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Time-to-death and predictors of mortality among preterm neonates diagnosed with neonatal sepsis, Southwest Ethiopia, 2022: prospective follow-up study

Original article

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Abstract: **Objective:** Neonatal sepsis is a critical pathology that particularly affects neonates, especially preterm and low birth weight neonates, with varying incidence according to the onset (early or late) of the disease. Although preterm neonatal mortality related to sepsis is high in Ethiopia and in the study area, limited studies have been conducted on the time-to-death and predictors of mortality among preterm neonates diagnosed with neonatal sepsis. Therefore, this study aimed to determine the time-to-death and predictors of mortality among preterm neonates with neonatal sepsis admitted to government hospitals in Southwest Ethiopia in 2022.

Methods: A prospective cohort study was conducted at the Southwest government hospitals between March 2021 and January 30, 2022. The data were entered into Epi-data version 4.4.2.1 and exported to Stata version 14 for editing, cleaning, and analysis. The Cox proportional hazards (CPH) model was used to identify the predictors of mortality.

Results: In this study, out of 354 preterm neonates diagnosed with neonatal sepsis, 121 (34.18%) had died with an incidence rate of 59.8% (95% confidence interval [CI]: 50–71.5) deaths per 1000 person-day-observations. The median survival time of preterm neonates diagnosed with neonatal sepsis was 15 days. The following factors were the predictors of mortality among preterm neonates diagnosed with neonatal sepsis: (1) the neonate's mother did not have antenatal care (ANC) follow-up (adjusted hazard ratio [AHR] 2.5 [95% CI: 1.3–4.84]); (2) the neonates had an APGAR score <7 (5th-minute activity, pulse, grimace, appearance, and respiration) (AHR 1.5 [95% CI: 1.29–3.46]); (3) and they had comorbidities such as respiratory distress syndrome (RDS) (AHR 1.50 [95% CI: 1.13–2.31]) and jaundice (AHR 1.89 [95% CI: 1.26–2.84]).

Conclusions: In this study, preterm neonates diagnosed with neonatal sepsis showed a higher incidence of mortality compared with other national and local studies. The median survival time of neonates was 15 days. Born from mothers who did not have ANC follow-up, 5th-minute APGAR score <7, and comorbidities such as RDS and jaundice were independent predictors of mortality among preterm neonates diagnosed with neonatal sepsis. Therefore, healthcare providers and other stakeholders should consider prompt and timely diagnosis and therapeutic interventions to preterm neonates with neonatal sepsis.

Keywords: *mortality • neonatal sepsis • predictors • preterm neonate • Southwest Ethiopia • time-to-death*

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1. Introduction

Among infants, there is approximately 5.4 million under-5 mortality in the world, of which 2.5 million die during the neonatal period, and approximately two-third of neonates are born prematurely.[1,2] Approximately 1 million deaths per year are caused by infection occurring in the neonatal period (0–28 days), accounting for over 25% of global neonatal deaths, and 99% of these deaths occur in the developing countries.[2]

Neonatal sepsis is a systemic infection that occurs in infants during the first 4 weeks of life and is a major cause of mortality and morbidity in preterm newborns.[3] Neonatal sepsis is a severe problem affecting the neonates, especially if they are preterm and of low birth weight, with an incidence varying between 1% and 40%.[4]

Neonatal sepsis can be classified into 2 types based on the time of onset after delivery: Early onset sepsis (EOS) (infection occurring during the first 3 days of life) and late-onset sepsis (LOS), which manifests after 3 days and is mainly due to acquiring the pathogen from prolonged hospitalization, especially in preterm newborns.[4,5] Early-onset neonatal sepsis (EONS) is often fatal and remains severe among preterm infants, especially newborn preterm infants, often for prolonged periods.[6]

Most early onset neonatal sepsis is associated with maternal and neonatal characteristics, with preterm being the cause of neonatal intensive care unit (NICU) admissions.[7] Current evidence has revealed that healthcare systems are burdened due to prolonged hospital stays by neonates.[8,9]

The chance of survival for preterm babies in the low resource settings is very low[3] and sepsis accounts for 25% of all neonatal deaths in sub-Saharan Africa (SSA) and southern Asia.[10] In this study area, most of the neonates died due to prematurity (31%) and neonatal sepsis (29.7%).[11]

Despite advances in healthcare to improve neonatal survival rates and reduce complications in preterm infants, preterm neonatal mortality due to sepsis remains high. According to a systematic review and meta-analysis report, the prevalence of neonatal sepsis was approximately 45% in Ethiopia,[12] and based on the 2019 Ethiopian mini demographic health survey report, the neonatal mortality rate was 30 deaths per 1000 live births;[13] prematurity accounts for 11% of under-5 mortality.[14]

Therefore, the third sustainable development goal for child health aims to end and reduce newborns and under-5 mortalities to as low as 12/1000 and 25/1000 by 2030: through better prevention and management of preterm births and severe infections.[15] Although neonatal sepsis and preterm birth are the leading causes of mortality, the studies previously done were focused on either the prevalence or mortality rate of preterm neonates. To the best of our knowledge, limited studies have been conducted on the time-to-death of preterm neonates diagnosed with neonatal sepsis and predictors of mortality in Ethiopia. This study was conducted to fill the evidence gap and to enhance the utility of the evidence on time-to-death and predictors of mortality among preterm neonates with neonatal sepsis. Therefore, this study aimed to determine the time-to-death and predictors of mortality among preterm neonates diagnosed with neonatal sepsis and admitted to governmental hospitals, Southwest Ethiopia.

2. Methods

2.1. Study area and period

The study was conducted in government hospitals at the Southwest Region; officially the South West Ethiopia Peoples' Region is a regional state in southwestern Ethiopia. It was split off from the Southern Nations, Nationalities, and Peoples' Region (SNNPR) on November 23, 2021 after a successful referendum. It consists of Keffa, Sheka, Bench Sheko, Dawro, West Omo Zones, and Konta special woreda. The 3 hospitals are Mizan-Tepi University teaching hospital (MTUTH), Tepi general hospital, and G/tsaddik shewa general hospital. MTUTH is located 584 km far from Addis Ababa. The Tepi general hospital is in the Sheka administrative Zone, 622 km away from Addis Ababa. The G/tsaddik Shewa general hospital is in Keffa zone, 464 km away from Addis Ababa. Hospitals provide delivery and other maternal and newborn care including NICU services. The study was conducted between March 2021 and January 30, 2022 at the government hospitals.

2.2. Study design

A prospective cohort study was conducted among preterm neonates with neonatal sepsis admitted to the NICU wards of hospitals between March 2021 and January 30, 2022.

2.3. Population and eligibility criteria

2.3.1. Source population

All preterm neonates diagnosed with neonatal sepsis and admitted in the NICU ward to government hospitals during the study period.

2.3.2. Study population

All selected neonates diagnosed with neonatal sepsis and admitted in the NICU ward to government hospitals during the study period.

2.3.3. Inclusion criteria

Live preterm neonates diagnosed with neonatal sepsis and admitted in the NICU were eligible for the study.

2.3.4. Exclusion criteria

Preterm neonates diagnosed with neonatal sepsis that had an incomplete observation during follow-up, and unknown date of admission and date of death were excluded.

2.4. Sample size determination

Power log rank estimated sample sizes for 2-sample comparison of survivor functions—Log-rank test; Freedman method was used to obtain representative samples of preterm neonates admitted to the NICU with diagnosed neonatal sepsis as follows:

$$E = \frac{\left(z@\frac{1}{2} + ZB\right)^2}{(lnHR)2\ p(1-P)} = \frac{\left(z@\frac{1}{2} + ZB\right)^2}{\theta 2\ \pi(1-\pi)}$$

Where:
z@1/2: z value at 95% confidence interval (CI) = 1.96;
ZB: the power of the study = 80%;
P = 50% cumulative mortality rate;
p = mortality rate;hazard ratio (HR) = 0.5;
Θ = ln (HR), i.e., HR = exp. (Θ) and then Θ = ln (HR).

The total sample size was calculated as $n = \frac{E}{p(E)}$.

Adding a 10%, for incomplete data/missing data the final minimum sample size required was 363.

2.5. Sampling techniques and procedure

From 7 government hospitals in the southwest region, MTUTH, Tepi general hospital, and G/tsaddik Shewa general hospital were selected using the lottery method.

Proportional allocation was performed for each hospital based on the previous number of preterm neonates diagnosed with neonatal sepsis and admitted to the NICU. Thereafter, we included all preterm neonates diagnosed with neonatal sepsis who were admitted to the NICU. The study participants were selected from each hospital using a consecutive sampling technique. All recruited study participants were followed until the outcome of interest (i.e., either death or censure) appeared.

2.6. Study variables

Dependent variable: Time-to-death and dichotomized into death or censored.

Independent variables: Include maternal and neonatal socio-demographic variables, medical, obstetric, surgical, and neonatal characteristic variables.

2.7. Operational definitions

Median survival time: The median survival of time of 50% of neonates.

Survival status: The outcome of premature neonates diagnosed with sepsis, either death or censored.

Death/Event: Refers to the neonates that have died while in the therapeutic units and declared as dead in the treatment logbook by the physician.

Censored: Preterm neonates diagnosed with neonatal sepsis and admitted in the NICU. Those alive beyond 28 days of neonatal age, those left against medical advice, or discharged with improvement and referred.

Time origin: Specific time of admission of preterm neonates at NICU with diagnosis of neonatal sepsis.

Time of exit: Specific time of observation outcome (death or censored).

2.8. Data collection tools and procedures

After reviewing the literature, the tool was adapted and prepared in English and translated into the local language, Amharic, and re-translated back into English (Supplementary File 1). Data were collected through face-to-face interviews with the mothers and neonatal chart reviews (primary and secondary). Secondary data were used to obtain baseline information that the mothers could not address. After excluding all baseline data on different related factors, data on factors that can occur starting from the first day of follow-up were collected during follow-up (i.e., from the time of admission to 28 days of neonatal age) or at the occurrence of an event of interest (i.e., death or censored). Only the first episode was included if the patients were admitted with >1 episode of neonatal sepsis over 28 days.

2.9. Data processing and analysis

After coding, editing, and cleaning data were entered into Epi-data manager version 4.4.2.1 (The EpiData

Association, Odense, Denmark) and exported to Stata version 14 (StataCorp LLC, Texas, USA) for analysis. The median survival time was estimated using Kaplan–Meier survival estimates. Predictors of mortality were identified using the Cox proportional hazards (CPH) model. The assumptions of the CPH model were assessed using the Schoenfeld residual/global test (0.2194). Multi-collinearity was assessed using the variance inflation factor (VIF) (1.21). Based on bivariate analysis, variables with *P*-value <0.25 were transferred to the multivariable analysis. Variables with *P*-value <0.05 at 95% confidence level in multivariable analysis were considered as independent predictors for mortality.

2.10. Data quality assurance

Pretest was conducted on 5% of sample size at Chena General Hospital, before actual data collection period and then editions and wording were made. Training was provided to the data collectors and supervisors on data collection techniques and ethical issues. Supervisors regularly checked the completed questionnaires.

3. Results

In this study, the total sample of 363 preterm neonates with diagnosis of sepsis were reviewed. Of these, 9 (2.5%) were excluded since they had incomplete medical charts. The remaining 354 (97.5%) preterm neonates were included in the analysis making response rate of 97.5%. Each preterm neonate diagnosed with neonatal sepsis had a different length of hospital stay: a minimum of 1 day and a maximum of 28 days.

3.1. Maternal and neonatal sociodemographic-related factors

In this study, 178 neonates (50.28%) were male and 176 (49.72%) were female. A majority (97.46%) of the preterm neonates were in the age category of ≤7 days during admission. About 306 (86.44%) of women were found in the age range of 20–35 years with a median age of 25 years (interquartile range of 22–30) (Table 1).

3.2. Medical and surgical complication/ comorbidity-related factors

A total of 116 (32.77%), 92 (25.99%), 164 (46.33%), and 42 (11.86%) preterm neonates with neonatal sepsis also had comorbidity of respiratory distress syndrome (RDS), hypoglycemia, hypothermia, and prenatal asphyxia, respectively (Table 2).

Variables and category	Total	Outcome status	
		Censored	Death
Age (days)			
≤7	345 (97.46)	224 (64.93)	121 (35.07)
8–28	9 (2.54)	9 (100.0)	-
Gender			
Female	176 (49.72)	122 (69.32)	54 (30.68)
Male	178 (50.28)	111 (62.36)	67 (37.64)
Maternal age (years)			
<20	22 (6.21)	12 (54.55)	10 (45.45)
20–35	306 (86.44)	204 (66.67)	102 (33.33)
≥35	26 (7.34)	17 (65.38)	9 (34.62)
Residency of mothers			
Urban	109 (30.79)	81 (74.31)	28 (25.69)
Rural	245 (69.21)	152 (62.04)	93 (37.96)

Note: NICU, neonatal intensive care unit.

Table 1. Sociodemographic characteristics of preterm neonates diagnosed with neonatal sepsis admitted in NICU ward of Government Hospitals in Southwest Ethiopia, from March 2021 to January 30, 2022 (N = 354), N (%).

Variables and category	Total	Outcome status	
		Alive	Death
RDS			
No	238 (67.23)	170 (71.43)	68 (28.57)
Yes	116 (32.77)	63 (54.31)	53 (45.69)
Jaundice			
No	313 (88.42)	202 (64.54)	111 (35.46)
Yes	41 (11.58)	31 (75.61)	10 (24.39)
Anomaly			
No	342 (96.61)	224 (65.50)	118 (34.50)
Yes	12 (3.39)	9 (75.00)	3 (25.00)
Hypoglycemia			
No	262 (74.01)	187 (71.37)	75 (28.63)
Yes	92 (25.99)	46 (50)	46 (50)
Hypothermia			
No	190 (53.67)	143 (75.26)	47 (24.74)
Yes	164 (46.33)	90 (54.88)	74 (45.12)
Asphyxia			
No	312 (88.14)	208 (66.67)	104 (33.33)
Yes	42 (11.86)	25 (59.52)	17 (40.48)

Note: NICU, neonatal intensive care unit; RDS, respiratory distress.

Table 2. Medical/surgical comorbidity characteristics of preterm neonates diagnosed with neonatal sepsis admitted in the NICU ward of Government Hospitals in Southwest Ethiopia from March 2021 to January 30, 2022 (N = 354), N (%).

Characteristics and category	Total	Outcome status	
		Censored	Death
Where delivery was conducted			
Health institution	340 (96.05)	225 (66.18)	115 (33.82)
Home	14 (3.95)	8 (57.14)	6 (42.86)
Neonatal Wight (g)			
<2500	303 (85.59)	189 (62.38)	114 (37.62)
≥2500	51 (14.41)	44 (86.27)	7 (13.73)
GA (weeks)			
28–31	51 (14.41)	24 (47.06)	27 (52.94)
32–36	303 (85.59)	209 (68.98)	94 (31.02)
First minute APGAR score			
<7	238 (67.23)	142 (59.66)	96 (40.34)
≥7	116 (32.77)	91 (78.45)	25 (21.55)
5th minute APGAR			
<7	122 (34.46)	53 (43.44)	69 (56.56)
≥7	232 (65.54)	180 (77.5)	62 (22.41)
Application of KMC			
Yes	154 (72.73)	112 (72.73)	42 (27.27)
No	200 (56.50)	121 (60.50)	79 (39.50)
Weight for GA			
LGA	17 (4.8)	13 (76.47)	4 (23.53)
AGA	271 (76.55)	193 (71.22)	78 (28.78)
SGA	66 (18.64)	27 (40.91)	39 (59.09)
Breathing status at birth			
Didn't cry	113 (31.92)	36 (31.86)	77 (68.14)
Cry	241 (68.08)	197 (81.74)	44 (18.26)

Note: AGA, appropriate for gestational age; APGAR, activity, pulse, grimace, appearance and respiration; GA, gestational age; KMC, kangaroo mother care; LGA, large for gestational age; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; SGA, small for gestational age.

Table 3. Neonatal-related characteristics of preterm neonates diagnosed with neonatal sepsis admitted in the NICU of Government Hospitals in Southwest Ethiopia from March 2021 to January 30, 2022 (N = 354), N (%).

3.3. Characteristics of the neonates

A total of 340 (96.05%) of the preterm neonates diagnosed with neonatal sepsis were born at health institutions. Most (85.59%) of the preterm neonates were born with low birth weight (<2500 g) with a median weight of 1950.00 g. A total of 303 (85.59%) preterm neonates were born with gestational age (GA) of 32–36 weeks with median GA of 34 weeks and interquartile range of 32–36 weeks; 238 (67.23%) preterm neonates had 1st-minute Apgar score range <7; 232 (65.54%) preterm neonates also had 5th-minute activity, pulse, grimace, appearance, and respiration (APGAR) of ³7 and only 200 (56.50%) preterm neonates received kangaroo mother care (KMC) at the time of hospitalization in the NICU (Table 3).

Characteristics and category	Total	Outcome status	
		Censored N (%)	Death N (%)
Chronic medical disease			
No	339 (95.76)	218 (67.26)	111 (32.74)
Yes	15 (4.24)	5 (33.33)	10 (66.67)
Antenatal care			
No	23 (6.5)	11 (47.83)	12 (52.17)
Yes	331 (93.5)	222 (67.07)	109 (32.93)
Obstetric complications			
No	312 (88.14)	199 (63.78)	113 (36.22)
Yes	42 (11.86)	34 (80.95)	8 (19.05)
Mode of delivery			
C/S	73 (20.62)	57 (78.08)	16 (21.92)
Vaginal	281 (79.38)	176 (62.63)	105 (37.37)
Pregnancy type			
Single	269 (75.99)	188 (69.8)	81 (30.11)
Multiple	85 (24.01)	45 (52.94)	40 (47.06)
Febrile illness of the mother			
No	335 (94.63)	221 (65.97)	114 (34.03)
Yes	19 (5.37)	12 (63.16)	7 (36.84)
Presentation			
Cephalic	440 (96.05)	224 (65.88)	116 (34.12)
Non-cephalic	14 (3.95)	9 (64.29)	5 (35.71)
Parity			
Para I	166 (46.89)	113 (68.07)	53 (31.93)
Multi-para	188 (53.11)	120 (63.83)	68 (36.17)

Note: NICU, neonatal intensive care unit.

Table 4. Maternal medical and obstetrics-related characteristics of preterm neonates diagnosed with neonatal sepsis admitted in the NICU of Government Hospitals, in Southwest Ethiopia from March 2021 to January 30, 2022 (N = 354), N (%).

3.4. Maternal characteristics

A total of 330 women (93.5%) had a history of at least one antenatal care (ANC) follow-up during their current pregnancy. Only 42 (11.86%) women had a history of obstetric complications such as placental abruption, placenta previa, and pregnancy induced in current pregnancy. The majority (75.99%) were single tone type of pregnancy. Most preterm neonates were born from a multi-para mother, which was around 53.11% (Table 4).

3.5. Treatment outcome, mortality rate, and median survival time among preterm neonates diagnosed with neonatal sepsis

3.5.1. Treatment outcome of preterm neonates diagnosed with neonatal sepsis

From 354 neonates, 121 (34.18%) (95% CI: 29.40–39.30) have died during the follow-up period and the remaining 233 (65.82%) were censored (Figure 1).

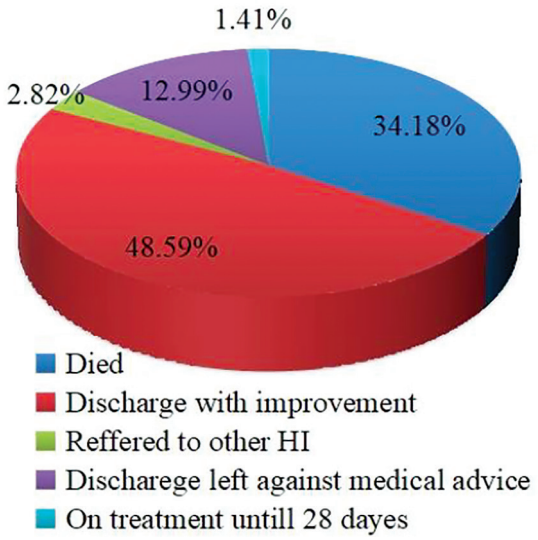

Figure 1. Treatment outcome among preterm neonates diagnosed with neonatal sepsis admitted in the NICU of Government Hospitals in Southwest Ethiopia from March 2021 to January 30, 2022 (N = 354).

Note: NICU, neonatal intensive care unit.

3.5.2. Median survival time among preterm neonates diagnosed with neonatal sepsis

Overall median survival time of preterm neonates with sepsis was 15 days (95% CI: 10–28). The 50% cumulative survival functions of preterm neonates with neonatal sepsis died at a median of 15 days' duration (Figure 2).

The fitness of the final model was checked graphically using the Cox Snell residual, showing that the hazard function follows the 45° line closely confirming that the final model is a good fit (Figure 3).

3.5.3. Predictors of time-to-death in preterm neonates diagnosed with sepsis

Bivariate analysis revealed the sex of the neonates, maternal residence, antenatal care status, pregnancy-related complications, RDS, jaundice, KMC, mode of delivery, breathing status, maternal parity, birth weight, hypoglycemia, hypothermia, GA, weight for gestational age (WFGA), type of pregnancy, APGAR 1st minute <7, and APGAR 5th minute <7 were significant at *P*-value <0.25, and were eligible for multivariate analysis. Significant variables in bivariate analysis were included in the multivariate analysis. Multivariate analysis covariates such as antenatal care status, RDS, jaundice, and APGAR score at 5 min were significant at *P*-value <0.05 and independent predictors of neonatal mortality.

Preterm neonates with neonatal sepsis who were born from mothers who did not attend at least one ANC had 2.5 times higher hazard of mortality than neonates born from mothers attending at least one ANC during the current pregnancy (adjusted hazard ratio [AHR] 2.5 [95% CI: 1.3–4.84]). Preterm neonates diagnosed with

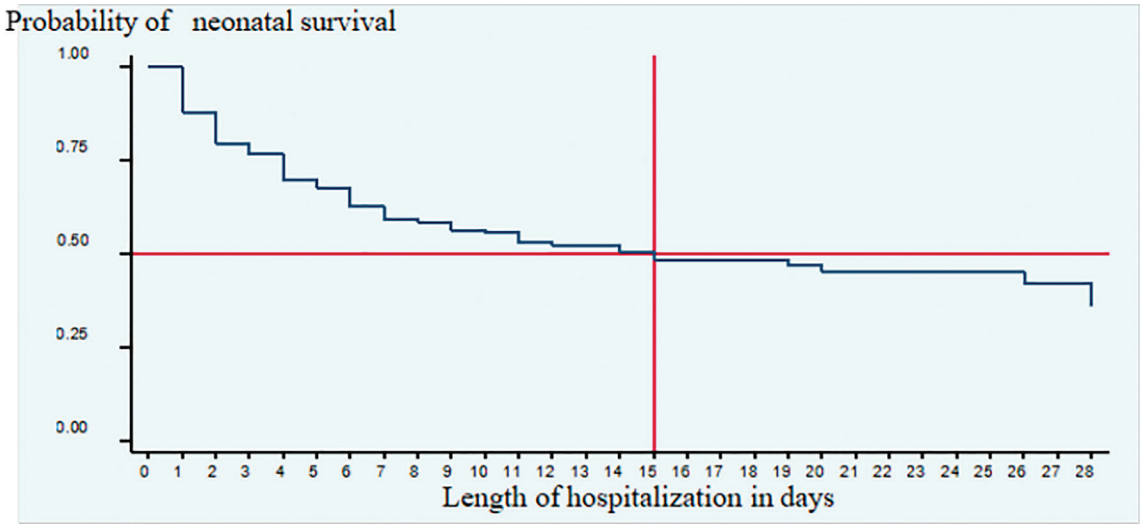

Figure 2. Kaplan–Meier survival estimate graph overall median survival time among preterm neonates diagnosed with sepsis admitted to Government Hospitals in Ethiopia, 2022 (N = 354).

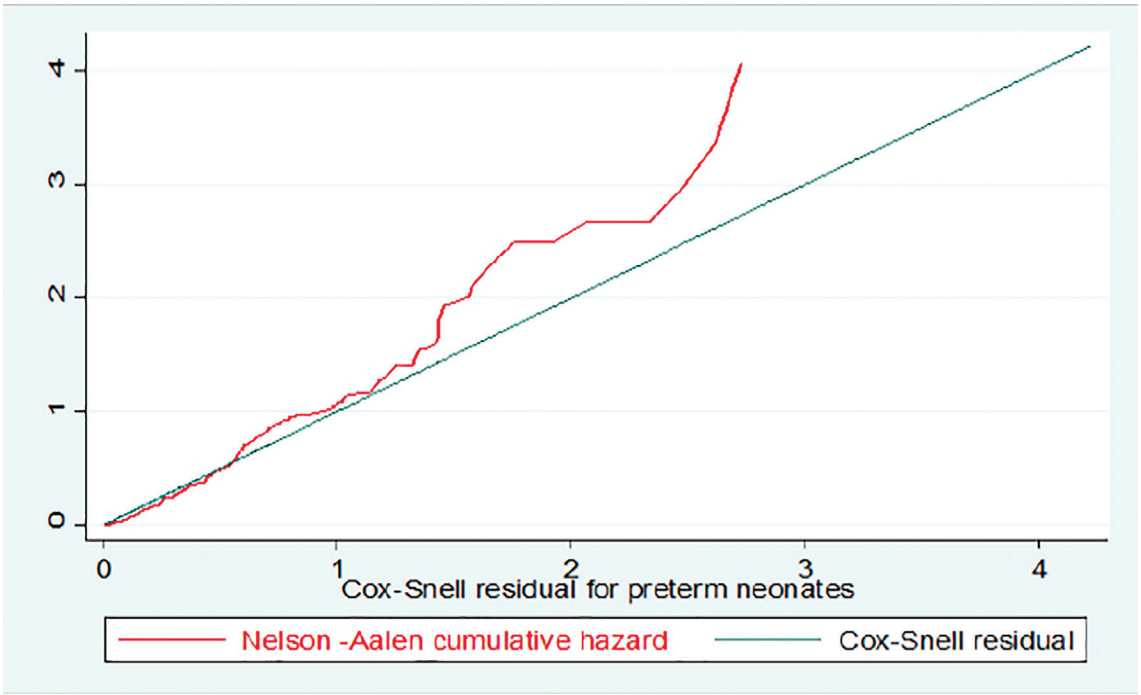

Figure 3. Cox-Snell residual, Nelson-Aalen cumulative hazard graph among preterm neonates diagnosed with sepsis and admitted to Government Hospitals in Southwest Ethiopia, 2022 (N = 354).

both neonatal sepsis and RDS had 1.5 times higher hazard of mortality than preterm neonates without RDS (AHR 1.50 [95% CI: 1.13–2.31]). Preterm neonates diagnosed with both neonatal sepsis and jaundice had 1.89 times higher hazard of mortality than preterm neonates without jaundice (AHR 1.89 [95% CI: 1.26–2.84]). In addition, preterm neonates diagnosed with neonatal sepsis who had 5 min APGAR scores <7 after birth had a 1.5 times higher hazard of mortality from neonatal sepsis than preterm neonates who had >7 APGAR scores after birth (AHR 1.5 [95% CI: 1.29–3.46]) (Table 5).

4. Discussion

In this study, the overall mortality rate of preterm neonates with neonatal sepsis was 121 (34.18%) 95% CI: 29.40–39.30). This study was in line with a study conducted at Jimma University Specialized Hospital,[16] where the mortality rate was 34.9%. This similarity may be due to the similarity in sociodemographic status. On the other hand, this study was higher than the studies conducted in Iran,[17] Pakistan,[18] and the University of Gondar Comprehensive Specialized Hospital,[19] where the overall proportion of deaths was 9.1%, 14%, and 28.8%, respectively. A possible explanation may that be in our study the participants were preterm neonates with a confirmed diagnosis of neonatal sepsis that would lead to higher mortality, whereas other studies were conducted on preterm neonates admitted to NICU. Another possible reason may be the differences in neonatal service provision.

The median survival time of neonates was 15 days (95% CI: 10–28) across the NICU during the hospitalization period. This result was lower than that reported in Ethiopia at the University of Gondar Hospital,[20] in which the overall median survival time was 28 days. A possible reason for this marked difference may be the difference in inclusion criteria of the study subjects and differences in neonatal care provision. In this study, all the subjects were cases of neonatal sepsis, whereas in the study conducted at the University of Gondar Hospital, the study participants were all preterm neonates with/without neonatal sepsis that may have contributed to the longer median survival time.

Preterm neonates who were born to mothers who did not have ANC follow-up and who had neonatal sepsis had 2.5 times higher hazard of death than preterm neonates who were born to mothers who had ANC follow-up (AHR: 2.5 [95% CI: 1.3–4.8]). This study was supported by a study conducted in Ethiopia at the University of Gondar Hospital.[20] A possible reason might be that lack of ANC visits may result in inadequate monitoring of pregnancy-related infections and may lead to neonatal complication during and after delivery, which may be associated with increased risk of neonatal death.

Variables and category	Outcome status		CHR (95% CI)	AHR (95%CI)	*P*-value
	Alive	Death			
Gender					
Female	122	54	1	1	
Male	111	57	1.38 (0.96–1.93)	1.38 (0.94–2.02)	0.098
Residency					
Urban	81	28	1	1	
Rural	152	93	1.48 (0.99–2.22)	1.44 (0.89–2.33)	0.132
Antenatal care					
Yes	222	109	1	1	
No	11	12	2.06 (1.13–3.80)	2.5 (1.3–4.84)	0.005*
Pregnancy complication					
No	199	113	1	1	
Yes	34	8	2.43 (1.27–4.65)	0.55 (0.22–1.39)	0.209
Respiratory distress					
No	170	68	1	1	
Yes	63	53	1.57 (1.06–2.23)	1.50 (1.13–2.31)	0.045*
Jaundice					
No	202	111	1	1	
Yes	31	10	3.08 (2.18–4.38)	1.89 (1.26–2.84)	0.002*
Application of KMC					
Yes	112	42	1	1	
No	121	79	1.66 (1.15–2.40)	0.97 (0.64–1.47)	0.891
Mode of delivery					
C/S	57	16	1	1	
Vaginal	176	105	0.54 (0.32–0.92)	0.56 (0.32–0.99)	0.075
Breathing status					
Cried	197	44	1	1	
Didn't cry	36	77	4.12 (2.88–5.90)	2.9 (1.88–4.51)	0.09
Parity					
Para I	113	53	1	1	
Multi-para	120	68	1.40 (0.98–2.02)	1.75 (1.19–2.58)	0.075
Weight (g)					
≥2500	189	114	1	1	
<2500	44	7	2.76 (1.29–5.94)	1.93 (0.83–4.47)	0.125
Hypoglycemia					
No	187	75	1	1	
Yes	46	46	1.78 (1.24–2.55)	1.54 (0.97–2.45)	0.064
Hypothermia					
No	143	47	1	1	
Yes	90	74	1.89 (1.32–2.67)	1.35 (0.86–2.12)	0.194
GA (weeks)					
≥32	24	27	1	1	
<32	209	94	0.60 (0.40–0.91)	0.84 (0.52–1.37)	0.494
WFGA					
AGA	193	78	1	1	
LGA	13	4	0.92 (0.34–2.51)	0.94 (0.32–2.79)	0.916
SGA	27	39	2.03 (1.3–2.96)	1.24 (0.81–1.94)	0.338

(*Continued*)

Table 5. (Continued)

Variables and category	Outcome status		CHR (95% CI)	AHR (95%CI)	*P*-value
	Alive	Death			
Pregnancy types					
Single tone	188	81	1	1	
Multiple	45	40	1.37 (0.94–1.99)	1.08 (0.71–1.65)	0.721
APGAR 1st min.					
<7	142	96	0.56 (0.36–0.85)	0.69 (0.39–1.24)	0.216
≥7	91	25	1	1	
APGAR 5th min					
<7	53	69	2.7 (1.91–3.93)	2.11 (1.29–3.46)	0.015*
≥7	180	52	1	1	

Note: NB: *significant at *P*-value < 0.05 in multi-variable analysis; 1, considered as reference category.
AGA, appropriate for gestational age; AHR, adjusted hazard ratio; APGAR, activity, pulse, grimace, appearance and respiration; CHR, crude hazard ratio; CI, confidence interval; GA, gestational age; KMC, kangaroo mother care; LGA, large for gestational age; NICU, neonatal intensive care unit; RDS, respiratory distress syndromerespirator syndrome; SGA, small for gestational age; WFGA, weight for gestational age.

Table 5. Bivariate and multivariate result of preterm neonates diagnosed with neonatal sepsis, admitted in the NICU of Governmental Hospitals, in Southwest Ethiopia from March 2021 to January 30, 2022 (N = 354).

In this study, neonates diagnosed with both sepsis and RDS had 1.5 times hazard of mortality as compared with preterm neonates who had been diagnosed with only neonatal sepsis (AHR 1.50 [95% CI: 1.13–2.31]). This finding was supported by the studies conducted in Nigeria,[21] and Tikur Anbessa Specialized Hospital, Ethiopia.[22] The possible reason might be the fact that preterm neonates develop RDS, a prematurity-related surfactant deficiency mostly involving risk of lung collapse, which leads to difficulty of breathing and unable to survive, finally ending up with death. Many studies have confirmed an inverse relationship between RDS and GA.[23]

In this study, preterm neonates diagnosed with both neonatal sepsis and jaundice had 1.89 times higher hazards of mortality than preterm neonates without jaundice (AHR 1.89 [95% CI: 1.26–2.84]). A possible reason could be that increased risk of jaundice induced neurological injury in preterm neonates, leading to death. In addition, in this study, preterm neonates diagnosed with neonatal sepsis and 5th-minute APGAR score of <7 had a 2.1 times higher hazard of mortality than preterm neonates who had an APGAR score >7 (AHR: 2.11 [95% CI: 1.29–3.46]). This is supported by studies conducted in China,[24] Brazil,[25] Iran,[17] and the University of Gondar Hospital.[19] This might be due to that neonates who were born with 5th minute APGAR score of <7 were severely asphyxiated and may end up with death.

4.1. Strength of the study

This study was conducted by considering censoring and time to event using survival analysis and it was easy to establish a temporal relationship between the dependent and independent variables. The study used prospective data, and the better quality of data on the primary exposure and exposures are assessed before outcomes occur, hence there is less likelihood for bias. In addition, the study was conducted in multicenter settings using prospective follow-up, which increases the reliability and generalizability of data. Finally, the study has novel findings on an important topic that has not been explored before.

4.2. Limitations of the study

We had a relatively small sample size, which is difficult to generalize to all preterm neonates diagnosed with neonatal sepsis. Second, since the study was conducted among preterm neonates diagnosed with neonatal sepsis and were admitted to only government hospitals, it cannot be generalized to the preterm neonates admitted to private hospitals and healthcare centers.

5. Conclusions

In this study, preterm neonates diagnosed with neonatal sepsis showed a higher incidence of mortality than in other national and local studies, and the median survival time of neonates was 15 days during the hospitalization period. Born from a mother who did not have ANC follow-up, 5th-minute Apgar score <7, and having comorbidities such as RDS and jaundice were the independent predictors of mortality among preterm neonates diagnosed with neonatal sepsis. Therefore, healthcare professionals and other stakeholders should encourage mothers to

attend antenatal care, work hard to diagnose accurately and provide therapeutic interventions for comorbidities of preterm neonates with neonatal sepsis, all of which could reduce the high incidence of mortality among preterm neonates diagnosed with neonatal sepsis.

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Author contributions

Conceptualization: B.F., Y.D., T.B., A.Y., and E.A.; methodology: B.F. and Y.D.; software: T.B. and A.Y.; validation: B.F. and A.Y.; formal analysis B.F. and E.A.; investigation: Y.D. T.B., and A.Y.; data curation: B.F. and E.A.; writing-original draft preparation and writing, review and editing: all authors; supervision: Y.D. and B.F. All authors have read and agree to the published version of the manuscript.

Data availability statement

The data are available on request to the corresponding author.

Ethical approval

Ethical clearance was obtained from the Mizan Tepi University institutional ethical review board (IRB No. R/C/S/D10067/2014) and letters of cooperation were handled by each hospital. Oral informed consent was obtained from the mother of each participant. Additionally, the names of participants were not mentioned anywhere in the study questionnaires. Only identification numbers and the information obtained were held confidentially.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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