feeding, 506 preterm newborns (82.41%) were given breast milk, and 100 preterm neonates (16.29%) did not start any kind of feeding due to extreme prematurity, surgical and medical complications and being too sick to be fed. The hospital protocol also did not allow the initiation of feeding for neonates born before 32 weeks of gestation. More than half (58.50%) of preterm neonates who had breast milk obtained it after 2 hours from those who had taken it. In terms of weight for GA, 155 neonates (25.24%) were born small for GA, and approximately 180 (29.32%) experienced feeding difficulties (table 2).

Maternal and obstetrics-related characteristics

Neonatal births from mothers with a single pregnancy accounted for 470 (76.55%) of neonates. Only 69 (13.69%) of the neonates were delivered from mothers who took corticosteroids throughout pregnancy, out of the 499 (81.27%) neonates who were spontaneously delivered via vaginal birth. Only 64 (10.14.2%) preterm babies were born to mothers who had obstetric problems, and only 46 (7.49%) mothers had chronic disorders (online supplemental file 1).

Medical and surgical preterm-related complications predictors

Among preterm neonates, nearly two-thirds (394, 64.17%) of neonates had RDS complications and 437 (46.55%) had sepsis issues. Among the total number of babies with RDS diagnosis, 370 neonates (93.91%) underwent resuscitation treatment (online supplemental file 2).

Institutional and professional characteristics

In the hospital during neonatal admission, approximately 274 (44.63%) neonates received KMC services, of which 172 (62.77%) KMC services were provided with beds in the NICU (online supplemental file 3).

Survival status, mortality rate and median survival time among preterm neonates

200 (32.57%) of the 614 neonates died during the follow-up period, and 414 (67.43%) were censored (of which, 353 (85.23%) were sent home, 39 (9.4%) left against doctors' orders, 10 (2.4%) were still alive at the end of the study period and the remaining (2.9%) were sent to other institutions). Incidence rate of 61.69 (95% CI: 53.7 to 70.86) deaths per 1000 person-day observations was observed in neonates throughout the course of 3242 person-day observations. Each GA group had a different incidence rate of preterm neonates, with rates for extremely preterm, very preterm and late preterm neonates being 66.67 (95% CI: 16.67 to 266.56), 91.47 (95% CI: 76.37 to 109.5) and 41.62 (95% CI: 33.43 to 51.82), respectively. The median survival time or the survival time at which the cumulative survival function is equal to 0.5 was undetermined. Because the largest observed analysis time was censored, the survivor function did not lead to zero; in this case, the mean is the best estimate of survival time. The mean survival time for preterm neonates was 17.46 (95% CI: 16.34 to 18.98) days.

Mortality rate and mortality-free survival among preterm neonates

The study's Kaplan-Meier survival function estimate revealed that the largest percentage of deaths (81, 49.5%) occurred on the first day of the follow-up period. Additionally, using the Kaplan-Meier estimate of the survivor function, the cumulative survival probabilities at the end of the follow-up periods of 1 day, 7 days and 28 days were 86.81 (95% CI: 83.87 to 89.25), 61.75 (95% CI: 57.10 to

Table 2 Neonatal-related characteristics of preterm neonates admitted to the intensive care unit of Bench Sheko Zone, Keffa Zone and Sheka Zone Hospitals, Southwest Ethiopia, 2021

Characteristics	Category	Total, N (%) N=614	Censored, N (%) N=414	Died, N (%) N=200
Place of delivery	Health institution	586 (95.44)	402 (68.60)	184 (31.40)
	Home	28 (4.56)	12 (42.86)	16 (57.14)
Gestational age	<28	13 (2.12)	11 (84.62)	2 (15.38)
	28–32	233 (37.95)	115 (49.36)	118 (50.64)
	32–37	368 (59.93)	288 (78.26)	80 (21.74)
Birth weight	<1000	32 (5.21)	7 (21.88)	25 (78.13)
	1000–1499	240 (39.09)	135 (56.25)	105 (43.75)
	1500–2499	332 (54.07)	263 (79.22)	69 (20.78)
	≥2500	10 (1.63)	9 (90.00)	1 (10.00)
1-minute Apgar	<7	439 (71.50)	275 (62.64)	164 (37.36)
	7–10	175 (28.50)	139 (79.43)	36 (20.57)
5-minute Apgar	<7	103 (16.78)	54 (52.43)	49 (47.57)
	7–10	511 (83.22)	360 (70.45)	151 (29.55)
Cried immediately after birth	Yes	470 (76.55)	338 (71.91)	132 (28.09)
	No	144 (23.45)	76 (52.78)	68 (47.22)
Feeding type	Breast feeding	506 (82.41)	377 (74.51)	129 (25.49)
	Formula feeding	8 (1.30)	8 (100.00)	–
	Not initiated until the first day of observation	100 (16.29)	29 (29.00)	71 (71.00)
Time feeding was initiated	Within 1 hour after delivery	142 (28.06)	110 (77.46)	32 (22.54)
	Between 1 and 2 hours after delivery	68 (13.44)	62 (91.18)	6 (8.82)
	Greater than 2 hours after delivery	296 (58.50)	205 (69.26)	91 (30.74)
Encountered any feeding difficulty	No	434 (70.68	288 (66.36)	146 (33.64)
	Yes	180 (29.32	126 (70.00)	54 (30.00)
Got breast milk pumps for feeding difficulties	Yes	164 (26.71)	117 (71.34)	47 (28.66)
	No	16 (2.61)	11 (68.75)	5 (31.25)
Weight for GA	AGA	450 (73.29)	326 (72.44)	124 (27.56)
	LGA	9 (1.47)	8 (88.89)	1 (11.11)
	SGA	155 (25.24)	80 (51.61)	75 (48.39)

AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

66.05) and 56.92 (95% CI: 51.47 to 61.98), respectively (figure 1).

Comparison of survivorship functions for different categorical variables

Comparisons of survival time difference between different groups of categorical covariates were done through a Kaplan-Meier survival graph and statistical log-rank test. In this study, in preterm neonates, there were statistically significant differences between groups in place of delivery ($Pr>X^2=0.0001$), breathing status ($Pr>X^2=0.0000$), feeding status ($Pr>X^2=0.0000$), diagnosed RDS ($Pr>X^2=0.0000$), asphyxia ($Pr>X^2=0.0129$), anaemia ($Pr>X^2=0.0000$), 5-minute Apgar score ($Pr>X^2=0.0017$) and antenatal care visit ($Pr>X^2=0.0004$), as compared with their counterparts (figure 2).

Predictors of preterm neonates' mortality

The relationship between independent variables and the risk of mortality was analysed using the Cox proportional hazards regression model. In the bivariate analysis, factors such as being male, place of delivery, KMC service, not crying at birth, not initiating feeding for the first time, RDS, asphyxia, hypothermia, anaemia, no antenatal care visit, mode of delivery, no KMC, GA category and 5-minute Apgar score were found to have a p value of <0.25.

Cox proportional hazards assumption test

Assumptions of the Cox proportional hazards model were assessed using the Schoenfeld residual/global test, which became non-significant (0.077), indicating that the proportional hazards assumption of Cox proportional

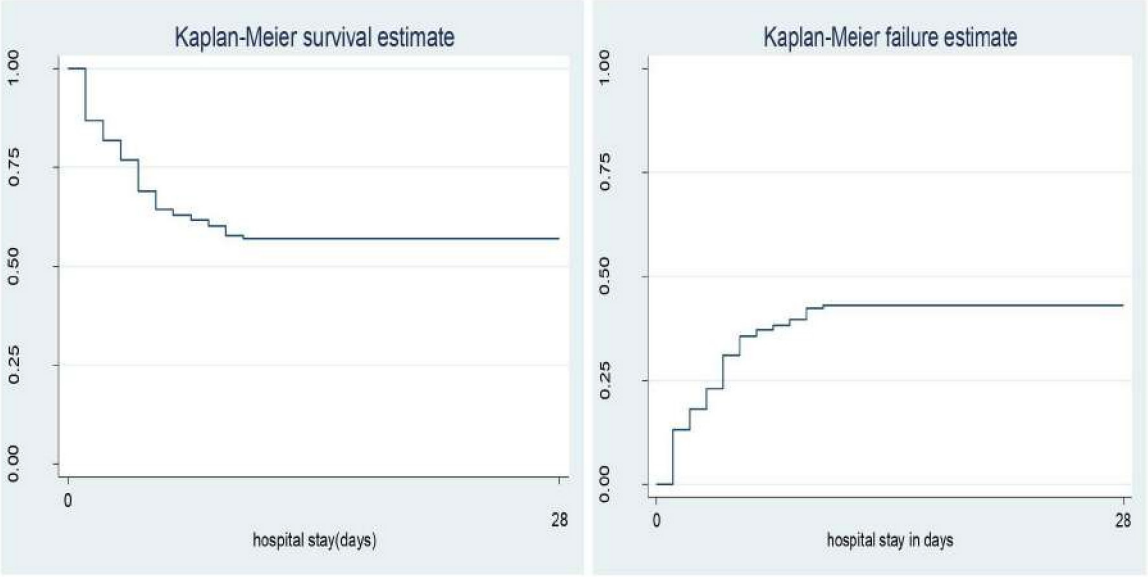

Figure 1 Overall Kaplan-Meier survival and failure estimates of preterm neonates.

hazards regression was met. The multicollinearity of each independent variable was checked using the VIF, and the mean VIF for those variables was 1.35.

Cox proportional hazards model fitness test

The fitness of the final model was checked graphically by using the Cox-Snell residual and showed the hazard function followed the 45° line closely, which confirmed that the final model was a good fit (online supplemental file 4).

Significant variables in the bivariate analysis were included in the multivariable analysis. Finally, sex, KMC service, feeding status, hypothermia, anaemia and GA category were found to be independent predictors of mortality in preterm neonates in the multivariable analysis.

As a result, there was a 66% (adjusted HR (AHR)=0.66, 95% CI: 0.47 to 0.94) lower risk of death among preterm male neonates compared with preterm female neonates, or a 34% increase in survival time of preterm male neonates compared with preterm female neonates. The risk of death of preterm neonates with a GA lower than 28 weeks was 9.28 times higher (AHR=9.28, 95% CI: 1.78 to 48.42) as compared with those with GA of 28–32 weeks and greater than 32 weeks. The risk of death of preterm neonates who had not been initiated with either formula or breast milk until the time of the first observation was 2.78 times (HR=2.78, 95% CI: 1.8 to 4.28) as compared with those who were initiated breast milk or formula feeding. The risk of death of preterm neonates who were anaemic was 6.2 times (AHR=6.2, 95% CI: 2.34 to 16.43) as compared with that of non-anaemic preterm neonates. Preterm neonates who were not hypothermic had 63% (AHR=0.63, 95% CI: 0.44 to 0.92) lower risk of death as compared with hypothermic preterm neonates. Preterm neonates who got KMC services had 19% (AHR=0.19, 95% CI: 0.12 to 0.29) lower risk of death as compared with preterm neonates who did not get KMC services (table 3).

DISCUSSION

In this study, the overall incidence rate of mortality was found to be 61.69 (95% CI: 53.7 to 70.86) deaths per 1000 person-day observations, and the highest (81, 49.2%) proportion of deaths was observed on the first day of the follow-up period. The study's overall findings showed that 32.57% of preterm neonates died, while the mean survival time for preterm neonates was 17.46 (95% CI: 16.24 to 18.89) days.

The same finding was observed in Jimma University Specialized Hospital where 34.9% of preterm neonates died,[23] and in Iran where 28.7% died.[24] In contrast, a lower finding was recorded in Gondar University Hospital (25.2%).[13] The discrepancy could be attributed to differences in the study design (retrospective vs prospective) that all events are not recorded in the patients' card (limitation of a retrospective study). Additionally, including a large sample size in our study might have led to a higher record. A retrospective study conducted in Black Lion Hospital showed that the incidence rate was 39.1 per 1000 person-day observations.[25] This indicates that the quality of health service provision has a significant role in reducing incidence rates of neonatal mortality. Another study in Northern Ethiopia reported a better mean survival time of the preterm neonates (47.0, 95% CI: 43.1 to 48.9 days)[26] compared with this study. This discrepancy might be due to the study setting and the differences in the event of origin and survival time. A lower finding of preterm neonatal deaths that occurred in the first 24 hours of life was observed in the University of Gondar Comprehensive Teaching Hospital (3.29%)[13] and Felege Hiwot Referral Hospital (16.6%),[19]

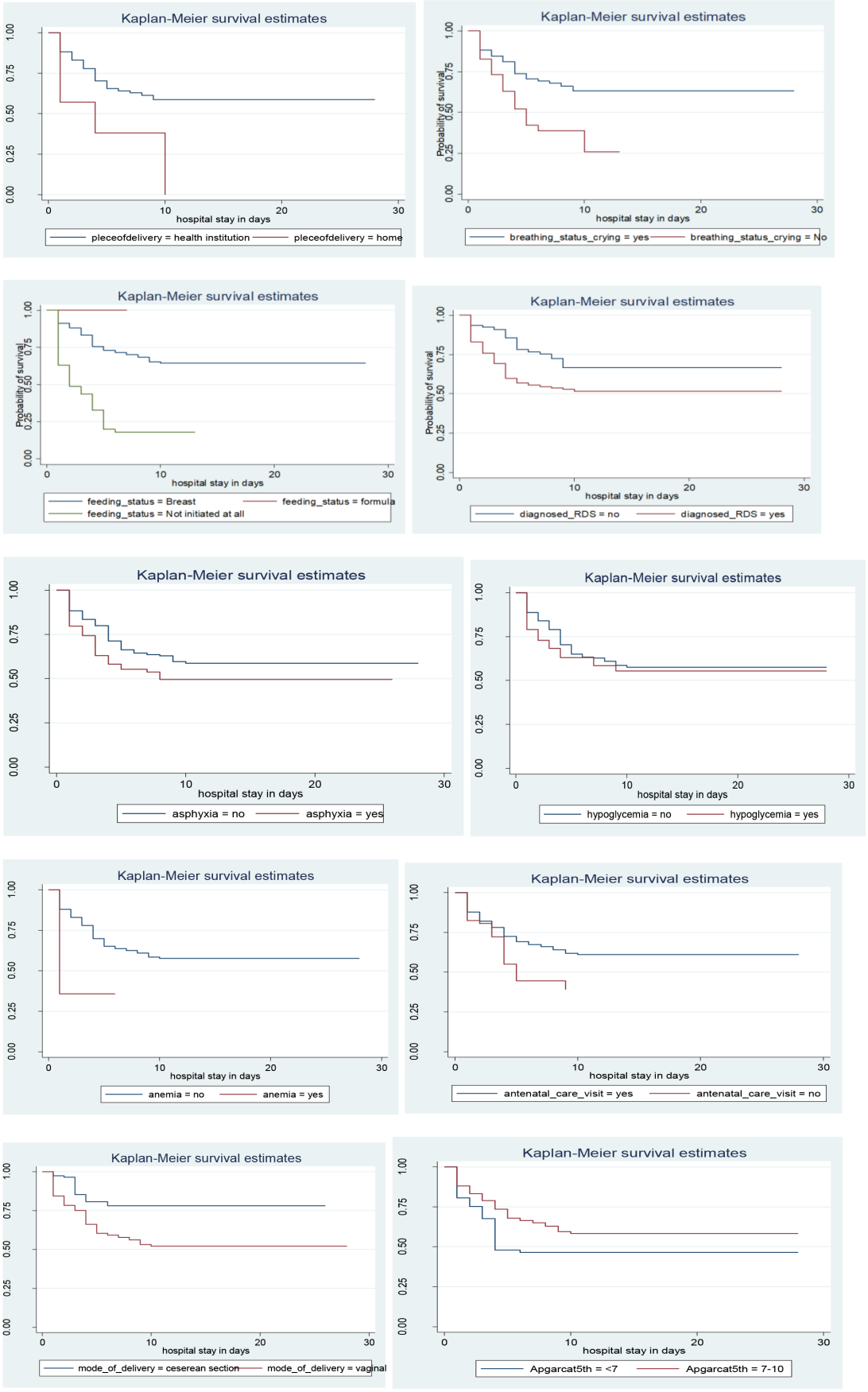

Figure 2 Kaplan-Meier survival curves compare survival time of preterm neonates with the following categories: place of delivery, RDS, hypoglycaemia, breathing status, anaemia, antenatal care visit and mode of delivery. RDS, respiratory distress syndrome.

Table 3 Results of the bivariable and multivariable analyses of preterm neonates admitted to the NICU of Bench Sheko Zone, Keffa Zone and Sheka Zone Hospitals, Southwest Ethiopia, 2021

Predictor	Category	Censored	Died	CHR (95% CI)	AHR (95% CI)	P value
Sex	Female	148	88	1	1	
	Male	266	112	0.75 (0.56 to 0.98)	0.66 (0.47 to 0.94)	0.021*
Mode of delivery	CS	94	21	1	1	
	SVD	320	179	2.29 (1.46 to 3.60)	1.51 (0.77 to 2.95)	0.227
RDS	No	175	45	1	1	
	Yes	239	155	2.17 (1.55 to 3.02)	1.22 (0 .83 to 1.81)	0.31
Hypothermia	No	267	104	0.69 (0.52 to 0.90)	0.63 (0.44 to 0.92)	0.017*
	Yes	147	96	1	1	
Asphyxia	No	352	154	1	1	
	Yes	62	46	1.49 (1.07 to 2.06)	1.2 3 (0.83 to 1.80)	0.30
GA	<28	11	2	1.13 (0.28 to 4.61)	9.28 (1.78 to 48.42)	0.008*
	28–32	115	118	2.45 (1.84 to 3.25)	1.06 (0.70 to 1.62)	0.756
	32.1–36.9	288	80	1	1	
Place of delivery	Health institution	402	184	1	1	
	Home	12	16	2.60 (1.55 to 4.35)	1.17 (0.63 to 2.19)	0.61
KMC provided	Yes	306	34	0.44 (0.29 to 0.66)	0.1 9 (0.12 to 0.29)	0.000*
	No	108	166	1	1	
Cried immediately after birth	Yes	338	132	1	1	
	No	76	68	2.11 (1.57 to 2.83)	1.17 (0.78 to 1.75)	0.44
Feeding type	Breast milk	377	129	1	1	
	Formula	8	–	2.88 (0.25 to 1.28)	5.72 (0.99 to 1.99)	1.000
	Not initiated until the time of first observation	29	71	4.05 (3.02 to 5.43)	2.78 (1.8 to 4.28)	0.000*
Anaemia	No	409	191	1	1	
	Yes	5	9	4.09 (2.08 to 8.06)	6.2 (2.34 to 16.43)	0.000*
ANC visit	Yes	355	145	1	1	
	No	59	55	1.67 (1.24 to 2.32)	1.07 (.66 to 1.75)	0.676
5-minute Apgar score	<7	54	49	0.61 (0.44 to 0.84)	0.96(.63 to 1.48)	0.873
	7–10	360	151	1	1	

1=reference.
*Significant at p<0.05 in the multivariable analysis.
AHR, adjusted HR; ANC, antenatal care; CHR, crude HR; CS, caesarean section; GA, gestational age; KMC, kangaroo mother care; RDS, respiratory distress syndrome; SVD, spontaneous vaginal delivery.

respectively. This might be due to the variation in NICU services (ie, NICU services at the University of Gondar Comprehensive Teaching Hospital and Felege Hiwot Referral Hospital are organised with personnel and equipment based on newborn conditions (severity) and classified as level 1 (basic), level 2 (specialty) and level 3 (subspecialty)) and study design (retrospective follow-up) that not all deaths might be documented.

A controversial finding observed in this study was that being male increases a 34% chance of survival (AHR=0.66, 95% CI: 0.47 to 0.94) compared with records observed in Australia (adjusted OR (AOR)=5.7),[20] Iran (AOR=1.47)[21] and Northeast Brazil (AHR=2.01).[14] Possible reasons for this might be the difference in the study population (>61% of participants in this study were male neonates and were only very preterm neonates) and data used (they used secondary data or a retrospective cohort study design).

A similar research finding in Iran,[27] Australia[28] and Northeast Brazil[21] was observed that neonates with GAs below 28 weeks were substantially more likely to die (AHR=9.28, 95% CI: 1.78 to 48.42) compared with neonates whose GA was greater than 28 weeks. According to this study's findings, preterm neonates who were not started on breast milk or formula milk had a higher risk of dying than those who were (AHR=2.78, 95% CI: 1.8 to 4.28). This result is comparable with research from Northwest Ethiopia (AHR=0.1021, 95% CI: 0.04480)[29] and Uganda (AHR=9.49; 95% CI: 2.84 to 31.68).[17]

Additionally, this study showed that anaemia is a substantial predictor of death (AHR=6.2, 95% CI: 2.34 to 16.43), which is comparable with one study done in Northwest Ethiopia (AHR=4.6699, 95% CI: 1.7687 to 12.3297).[29] Moreover, the risk of death was 63% (AHR=0.63, 95% CI: 0.44 to 0.92) lower in preterm neonates who were not hypothermic than in those who were. This study and one study completed in Uganda are comparable (AHR=1.98; 95% CI: 1.18 to 3.33).[17]

Finally, providing KMC services for preterm neonates can improve their survival time to 81% as compared with that of preterm neonates who did not receive KMC services. This is comparable with a study conducted in Uganda (AHR=9.50; 95% CI: 5.37 to 16.78)[17] and Gondar (73%) (AHR=0.25, 95% CI: 0.13, 0.58).[13]

Since this study was conducted in a multicentre setting, it increases the generalisability of the findings to the entire population. Moreover, this study was prospective; it helps to address probable service-related predictors and control missing data. As the study was conducted in a healthcare setting, those preterm neonates who were born at home and were not admitted to the hospital were not incorporated. Further, this study had a limitation in physician diagnosis subjectivity due to the fact that we did not use consistent diagnostic criteria for each participant, since we already used what they had been diagnosed using history, physical examination and laboratory diagnostic criteria. In addition, this study may lead to missing associated factors after leaving the hospital since this study uses phone calls to follow up for those neonates who were discharged before experiencing the event of interest.

Conclusion and recommendation

This study included a significant proportion of premature newborn deaths. Poor health indicators in preterm neonates, such as delayed initiation of breast feeding and formula feeding, lack of access to a KMC service, home birth, GA of 28 weeks and low initial temperature, have been proven to be predictors of mortality in preterm neonates. Similarly, preterm infants with female sex and anaemia were less likely to survive. Therefore, healthcare workers should encourage KMC services and breastfeeding initiation and avoid bleeding complications to prevent neonates from being anaemic and to increase their chances of survival. Future studies should assess the level of awareness, treatment and control of these risk factors.

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Contributors EM conceptualised the study, wrote the proposal, and performed data analysis and manuscript preparation. Beside this EM take the overall responsibility as principal investigator(PI) for the work. YDG performed data analysis and wrote the results. EA supervised subsequent drafts of the paper. ATS supervised the data analysis. All authors contributed to the article and approved the submitted version.

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Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval A formal letter of collaboration was subsequently written for each hospital after receiving ethical approval from the Mizan-Tepi University Ethical Review Board (ref. no: R/C/S/D/0023/2012). The mothers of the research participants were informed of the goals and aims of the study, and their input was essential to produce accurate and beneficial data. Each mother was given an explanation of the study's goals, selection criteria, confidentiality and advantages before providing oral informed consent. To maintain the confidentiality of the participants, all permission and data collection processes were conducted in a private setting. The participants were advised by the data collectors that they could pause, stop or end the survey at any moment.

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Supplementary File 1: Maternal and obstetrics related characteristics of preterm neonates and their mothers admitted in Intensive Care Unit of Bench Sheko, Kafa and Sheka zone Hospitals, South west Ethiopia, 2021

Characteristics	Category	Total N (%) N=614	Censored N (%) N=414	Death N (%) N=200
Pregnancy status	Single	470(76.55)	306 (65.11)	164(34.89)
	Multiple	144 (23.45)	108 (75.00)	36(25.00)
ANC visit	Yes	500 (81.43	355(71.00	145(29.00)
	No	114 (18.57)	59 (51.75)	55(48.25)
Number of ANC visit	< 4	342 (68.40)	227 (66.37)	115(33.63)
	≥ 4	158 (31.60)	128 (81.01)	30(18.99)
Maternal corticosteroid intake	Yes	69 (13.69)	50 (72.46)	19(27.54)
	No	435 (86.31)	305(70.11)	130(29.89)
Mode delivery	Cesarean section	115(18.73)	94 (81.74)	21(18.260
	Vaginal	499(81.27)	320 (64.13)	179(35.87)
Presentation at delivery	Cephalic	529(86.16)	353 (66.73)	176(33.27)
	Non-cephalic	85 (13.84)	61 (71.76)	24(28.24)
Parity	≤ 1	298 (48.53)	201 (67.45)	97(32.55)
	≥ 2	316(51.47)	213 (67.41)	103(32.59)
Chronic medical problems previously	No	568(92.51)	379(66.73)	189(33.27)
	Yes	46 (7.49)	35 (76.09	11(23.91)
HIV	No	590 (96.09)	392(66.44)	198(33.56)
	Yes	24(3.91)	22 (91.67)	2(8.33)
DM	No	608 (99.02	411 (67.60)	197(32.40)
	Yes	6(0.98	3 (50.00)	3(50.00)
HTN	No	597 (97.23	403 (67.50)	194(32.50)
	Yes	17(2.77	11(64.71)	6(35.29)

Obstetric complications	No	550(89.58)	373 (67.82)	177(32.18)
	Yes	64(10.42)	41 (64.06)	23(35.94)

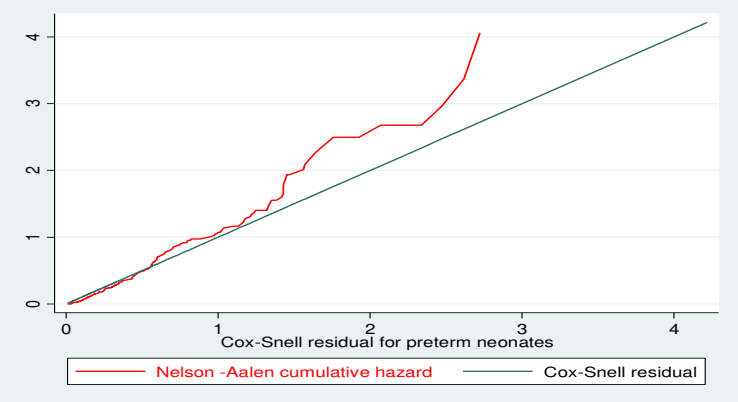
Supplementary File 2: Medical and surgical preterm related Complications characteristics of preterm neonates and their mothers

Characteristics	Category	Total N (%) N=614	Censored N (%) N=414	Death N (%) N=200
Sepsis	no	144 (23.45)	108(75.00)	36(25.000
	Yes	470 (76.55)	306(65.11)	164(34.89)
RDS	No	220 (35.83	175(79.55)	45(20.45)
	Yes	394 (64.17)	239(60.66)	155(39.34)
did the neonate receive resuscitation service	Yes	370 (93.91)	229(61.89)	141(38.11)
	No	24 (6.09)	10 (41.67)	14(58.33)
Necrotizing enterocolitis	No	588 (95.77)	396(67.35)	192(32.65)
	Yes	26 (4.23)	18 (69.23)	8(30.77)
Jaundice	No	533 (86.81)	361 (67.73)	172(32.27)
	Yes	81 (13.19)	53 (65.43)	28(34.57)
Hypoglycemia	No	495 (80.62)	337(68.08)	158(31.92)
	Yes	119 (19.38)	77 (64.71)	42(35.29)
Hypothermia	No	243 (39.58)	147(60.49)	96(39.51)
	Yes	371(60.42)	267 (71.97)	104(28.03)
Perinatal asphyxia	No	506 (82.41)	352(69.57)	154(30.43)
	Yes	108(17.59)	62 (57.41)	46(42.59)
Anemia	No	600 (97.72)	409 (68.17	191(31.83)
	Yes	14 (2.28)	5 (35.71)	9(64.29)

Supplementary File 3: Institutional and professional characteristics of preterm neonates and their mothers admitted in Intensive Care Unit of Bench Sheko, Kafa and Sheka zone Hospitals, South west Ethiopia, 2021

Characteristics	Category	Total N (%) N=614	Censored N (%) N=414	Death N (%) N=200
neonate received KMC	yes	274(44.63)	108(39.42)	166(60.58)
	No	340 (55.37)	306 (90.00)	34(10.00)
KMC service provided room	KMC beds in NICU	172(62.77)	87(50.58)	85(49.42)
	In separate room	72(37.23)	43(59.72)	29(40.28)
Level of NICU	Second level	185 (30.13)	123 (66.49)	62(33.51)
	Third level	429 (69.87)	291(67.83)	138(32.17)

Supplementary File 4: Cox-Snell residual, Nelson -Aalen cumulative hazard graph on preterm neonates



English Version Questionnaire

Instruction: Circle the correct and choose for closed ended questions and write on the space provided for open ended questions

Code number_____Name of hospital_____

Data collection tools for survival and predictors of mortality among preterm neonates in Bench Sheko, Sheka and Keffa Zone Governmental Hospitals			
Part one: Maternal and neonatal socio demographic related variables			
Q.no	**Questions**	**Response column**	**Skip column**
101	Date of birth	___/___/_____days/month(/years)	
102.	Date of admission (Day/Month/Year)	_____	
103	Age of the neonate at admission	_____ minutes/ hours/days	
104	Sex	Male Female	
105	Place of delivery	Home Health institution (hospital, health centre)	
106	Maternal age	_____years	
107	Maternal residency	Urban Rural	
Part two: Neonatal related variables			
201	Birth weight (in gram).	_____	
202	Gestational age at birth	_____ weeks	
203	Had received Kangaroo mother care	A. Yes B. No	
204	APGAR score after delivery	A. Known B. Unknown	If known skip to Q.206
205	If APGAR score unknown, did the neonate cried immediately after birth	A. Yes B. No	

206	If the APGAR score known	A. Score at 1st min-____ B. Score at 5th min_____		
207.	Weight for gestational age at birth	A. Appropriate for gestational age B. Small for gestational age C. Large for gestational age		
208.	Feeding status and type of the neonate	A. Formula feeding B. Breast milk feeding C. Not initiating any feeding at all		If formula and not skip to Q. 210.
209.	If breast milk feeding, the time feeding initiated	A. Within one hour B. Between 1 and 2 hour C. Greater than 2 hours		
210	If breast milk feeding, did neonate had Feeding difficulties	A. Yes B. No		If no skip to 212
211	If yes to no,210 did the neonate get breast milk pumps for feeding in the NICU	A. Yes B. no		
212.	Had the neonate been diagnosed with preterm related medical and surgical neonatal complications **at admission** and at **each day of follow up period?**	1. Sepsis	A. Yes B. No	
		2. Respiratory distress syndrome	A. Yes B. No	If no skip to no,4
		3. If yes to no,2 did received oxygen	A. Yes B. No	
		4. Necrotizing enterocolitis (specify the grade_____)	A. Yes B. No	
		5. Perinatal Asphyxia specify the stage_____)	A. Yes B. No	If no skip to 7
		6. If yes to no,5 did the neonate get neonatal resuscitation (bag-and mask in NICU)	A. Yes B. No	
		7. Pulmonary haemorrhage	A. Yes B. No	

		8. pulmonary hypertension	A. Yes B. No	
		9. Congenital anomalies(specify_____)	A. Yes B. No	
		10. Jaundice	A. Yes B. No	If no skip to 12
		11. if yes to no, 10 received phototherapy or Exchange transfusion	A. Yes B. No	
		12. hypoxic ischemic encephalopathy (specify the grade_____)	A. Yes B. No	
		13. Hypoglycaemia	A. Yes B. No	
		14. Hypothermia	A. Yes B. NO	If no skip to no 16
		15. Did the neonate was received thermal care in NICU (radiant warmer, over heater)	A. Yes B. no	
		16. Anemia	A. Yes B. No	
		17. Other specify_____		
Part three: Maternal and obstetric related predictors				
301.	Parity of the mother	_____		
302.	Mother had antenatal care visit during pregnancy	A. Yes B. No		(If no skip to Q. 304).
303.	If yes, write the number of visits	_____		
304.	Mother had taken antenatal corticosteroid before delivery	A. Yes B. No		
305.	Mother had pregnancy induced hypertension (preeclampsia/	A. Yes B. No		

	eclampsia)			
306.	Mother had chronic diseases	HIV	A. Yes B. No	
		HTN	A. Yes B. No	
		DM	A. Yes B. No	
		If other specify_____		
307.	Mother had obstetric complications during delivery	A. Yes B. No		
308.	Pregnancy type	A. Multiple pregnancy B. Single tone pregnancy		
309.	Mode of delivery	A. SVD B. C/S C. Instrumental delivery		
310.	Presentation at delivery	A. Cephalic B. Non cephalic		
Part four: Institutional and professional factors				
401	Where does the KMC service provided	A. Designated space for KMC B. KMC beds in NICU		
402	Level of NICU	A. 1st level B. 2nd level C. 3rd level		
403	Hospital level	A. Primary B. General C. Referral or specialized		
404	Availability of resuscitation equipment	A. adequately available B. available but not adequate C. not available		
Part five: final outcome status				
401	What was the end outcome status of neonate in the hospital?	A. Death B. Referred C. Left against medical advice D. Discharged with improvement E. Alive until 28 days in NICU		

402	When was the above outcome occurred	_____(days/months/years)	