ASRAT WOLDEYES HEALTH SCIENCE CAMPUS

SCHOOL OF NURSING AND MIDWIFERY

DEPARTMENT OF PEDIATRICS AND CHILD HEALTH NURSING

TIME TO RECOVERY OF NEONATAL SEPSIS AND DETERMINANT FACTORS AMONG NEONATE ADMITTED AT NICU IN PUBLIC COMPREHENSIVE SPECIALIZED HOSPITALS IN SOUTH NATION NATIONALITY AND PEOPL`S REGIONAL STATE, ETHIOPIA, 2023

BY: ELIAS GENETI (BSc)

A THESIS SUBMITTED TO ASRAT WOLDEYES HEALTH SCIENCE CAMPUS SCHOOL OF NURSING AND MIDWIFERY, DEBRE BREHAN UNIVERSITY, FOR PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR MASTER'S IN PEDIATRICS AND CHILD HEALTH NURSING.

AUGAST, 2023

DEBRE BREHAN, ETHIOPIA

DEBRE BREHAN UNIVERSITY

ASRAT WOLDEYES HEALTH SCIENCE CAMPUS

SCHOOL OF NURSING AND MIDWIFERY

DEPARTMENT OF PEDIATRICS AND CHILD HEALTH NURSING

TIME TO RECOVERY OF NEONATAL SEPSIS AND DETERMINANT FACTORS AMONG NEONATE ADMITTED AT NICU IN PUBLIC COMPREHENSIVE SPECIALIZED HOSPITALS IN SOUTH NATION NATIONALITY AND PEOPL`S REGIONAL STATE, ETHIOPIA, 2023

NAME OF INVESTIGATOR: **ELIAS GENETI** (BSC NURSING)

NAME OF ADVISORS:

1. **AYELE MAMO** (BSc, MSC, ASSISTANT PROFESSOR IN PEDIATRICS & CHILD HEALTH NURSING)
2. **MOHAMMED TESSEMA** (BSc, MSC IN NEONATOLOGY NURSING)

A THESIS SUBMITTED TO ASRAT WOLDEYES HEALTH SCIENCE CAMPUS SCHOOL OF NURSING AND MIDWIFERY, DEBRE BREHAN UNIVERSITY, FOR PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR MASTERS IN PEDIATRICS AND CHILD HEALTH NURSING.

AUGAST, 2023

DEBRE BIRHAN, ETHIOPIA

APPROVAL SHEET

This proposal is developed by Elias Geneti (BSc nurse) on the title Time to Recovery of Neonatal Sepsis and determinant factors among neonate admitted at NICU in Public Comprehensive Specialized hospitals, SNNPRS, Ethiopia 2023. It is accepted in its present form by board of examiners as satisfying thesis requirement for the masters in pediatric and child health nursing 2023 for requirement for the degree of masters in pediatrics and child health nursing.

Name of Investigator: **Elias Geneti** **Signature**: _____ **Date:** _____

EXAMINER

NAME OF EXAMINER	**SIGNATURE**	**DATE**

NAME OF ADVISOR (s)

Ayele Mamo		
MAINE-ADVISOR	**SIGNATURE**	**DATE**
Mohammed Tessema		
CO-ADVISOR	**SIGNATURE**	**DATE**

Abstract

Background:-Neonatal sepsis is a clinical syndrome of bacteraemia characterized by systemic signs and symptom of infection in the first 28 days of life. Several studies were assessed the magnitude and associated factors of neonatal sepsis but there was a limited data on recovery time of neonatal sepsis. Therefore, this study aimed to assess the recovery time of neonatal sepsis among neonates admitted to the neonatal intensive care unit of public comprehensive specialized hospitals which is not well known.

Objective:-The objective of this study was to assess time to recover of neonatal sepsis and its determinant factors among admitted neonates at NICU in selected public comprehensive specialized of SNNPRS, Ethiopia, 2023.

Method:-A retrospective follow up study was conducted among 643 charts of neonates with neonatal sepsis who was admitted in NICU at public comprehensive specialized hospitals in SNNPRS from 1st January 2021 to January 1st, 2023 using systematic random sampling. Kaplan Meier curve and log-rank were used to estimate recovery time and to compare the probability of survival time. Cox Proportional Hazard regression model was used. Variables with p-value < 0.05 in multivariable analysis using the cox proportional hazard model was stated as statistically significant predictors of recovery from neonatal sepsis.

Result: The overall median recovery time was 8 days. The incidence rate of recovery from neonatal sepsis was 9.86 per 100 neonate day's observation and the recovery rate of neonate admitted with neonatal sepsis was 83.2%. The factors significantly associated with recovery time of neonatal sepsis includes; respiratory distress (AHR: 0.71, 95% CI (0.59, 0.85)), resuscitation at birth (AHR: 0.65, 95% CI (0.49, 0.87)), having fever (AHR: 0.82, 95% CI (0.67, 0.99)) and frequency of antibiotics change (AHR: 2.0, 95% CI (1.57, 2.63)).

Conclusion: The time to recovery from neonatal sepsis was significantly affected by resuscitation at birth, respiratory distress, having fever and frequency of antibiotics change. Therefore, giving special attention to neonates with identified predictors is for their recovery.

Acknowledgements

I would like to thank Debre Brehan University, Asrat Woldeyes Health Science Campus School of nursing and midwifery Department of pediatrics and child health nursing for giving me a chance to conduct this thesis. Then, I express my heartfelt gratitude to my advisors Ayele Mamo (Assistant professor in pediatrics and child health nursing) and Mohammed Tessema (MSc in Neonatology nursing) for their commitment to supervision, guidance, and encouragement throughout in the development of research proposal.

Finally I would like to extend my thanks to Wachemo University Nigist Eleni Mohammed Memorial Comprehensive specialized Hospital for sponsoring my master program.

Contents

List of table

List of figure

ABBREVIATIONS

APGAR	Appearance Pulse Grimace Activity Respiration
EONS	Early Onset Neonatal Sepsis
LMIC	Low- and Middle-Income Countries
LONS	Late onset neonatal sepsis
LDOHS	Long Duration of Hospital Stay
MAS	Meconium Aspiration Syndrome
NICU	Neonatal Intensive Care Unit
NS	Neonatal Sepsis
PROM	Premature Rapture of Membrane
SIRS	Systemic inflammatory response syndrome
SNNPRS	South Nation Nationality & Peoples Regional State
WCUNEMMCSH	Wachemo University Nigist Eleni Mohammed Memorial Comprehensive Hospital

1. INTRODUCTION

1.1. Background

Neonatal sepsis is a clinical syndrome of bacteraemia characterized by systemic signs and symptom of infection in the first 28 days of life (1-3). Sepsis is a life-threatening condition that can cause organ dysfunctions and affect the health of neonates due to late initiation of treatment to infection(4). It presents with clinical features of temperature instability, respiratory distress, cyanosis, apnea, feeding difficulties, lethargy or irritability, and poor perfusion(3-5).

Based on time of infection onset the two major category of neonatal sepsis (NS) are: Early-onset neonatal sepsis which is diagnosed before 7 days of life which is caused by vertical transmission from mothers to infants during the intrapartum period that causes around 8% of all neonatal deaths(4). The most common causative agents of EONS are Group B Streptococcus (GBS) and E. coli(6). And Late onset neonatal sepsis (LONS) that occurs after 8 to 28 days of infants life which is caused by postnatal horizontal transmission, mainly from organisms acquired after birth(4, 7).

Sepsis is diagnosed by: a complete white blood cell count, blood culture and the most commonly used way of diagnosis is clinical features of the neonate like; temperature instability, respiratory distress, apnea, feeding difficulties, and poor perfusion(8). To confirm the diagnosis of early onset neonatal sepsis factors that predispose the neonate for sepsis such as maternal infection, exposure to infected blood at delivery and prolonged rupture of membranes, and prematurity are also considered(9).

The survival time of neonatal sepsis(NS) was mainly influenced by factors like intra-partum fever, induced onset of labor, chest indrawing, enteral feeding, sepsis type, non-oral enteral feeding, assisted with bag and mask, infectious complications, being in critical conditions, Birth weight of neonates, oxygen supply, Intubation and gestational age (10, 11).

Antibiotic therapy is the preferred management of neonatal sepsis and administered empirically to infants when there is clinical suspicion of infection. Due to the non-specific clinical findings and limited diagnostic facilities, this treatment approach remains challenging in low and middle income countries (LMICs), with possible risk of either under or over treatment(12).

1.2. Statement of the problem

Neonatal sepsis is a primary cause of neonatal mortality and an urgent global health issue, particularly in low and middle-income countries (13). Globally, 15% of neonatal deaths are due to neonatal sepsis (14, 15). In developing countries, the rate of neonatal mortality with sepsis is ranged from 14.6% to 36%(16).

The estimated global incidence of neonatal sepsis is 2824 per 100,000 live births(17), while the report in 2018 shows 2202 per 100,000 live births(18). According to World Health Organization (WHO) report the global burden of neonatal sepsis was 1.3 to 3.9 million annual neonatal sepsis cases occur among neonates, with a global mortality of 400,000–700,000 every year(4).

In Africa sepsis accounts for 28% of neonatal death and it is also assumed that early detection and treatment of NS can prevent about 84% of neonatal sepsis-related mortality(4). The case fatality rates of neonatal sepsis in Africa was 52%(19) The magnitude was vary from country to country; Cameroon 37.9% (20), Ghana 20.2%(21), Tanzania 31.4% (22), Kenya 23.9%(23) and Egypt 8.6% (24). Sepsis is the most common cause of neonatal mortality and probably responsible for 30 to 50 percent of the total neonatal deaths each year in developing countries(4).

According to EMDHS 2019 the neonatal mortality rate was 30 deaths per 1,000 live births, and the post neonatal mortality rate was 13 deaths per 1,000 live births, which indicates that; childhood mortality rates have decreased over time(25).

In Ethiopia, 40% of under-five death is occurs during the neonatal period; from this, neonatal sepsis accounts for 30-35% of neonatal deaths(14). The magnitude of the neonatal sepsis in Ethiopia is still high (48%) and varies from region to region; in Gondar 64.4%(26), in Mekele 76.8% (27) in Shashamane 77.9%(28), in Woldia and Dessie Comprehensive Specialized Hospitals 79.4%(29) and Southern Nations, Nationality, and People in Arbaminch 78.3%(30) and in Wolaita Sodo 33.8%(31).

The Ethiopian government has made various efforts to reduce neonatal morbidity and mortality. However, different studies conducted in the country revealed that neonatal morbidity and mortality related to neonatal sepsis are still high (26, 28-30). Therefore data from different area with different design is required.

Several studies were assessed the prevalence and associated factors of neonatal sepsis. However the recovery time and its important determinants are not well established. Therefore, this study aim to assess the recovery time of neonatal sepsis and identify important determinants factors that could affect the survival time of neonates with NS admitted to the neonatal intensive care unit (NICU). Accordingly reducing length of hospital stay can decrease the neonatal mortality by early initiation of further investigation and treatment. Therefore the exact recovery time of NS is required.

1.3. Significance of the study

Though Ethiopia has made considerable achievement in the reduction of under-five mortality rate, the neonatal mortality burden has not experienced the same reduction as well as unacceptably high and the trend in reduction is slower(32). To prevent further; this neonatal problem data from different geographical area of Ethiopia on recovery of NS is required.

For health care provider; it delivers information on the recovery time from sepsis that may help them for early initiation of further investigation and treatment for reducing extended time as well as risk of nosocomial infection in treatment units.

To council the parents on how long the new born will be in the hospital and infection prevention. This allows them to mobilize resources for the newborn's hospital care, reduce the number of defaulters and prepare for any disruption that the admission may cause.

This study also contributes to identify determinants of recovery from neonatal sepsis which is crucial for effective intervention strategies. Additionally, the results of this study will serve as an input for future studies.

2. LITERATURE REVIEW

2.1. Time to recovery of neonatal sepsis

According to the study done in India and Brazil the median time to recovery of neonates sepsis was 5.5 days and 19 days respectively (33, 34). The study conducted in Uganda showed that, the median survival time of septic neonates was 5.4 days and underweight was a predictor of slower recovery (35).

Another facility based retrospective cohort research done in Bahir Dar City among 225 neonates shows that the median time of recovery of neonatal sepsis is 6 days(36). Similarly the study conducted in Arbaminch, Addis Ababa Tikur Anbessa Hospital, Gondar and Dire Dawa the survival time of septic neonates was 12.74 days, 8.92 days, 7 days and 7 days respectively (10, 11, 37, 38). According to the study conducted in Gondar showed that neonate day's observation and the median time to recovery was 7 days with the incidence rate of 10.78 per 100 neonate days(10).

2.2. Predictors of recovery among neonates with neonatal sepsis

2.2.1. Socio demographic predictors

The study conducted in Nepal and India shown that, Female neonates were found to have lower risk of death than male(39, 40).

The two study done in Nigeria revealed that, the mean age at admission 6.60 ± 7.55 days are late survival time than 8.62 ± 8.37 days(AHR=1.049) as well as male newborns are more likely to die of sepsis as compared to female (AHR=1.24), (41, 42). And another study in Tanzania showed that newborn from maternal age of >35 years (AHR=6.7) had long hospital stay(22).

Moreover; another hospital based retrospective study conducted in Addis Ababa Tikur Anbessa Specialized Hospital among 206 neonates with sepsis to determine the treatment outcome and length of stay in hospital. The finding of this study showed that, male neonates(AHR: 2.63) stay longer compared female neonates(38). And the age of neonates between 1–6 days after birth (AHR=0.521) was factor for recovery(11).

2.2.2. Maternal factors

According to some evidence; in developed and developing countries, majority of them reported that premature rupture of membrane, intra partum fever, chorioamniotis and Hypertension in pregnancy were common maternal factors that significantly affect the survival time and status of neonates with sepsis(14, 41, 43, 44).

Different researchers in different parts of the world straggle to determine the treatment outcomes of neonates admitted due to sepsis. For instance, a study was done in Iraq among 126 neonates to identify the outcome of neonates hospitalized with neonatal sepsis. The finding of this study shown that prolonged rupture of membrane(AHR = 2.12) and fever(AHR = 1.969) were the predictors for recovery of neonate with neonatal sepsis (45). Another prospective study conducted in central India showed that neonates born to mothers, who had premature rupture of membranes (AHR:11.14) are less likely to recover than their counter part(46).

A study conducted in Nigeria indicated that neonates born to mothers who had prolonged rupture of membrane (PROM) (AOR=2.470) had significant effect on neonatal sepsis(47). Another study conducted in Kenya revealed that Neonates born from mothers with history of PROM (AOR = 6.124) and multiple gestation were at higher risk for long stay of neonatal sepsis(48).

According to the study conducted in Arbaminch chorioamniotis (AHR:5.7) and Having a history of intrapartum fever (AHR: 14.5)(14) was factor that affect the survival time of NS. In addition the study conducted in Gondar showed that neonates who had been delivered with mothers having intra-partum fever, induced onset of labor and chest indrawing were delayed by 31%, 32% and 33% to recovery of NS as compared to their counterparts respectively(10).

Similarly, the study conducted in different parts of Ethiopia Shown that place of delivery(26, 49, 50), Antenatal follow up AOR:4.4)(50, 51) and PROM(30, 49, 50, 52, 53) were the factors that were associated to NS. Similarly the study conducted in Mizan and Tikur Anbessa Specialized hospital revealed that, neonates born from mothers who had a history of infection during pregnancy and hypertension had long recovery time by compared to those who were born from mothers who had no maternal infection and hypertension during pregnancy respectively(54, 55).

2.2.3. Neonatal factors

According to pervious study the length of hospital stay was influenced by prematurity, Low Birth Weight (LBW), low APGAR score, assisted ventilation, infectious complications, poor feeding, LONS and unable to initiate early Exclusive Breast feeding were contribute to NS (16, 49, 56).

A study conducted in Iraq revealed that neonates who had low birth weight(<2500g) (AHR:3.314), history of previous hospitalization and preterm neonates in addition to sepsis were long time hospital stay than neonate with their counterpart(45).

The study done in Keniya shown that Neonates born of Pre-maturity(AOR:6.402), low Apgar score at 5^{th} minutes(AOR:8.212) and history of invasive procedure(AOR:2.464) were the neonatal factors independently associated with NS(48). Similarly the study done in Nigeria and Tanzania showed that birth weight (< 2500g AOR:7.214), low Apgar score and resuscitation at birth (AOR:1.251) were the factors that were associated with neonatal mortality due to sepsis(22, 47).

According to the study conducted in Harar and Dire Dawa, preterm neonates (AOR: 8.1) and low birth weight (AHR:1.648) were factors associated with NS (11, 57). Another study done in Bahir Dar shown that late initiation of exclusive breast feeding over one hour, comorbidities (AHR:1.8) and low birth weight (AHR:2.29) had risk of hospital stay compared to their counter parts (58). Similarly the study dine in Gondar showed that, time of the infection onset (AHR:0.55) and Gestational age (AHR:1.93) (10) were the factors for recovery of NS.

Furthermore, a retrospective study conducted in Mizan Tepi University Hospital, showed that neonates with Very low birth weight (AHR:1.692) and prolonged length of hospital stay (AHR:12.29) were the factors that affect the recovery time of NS(54).

2.2.4. Medical treatment related factors

The WHO recommends a standard empiric treatment of ampicillin plus gentamicin for neonatal sepsis, which needs to be administered within hours to prevent tissue damage and death in newborns(59). The another combinations of drug; such as ceftazidime-amikacin had three times higher susceptibility rates and associated with lower mortality than treatment with ampicillin–gentamicin (AHR:0.316)(60).

The study conducted in children`s hospital of Philadelphia show that, Prolonged time to antibiotic administration was associated with significantly increased risk of hospital stay for 14 days and 30 days (AOR:1.47(1.15-1.87))(61). Another study conducted in Saudi Arabia indicates that the survival rate of neonates who received antibiotics within the first 3 h of prescription was 72.6% (62).

The study done in India revealed that, neonatal sepsis has low recovery rate when newborns present with mechanical ventilation(41). The study conducted in Denmark shows that, within 3 days of administration, bacille Calmette-Guérin (BCG) vaccination can reduce mortality from neonatal sepsis in newborns, but the underlying mechanism for this rapid protection was unknown(63).

Another study done in Lagos University Hospital in Nigeria frequent changes in antibiotics was the factor for recovery of neonatal sepsis(47). According to WHO guidelines recommendation the treatment for a neonate having known risk factors of sepsis should be for no less than 2 days(64).

Another study done in Gondar and Dire Dawa shown that; assisted with bag and mask (AHR: 0.72), none intubated (AHR 6.725) and not supply oxygen continuously (AHR: 1.36) were the factor that prolong the recovery time of NS (10, 11).

2.2.5. Clinical presentation related factors

According to the study conducted in china; apnea(AHR:3.12), bradycardia(AHR:1.35) and poor feeding(AHR:3.83) was a clinical presentation that contributes for poor recovery of NS(65). Another a study conducted in Nigerian tertiary hospital showed that; neonates presented with respiratory distress(AOR:1.23), jaundice(AOR:0.67), and fever were the factors that were factors affect the recovery of neonate with sepsis(66).

A study conducted in Bahir Dar showed that neonates more likely to develop poor neonatal outcome of neonatal sepsis were respiratory distress syndrome (AHR:0.26), intrapartum fever(AHR:7.3), comorbidity(AHR:1.81) and meconium aspiration syndrome(MAS) (AHR:0.19) than neonates with history of the counterpart (36).

The study conducted in Jinka general hospital show that, neonates who had hypothermia (AOR:2.34) were more likely to develop neonatal sepsis (53). Another study done Bahir Dar and showed that respiratory distress (AHR:0.258), history of fever AHR:7.37(2.28, 23.79) and meconium aspiration syndrome (AHR:0.1989) were factors for recovery of NS(36). According to a study done in Woldia and Dessie comprehensive specialized hospitals and Kaffa zone resuscitation at birth was significant factor with (AOR:2.3) for neonatal sepsis(29, 67).

Another study done in Gondar revealed that; chest indrowing (AHR: 0.67) was factor for time to recovery of NS. The study conducted in Addis Ababa and Northern Oromia shown that; neonate with meconium stained aspiration syndrome were long recovery time as compared to the counterpart(28, 55).

3. Conceptual framework

The conceptual framework is developed from different literature review to shows relationship of different variables with outcome variables that contains socio-demographic, neonatal factor, maternal factor and clinical and medical care factor which is adapted from different research and modified relationship between independent variables and outcome variable (10, 36, 57).

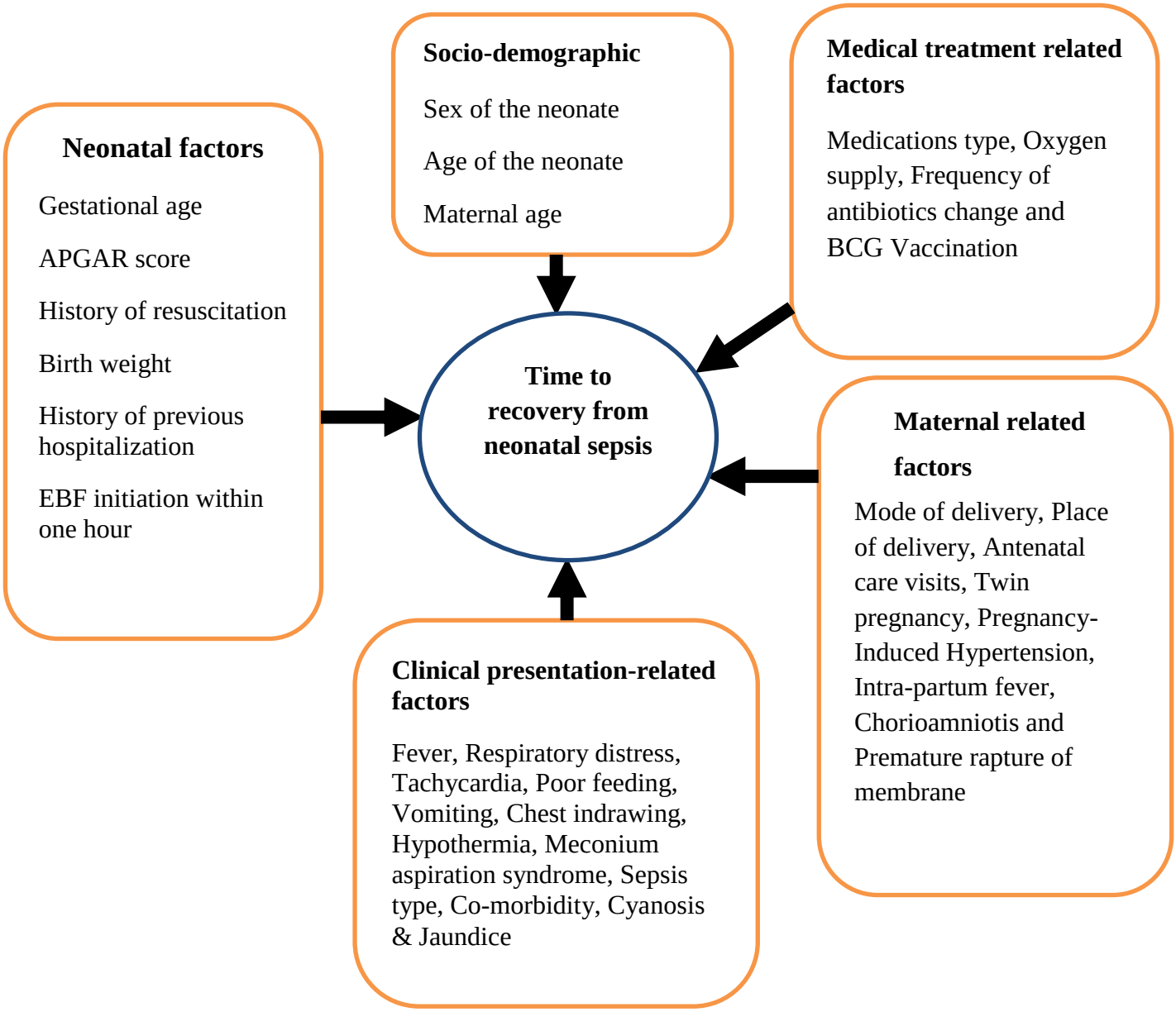


Figure 1: Conceptual framework is adapted & modified from related article to show the relationship between independent variables and outcome variable.

4. Objective of the study

4.1. General Objective

- To assess the recovery time of neonatal sepsis and its determinant factors among admitted neonates at NICU in selected public comprehensive specialized hospitals of SNNPRS, Ethiopia, 2023.

4.2. Specific Objective

- To determine the recovery time of neonate sepsis among neonate admitted to NICU in selected public comprehensive specialized hospital of SNNPRS, Ethiopia, 2023.
- To identify the determinants affecting recovery time of neonatal sepsis among neonate admitted to NICU in selected public comprehensive specialized, SNNR, Ethiopia, 2023.

5. METHODS AND MATERIALS

5.1. Study area and period

This study was carried out from April 1st to April 30th, 2023 among neonates with neonatal sepsis at selected comprehensive specialized hospitals in SNNPRS admitted from January 1st, 2021 to January 1st, 2023.

South Nation Nationality and People`s Regional state is one of the administrative regional states in southwestern Ethiopia. It is the most diverse region in the country in terms of culture, language and ethnicity. The SNNPRS border Kenya to the south and south Sudan to the southwest. There are five comprehensive specialized hospitals in the region namely;

Wolaita Sodo University comprehensive specialized hospital is located in Sodo town of Wolaita zone, which is 380 km away from the national capital of Addis Ababa. The NICU ward of this hospital has 34 patients. The 2nd study area was Wachemo University Nigist Eleni Mohammad memorial comprehensive specialized hospital which is located in Hadiya zone in SNNPR which is 232 km far from Addis Ababa, Ethiopia. It is one of the frontline hospitals in Ethiopia. The NICU ward of this hospital has 45 patient beds. It also has a very high patient flow of 200 neonates per month on average. 3rd area was Werabe comprehensive specialized hospital is found in Silte zone. The town werabe is located at 172 km south of Ethiopia's capital, Addis Ababa. The NICU ward of this hospital has 36 patient beds. Another area of this study was, Walkitie University Comprehensive Specialized Hospital, which is located in Gurage zone, Walkitie Town. It is 132 km far away from the capital city, Addis Ababa. The NICU ward of this hospital has 35 patient beds.

5.2. Study Design

Retrospective follow up study design was used.

5.3. Population

5.3.1. Source Population

The source population comprised all neonates with sepsis who were admitted for neonatal sepsis management and treated in public comprehensive specialized hospitals in SNNPRS from January 1st, 2021 to January 1st, 2023.

5.3.2. Study Population

All selected neonates admitted for neonatal sepsis management and treated in selected public comprehensive specialized hospitals of SNNPRS from January 1st, 2021 to January 1st, 2023.

5.3.3. Study unit

Each selected neonate's chart that fulfills the inclusion criteria.

5.4. Eligibility criteria

5.4.1. Inclusion criteria

Neonates admitted in NICU in Selected Public Comprehensive Specialized Hospitals of SNNPRS with the diagnosis of neonatal sepsis from January 1st, 2021 to January 1st, 2023.

5.4.2. Exclusion criteria

Neonate who have incomplete chart for study variables like date of admission, date of discharge and discharge status of the neonate was excluded.

5.5. Sample size determination

The sample size was determined by using STATA software version 14.0.

$$E = \frac{(Z\,\alpha/2 + Z\beta)2}{(\ln HR)2\ p(1-p)} \qquad P(E) = \frac{1-(\exp S1(t) + \exp S2(t) * HR)}{2}$$

Where: Zα/2 = standard normal variable at 95% confidence interval level = (1.96) Zβ = power of 80% =(0.8), P=cumulative survival probability at end of study (25 days) is 2.81%, Hazard ratio= 0.5, Pr (E)= probability of event for outcome variable(recovery) and IR = incidence rate (10.78% as obtained from a prospective study in Gondar on time to recovery of neonatal sepsis and predictors among admitted neonate(10).

E = number of events that are interested is 73.3 and the probability of an event (recovery) is 0.177 so the total sample size is calculated as

$$n = \frac{\mathrm{E}}{\mathrm{pr(E)}} = 73.3/0.177 = 414$$

The sample size for each predictor was determined by using Stata software version 14.0, by using the Hazard ratio (HR) of a co-variable.

Assumption: Ho; S1(t)=S2(t), two-sided significance level (α=5%) , Zα/2= Z value at 95% confidence interval=1.96, power 80%=0.842, IR= incidence rate of recovery (10.78 per 100 neonate days as obtained from study in Gondar on time to recovery of neonatal sepsis and predictors among admitted neonate(10). π= proportion allocated to each groups (for equal allocation Π * Π2 =1) and Pr(E)= probability of event for each variable.

$$E = \frac{(Z\,\alpha/2 + Z\beta 2}{\Pi 1\ \Pi\ 2(\ln HR)2} \qquad P(E) = \frac{1-(\exp S1(t) + \exp S2(t) * HR)}{2}$$

The total sample size is calculated by; $n = \frac{\mathrm{E}}{\mathrm{pr(E)}}$

Table 1:-The sample size calculation to determine time to recovery of neonatal sepsis and determinant factors among neonate admitted at NICU in Selected Public Comprehensive Specialized Hospitals, SNNPRS, Ethiopia, 2023.

Significantly associated variables	AHR	Power	Probability of event	Sample size
Chest indrawing	0.67	0.8	0.085	196(10)
Early initiation of treatment	1.83	0.8	0.15	**643**(10)
Assisted with bag and mask	0.72	0.8	0.088	291(10)
Gestational age	1.93	0.8	0.154	529(10)

By comparing the sample size obtained, the highest sample size was selected. Therefore, the final sample size was 643.

5.6. Sampling procedure

First, by using simple random sampling 4 hospitals was selected out of 5 Public Comprehensive Specialized Hospitals. The selected hospitals are (Wachemo University Nigist Eleni Comprehensive Specialized Hospital, Wolaita Sodo University Comprehensive Specialized Hospital, Werabe Comprehensive Specialized Hospital and Walkitie University Comprehensive Specialized Hospital). For record reviews, two consecutive years (January 2021 to January 2023) was chosen. Starting from the recent month backwards, based on the sequence of their card number, a systematic random sampling procedure was used to select an adequate number of samples (patient charts). During the two-year period, the total numbers of neonatal sepsis admissions was nine thousand four hundred seventy one (9,471).

By calculating the interval from the sampling frame, the total sample size for each year was proportionally allocated for (WUNEMMCSH, N=3200), (WSUCSH, N=2156), (WCSH, N=2170) and (WUCSH, N=1945) and the interval was calculated as (k=N/n) while N=9471 and sample size n=643. The interval (k=9471/643=14) so the data was collected every 14^{th} charts which is similar for each hospital. The first participant was selected using lottery method from 1-14 and number 10 was selected. Then, the selection was continued every 14^{th} after 10^{th} was selected.

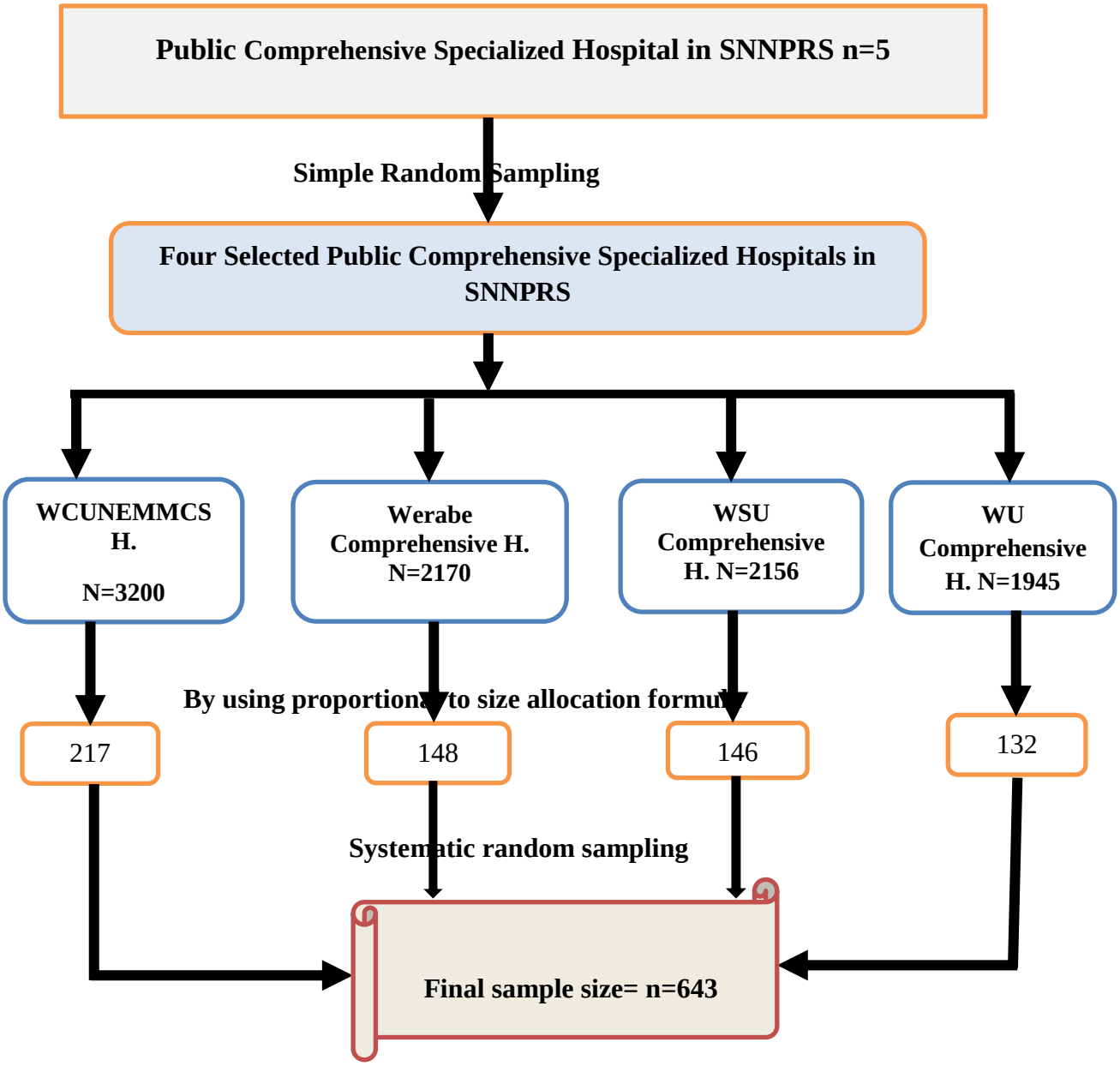


Figure 2: Schematic representation of sampling procedure for determining time to recovery and its determinant factors among neonates admitted with neonatal sepsis at public referral hospitals of SNNPRS, Ethiopia, 2023.

5.7. Variables

5.7.1. Dependent variable

- ✓ Time to recovery from neonatal sepsis

5.7.2. Independent variable

Socio demographic factors

- ✓ Maternal age in year, neonatal age in days and neonatal sex

Neonatal related factors

- ❖ Gestational age, APGAR score, History of resuscitation, Birth weight, History of previous hospitalization and EBF initiation within one hour

Maternal related factors

- ❖ Mode of delivery, Place of delivery, number of ANC visits, twin pregnancy, Pregnancy-Induced Hypertension (PIH), diagnosed chorioamniotis and Duration after ROM

Clinical presentation-related factors

- ❖ Fever, respiratory distress, tachycardia, poor feeding, dehydration, vomiting, hypothermia, meconium aspiration syndrome, chest indrowing, sepsis type, Co-morbidity, jaundice and cyanosis

Medical treatment-related factors

- ❖ Medications type, Frequency of antibiotics change, BCG Vaccine and Oxygen supply.

5.8. Operational definitions

Neonate: a live newborn aged 0 to 28 days(4).

Neonatal sepsis: Sepsis diagnosed and confirmed by physician using their clinical features and laboratory finding.

Early-onset neonatal sepsis: Sepsis diagnosed and confirmed by physician among neonates age less than seven days(68)

Late-onset neonatal sepsis: Sepsis diagnosed and confirmed by physician among neonates age seven days or more(68)

Poor feeding: unable to sucking and vomiting (69)

Hypothermia: Core body temperature < 36.5° C(4).

Co-morbidity: additional medical problem with neonatal sepsis (HIV, TB & CHD) (10)

Event: refers to recovery from neonatal sepsis during the study period

Recovery: Neonates improved from neonatal sepsis as declared by the clinician

Defaulter: Refers to neonate who stops the treatment against medical advice.

Death: A neonate died by NS during the treatment or at the treatment unit.

Censored: It refers to a neonate defaulted from the treatment, referred, died, or transferred.

Time to recovery: A time from the admission date with NS to the discharge date while the neonate is recovered. It was measured by subtracting the date of admission from the discharge date.

5.9. Data collection tool and procedure

5.9.1. Data collection tool

A data collection tool was adapted from another peer reviewed article conducted in Ethiopia (10, 36). Data abstraction was designed based on study objectives, and contains five parts; checklist related to socio-demographic information, maternal related information, neonatal related, clinical presentation and medical treatment related information which was collect from medical records.

5.9.2. Data collection procedure

All available information on patient records was checked in the selected public comprehensive specialized hospitals from January 1st, 2021 to January 1st, 2023 and retrieved from the inpatient Health Management Information System (HMIS) registry book.

The date of the diagnose of sepsis was the starting point for retrospective follow-up and the end point is the date of discharge, the date of lost to follow-up, referred, left against medical advice and the date of death. The records of all study participants were selected according to the eligibility criteria. Recovery was confirmed by discharge note complemented and registration book. Recovery time was calculated from the date of admission to the date of discharge.

Two Masters of Science for supervision and six BSc Nurse for data collection were assigned. One day training was given to data collectors and supervisors regarding significance of the study and ways of data collection process. The supervisors monitor the data collection process.

5.10. Data Quality Control

To ensure quality of the data, supervisor and data collectors were trained on how and what information they should collect from the targeted data sources. Prior to data collection, data extraction form was tested on 5% of sample size which was 32 charts to ensure that the data abstraction format is consistent with study requirements. Therefore, educational status of parent and maternal occupation were removed from the actual data collection tool.

Completeness of the collected data was checked on site daily basis during data collection and give prompt feedback by the supervisor and the principal investigator. During data management, storage, cleaning and review, all completed data collection forms was checked for completeness and accuracy. The super visors and principal investigator examines consistency by selecting cards at random and comparing their similarity.

5.11. Data processing and analysis

Consistency of data was checked before analysis to avoid errors during data entry. After that the collected data was coded and entered into Epi-data version 3.1 and exported into STATA version 14 for cleaning and analysis.

Before performing Cox-proportional hazard regression, model and goodness-of-fit was checked by Cox Snell residuals and assumptions was also check by using Schoenfeld residual test. Multicollinearity was checked for estimating the correlation between all pairs of variables by variance inflation factor (VIF) with the mean VIF of 1.20 which is <5, therefore there was no multicollinearity.

Outcome was dichotomized into censored “0” or recover “1”. Kaplan Meier survival curve and log-rank test was used to estimate recovery time and compare the probability of survival time. Result was presented in text, graph and tables. Median recovery time and Incidence rate (IR) was calculated for the entire study period.

The bivariate Cox-proportional hazards regression model was done and variables with p-vale <0.25 in bivariate was included in multivariable cox proportional hazard regression. And p values<0.05 was used to measure the strength of association and statistical significant predictors.

5.12. Ethical Consideration

Ethical clearance was obtained from Debre Brehan University Asrat Woldeyes health science campus. Upon approval of the proposal, the letter was obtained from institutional Review Board (IRB). Then a written permission letter to access patient's charts was gained from responsible body of each institution. All information collected from patients' chart was kept strictly confidential and was not be revealed to any person other than principal investigator.

5.13. Dissemination of the result

The results will be disseminated to Debre Brehan University Asrat Woldeyes health science campus school of Nursing and Midwifery, Department of pediatrics and child health nursing in partial fulfillment for Masters of pediatrics and child health nursing.

The finding and recommendations will be distributed to all public comprehensive specialized hospitals, SNNPRS health bureau and other organizations working on related area to be used as a baseline for intervention. Finally it will send for publication.

6. Result

6.1. Socio-demographic factors of the study participants

In this study, 643 neonatal charts were reviewed. More than half 62.1% (399) were male neonates and 336(52.3%) of them were recovered. About 406 (63.1 %) of the neonates had age less than seven days. Concerning to mothers' socio demographic characteristics, the mean (±SD) age of mothers was 27.07± 0.192 years range from 16 to 39 years (Table 2).

Table 2: Socio-demographic characteristics of neonates admitted with neonatal sepsis at public comprehensive specialized hospitals of SNNPRS, Ethiopia, 2023 (n=643).

Variables	Category	Total	Status	
			Recovered	Censored
Residence	Urban	395(62.0%)	339 (63.6%)	56 (51.8%)
	Rural	248(38.0%)	196 (36.4%)	52 (48.2%)
Sex of the neonate	Male	399(62.1%)	336 (62.8%)	63 (58.3%)
	Female	244(37.9%)	199 (37.2%)	45 (41.7%)
Place of delivery	Home	13(3.6%)	18 (3.4%)	5 (4.6%)
	Health institution	620(96.4%)	517 (96.6%)	103 (95.4%)
Age of Mother	<20	74(11.5%)	57 (10.6%)	17 (15.7%)
	20-34	516(80.2%)	440 (82.2%)	76 (70.4%)
	>34	53(8.2%)	38 (7.1%)	15 (13.9%)
Age of neonate	<7 days	406(63.1%)	348(65.1%)	58(53.7%)
	>7 days	237(36.9%)	187(34.9%)	50(46.3%)

6.2. Maternal related factors

In considering the number of ANC visits, about 10 (1.6%) of the mothers had no antenatal visits, while, 66(10.3%), 38 (5.8%), 288(44.8%) and 241(37.5%) of them had one, two, three and four and above visits respectively. Regarding to mode of delivery, more than half 432 (67.2%) of the mother were give birth by spontaneous vaginal delivery and cesarean section, forceps delivery and vacuum assisted were 112(17.4%), 69 (10.7%) and 30(4.7%) respectively (Table 3).

Table 3: Maternal-related characteristics of mothers having neonates admitted with neonatal sepsis at public comprehensive specialized hospitals of SNNPRS, Ethiopia, 2023.

Variables	**Category**	**Total**	**Status**	
			Recovered	**Censored**
Twin pregnancy	Yes	47(7.3%)	40 (7.5%)	7 (6.5%)
	No	596(92.7%)	495 (92.5%)	101 (93.3%)
Duration after ROM	<18hr	537(83.5%)	444 (83.0%)	93 (86.1%)
	>18hr	106(16.5%)	91 (17%)	15 (13.9%)
Pregnancy-induced hypertension	Yes	66(10.3%)	51 (9.5%)	15 (13.9%)
	No	577(89.7%)	484 (90.5%)	93 (86.1%)
ANC visit	No	10 (1.6%)	8 (1.5%)	2 (1.8%)
	One	66(10.3%)	57 10.6%	9 8.3%
	Two	38 (5.8%)	29 5.4%	9 8.3%
	Three	288(44.8%)	237 44.3%	51 47.2%
	Four & above	241(37.5%)	204 38.1%	37 34.3%
Intra-partum fever	Yes	64(9.9%)	53 (9.9%)	11 (10.2%)
	No	579(90.1%)	482 (90.1%)	97 (89.8%)
Diagnosed chorioamniotis	Yes	124(19.3%)	105 (19.6%)	19 (17.6%)
	No	519(80.7%)	430 (80.4%)	89 (82.4%)
Place of delivery	Home	23(3.6%)	18(3.4%)	5(4.6%)
	Health Institution	620(96.4%)	517(96.4%)	103(95.4%)

6.3. Neonatal related factors

From 643 neonates admitted with neonatal sepsis, the mean (±SD) weight of neonates at admission was 2906.43 ± 616.611 grams and more than half, 385 (63.79%) of recovery was seen among neonates with birth weight greater than 2,500 grams. Regarding gestational age, the mean (±SD) gestational age was 37.26±2.138 weeks ranging from 31-43 weeks. Of all neonate who were Resuscitated at birth 59(9.2%) of them were recovered while 18(2.8%) were censored (Table 4).

Table 4: Neonatal-related characteristics admitted with neonatal sepsis at public comprehensive specialized hospitals of SNNPRS, Ethiopia, 2023.

Variables	Category	Total	Category of status	
			Recovered	Censored
EBF initiated within one hour	Yes	205(31.9%)	167 (31.2%)	38 (35.2%)
	No	438(68.1%)	368 (68.8%)	70 (64.8%)
History of resuscitation	Yes	77(12%)	59 (11%)	18 (16.7%)
	No	566(88%)	476 (89%)	90 (83.3%)
Birth weight	<2,500	185(28.7%)	150 (28.0%)	35 (32.4%)
	>2,500	458(71.3%)	385 (72.0%)	73 (67.6%)
Gestational age	<37	363(56.4%)	292 (54.6%)	71 (65.7%)
	37-42	279(43.4%)	242 (45.2%)	37 (34.3%)
	>42	1(0.2%)	1 (0.2%)	- --
Body temperature at admission	<36.5	356(55.3%)	303 (56.6%)	53 (49.1%)
	36.5-37.5	122(19.0%)	104 (19.4%)	18 (16.7%)
	>37.5	165(25.7%)	128 (19.9%)	37 (34.3%)
Frist min Apgar score	<7	615(95.7%)	511 (95.5%)	104 (96.3%)
	>7	28(4.3%)	24 (4.5%)	4 (3.7%)
Fifth min Apgar score	<7	531(82.6%)	439 (82.1%)	92 (85.2%)
	>7	112(17.4%)	96 (17.9%)	16 (14.8%)

6.4. Medical treatment related factors

Majority of the neonate 543(84.4%) of newborns were treated with Ampicillin + Gentamicin and the remaining 36(5.6%) were treated with Vancomycin + Ceftazidime and 64(10%) of them were treated with Ampicillin + Ceftriaxone. Of all neonate who were treated with those antibiotics, for newborns 106(16.5%) the drug was changed once and above (Table 5)

Table 5: Medical treatment-related factors of neonate admitted with neonatal sepsis at public comprehensive specialized hospitals of SNNPRS, Ethiopia, 2023.

Variables	Category	Total	Status	
			Recovered	Censored
Oxygen supply	Yes	187(29.1%)	157 (29.4%)	30 (27.8%)
	No	456(17.9%)	378 (70.6%)	78 (72.2%)
Antibiotics given	Ampicillin+ Gentamycin	543(84.4%)	455 (85.1%)	88 (13.7%)
	Vancomycin Ceftazidime	36(5.6%)	24 (4.5%)	12 (1.9%)
	Ampicillin + Ceftriaxone	64(10%)	56 (10.5%)	8 (1.2%)
Frequency of antibiotics change	No	536(83.4)	460 (86.0%)	76 (70.4%)
	Once and above	107(16.6%)	75 (14.0%)	32 (29.6%)
BCG vaccination Administration	Yes	284(44.2%)	229(42.8%)	55(50.9%)
	No	359(55.8%)	306(57.2%)	53(49.1%)

6.5. Clinical features related factors

In this study about one-third 152(23.6%) of newborns were having hypothermia among those 121(22.6%) of them were recovered and the remaining 31(28.7%) were censored (table: 6).

Table: 6 Clinical features-related factors among neonate admitted with neonatal sepsis at public comprehensive specialized hospitals of SNNPRS, Ethiopia, 2023.

Variables	Category	Total	Status	
			Recovered	Censored
History of fever	Yes	194(30.2%)	154 (28.8%)	40 (37.0%)
	No	449(69.8%)	381 (71.2%)	68 (63.0%)
Tachycardia	Yes	144(22.4%)	117 (21.9%)	27 (25.0%)
	No	499(77.6%)	418 (78.1%)	81 (75.0%)
Poor feeding	Yes	415(64.5%)	344 (64.3%)	71 (65.7%)
	No	228(35.5%)	191 (35.7%)	37 (34.3%)
Co-morbidity	Yes	83(12.9%)	62 (11.6%)	21 (19.4%)
	No	560 (87.1%)	473 (88.4%)	87 (80.6%)
Vomiting	Yes	127(19.8%)	104 (19.4%)	23 (21.3%)
	No	516(80.2%)	431 (80.6%)	85 (78.7%)
MAS	Yes	154(23.9%)	130 (24.3)	24 (22.2%)
	No	489(73.1%)	405 (75.7%)	84 (77.8%)
Respiratory distress	Yes	354(55.1%)	281 (52.5%)	73 (67.6%)
	No	289(44.9%)	254 (47.5%)	35 (32.4%)
Cyanosis	Yes	113(17.6%)	95 (17.8%)	18 (16.8%)
	No	530(82.4%)	440 (82.2%)	90 (83.3%)
Jaundice	Yes	38(5.9%)	30 (5.6%)	8 (7.4%)
	No	605(94.1%)	505 (94.4%)	100 (92.6%)
Chest indrawing	Yes	197(30.6%)	159 (29.7%)	38 (35.2%)
	No	446(69.4%)	376 (70.3%)	70 (64.8%)
Hypothermia	Yes	152(23.6%)	121 (22.6%)	31 (28.7%)
	No	491(76.4)	414 (77.4)	77 (71.3%)
Sepsis type	EONS	416(64.7%)	354 (66.2%)	62 (57.4%)
	LONS	227(35.3%)	181 (33.8%)	46 (42.6%)

6.6. Recovery rate and median recovery time from neonatal sepsis

The overall median recovery time was 8days (IQR: 7, 10) with a minimum and maximum follow-up time of 2 and 21 days respectively. The probability of survival at the 5^{th}, 10^{th}, 15^{th} and 20^{th} was 90.19%, 18.26%, 5.65%, and 1.98% respectively.

During follow up time, 535(83.2%) neonates with neonatal sepsis were recovered while 108(16.8%) of neonates with neonatal sepsis were censored. From those censored, 33(5.1%) of the neonates were died, 47(7.3%) of the neonates were defaulted and 28(4.3%) were transferred). The total follow-up time is 5,424 with the incidence rate of 9.86 per 100 neonate/days of observation. In this study there was no recovery and censored recorded on the 1^{st} day of observation. The majority of neonates were recovered on the 10^{th} day of follow up time which was 133 (20.6%). (Table 7)

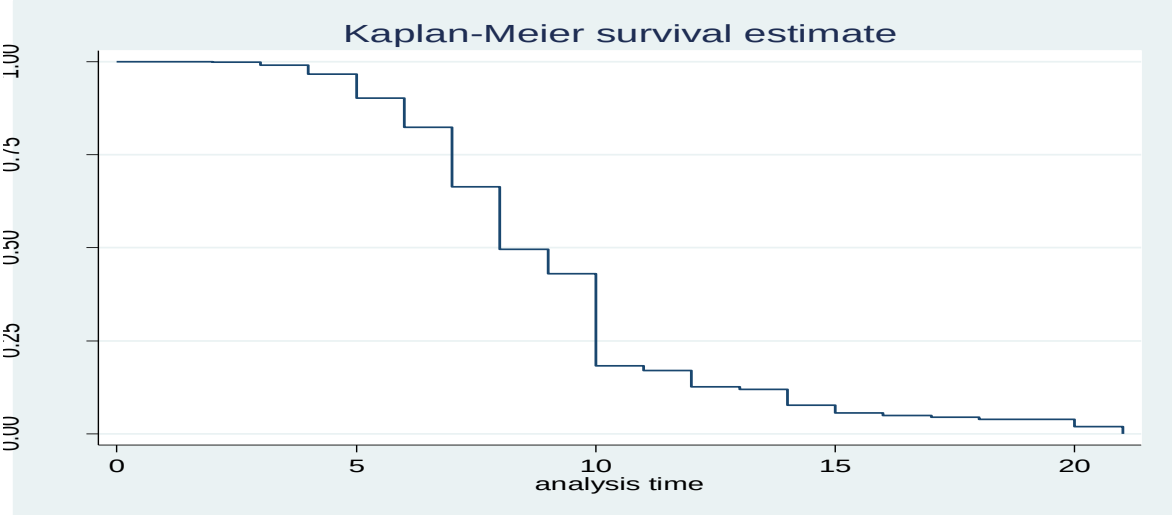
Table: 7 A life table showing survival probability to recovery of neonates admitted to selected comprehensive specialized hospitals in SNNPRS, Ethiopia, 2023.

Time	Total	Recovered	Censored	Survival prob.	[95% CI]	
1	643	0	0			
2	643	1	4	0.9984	0.9890	0.9998
3	638	5	7	0.9906	0.9792	0.9958
4	626	15	16	0.9669	0.9497	0.9783
5	595	40	14	0.9019	0.8757	0.9228
6	541	47	7	0.8235	0.7909	0.8515
7	487	94	6	0.6646	0.6252	0.7008
8	387	98	18	0.4963	0.4553	0.5359
9	271	36	4	0.4304	0.3898	0.4702
10	231	133	8	0.1826	0.1515	0.2160
11	90	6	2	0.1704	0.1401	0.2032
12	82	21	4	0.1268	0.1000	0.1569
13	57	3	1	0.1201	0.0939	0.1497
14	53	19	4	0.0770	0.0555	0.1030
15	30	8	5	0.0565	0.0378	0.0804
16	17	2	4	0.0498	0.0320	0.0734
17	11	1	2	0.0453	0.0278	0.0691
18	8	1	1	0.0397	0.0224	0.0643
20	6	3	1	0.0198	0.0067	0.0463
21	2	2	0	0.0000		

6.7. Kaplan-Meier survival recovery estimates of neonatal sepsis

The overall Kaplan Meier estimates shows the probability of recovery of patients admitted with NS on the first day was high and relatively decrease as follow up time increase. The overall median recovery time of admitted neonates with NS in this study was 8days (IQR: 7, 10).

During the first day of hospital stay, 99.84 % of recovery probability was observed with (95% CI: 98.90, 99.98). At end of the study follow-up day, the probability of recovery was also found to be 1.98% with (95%CI: 0.67, 4.63).



Y-axis is cumulative survival and X-axis is time follow up

Figure 5: Overall Kaplan-Meier estimates of neonatal sepsis that was admitted to selected public comprehensive specialized hospitals in SNNPRS, Ethiopia, January1st, 2021- January 1st, 2023

6.8. Survival function and comparison for different categorical variables

The Kaplan-Meier estimator survival curve gives the estimate of survival function among different categories to make a comparison. Survival function line lying below another means, groups defined by the lower line curve has better recovery time than other group line curve within the category.

In this study, neonates with birth weight <2,500gram during admission had longer recovery time as compared to neonates with birth weight >2,500gram. The difference was statistically significant with a p-value of 0.0000.

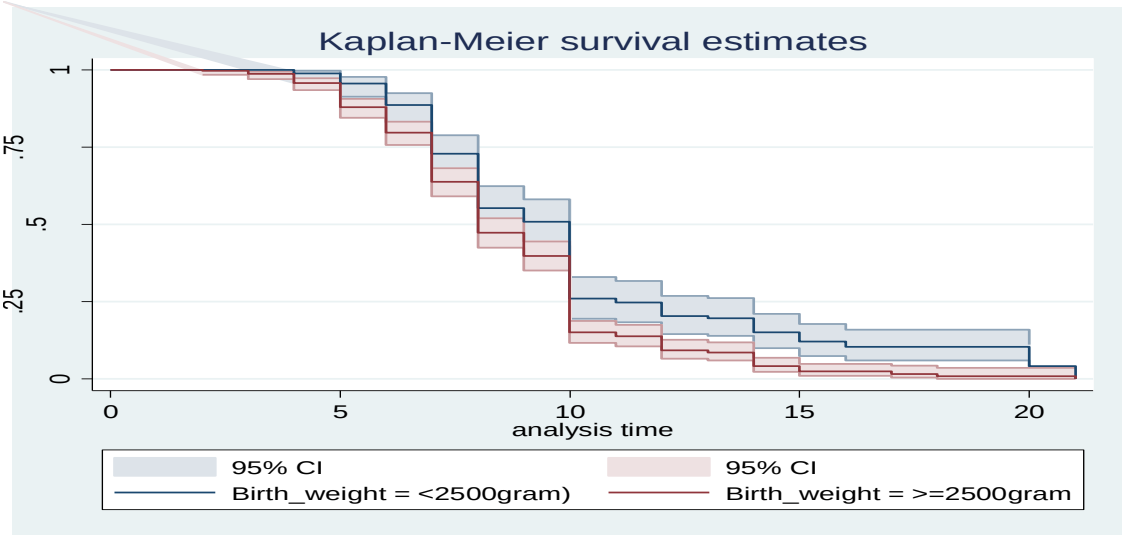


Figure 6: The Kaplan-Meier survival curve compare the survival time of the category of birth for participant admitted with NS in the selected public Comprehensive specialized hospitals in SNNPRS, Ethiopia from January 1st, 2021- January 1st, 2023.

In this study, participants who have no a history of antibiotic change have better recovery as compared to those who have history of antibiotic change once and above. The difference was statistically significant with a p-value of 0.0000.

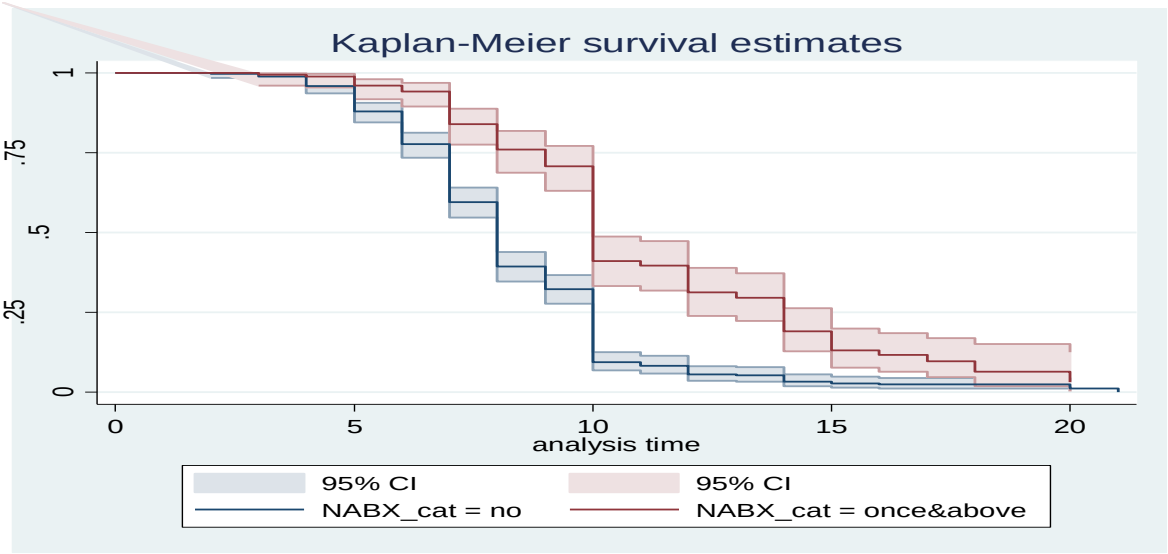


Figure 7: The Kaplan-Meier survival curve compare the survival time of the category of number of antibiotics change for participant admitted with NS in the selected public Comprehensive specialized hospitals in SNNPRS, Ethiopia, 1st, January, 2021- January 1st, 2023.

In this study, participants who have no respiratory distress had better recovery as compared to those neonates who had respiratory distress. The difference was statistically significant with a p-value of 0.0000.

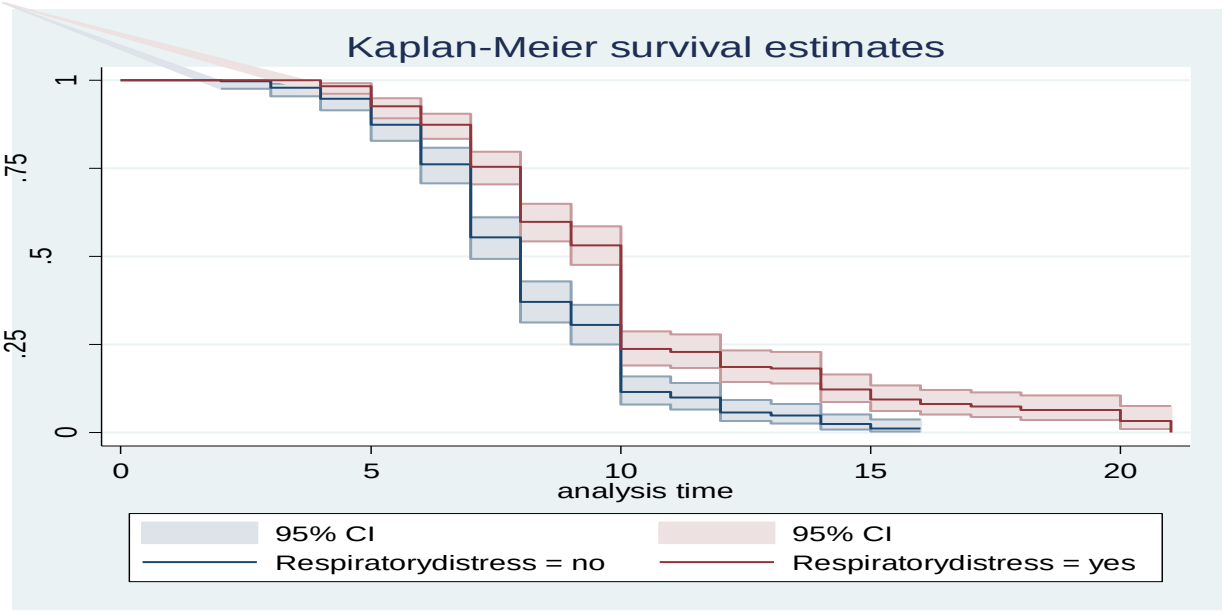


Figure 8: The Kaplan-Meier survival curve compare the survival time of the category of having respiratory distress for neonates admitted with NS in the selected public Comprehensive specialized hospitals in SNNPRS, Ethiopia, 1st, January, 2021- January 1st, 2023.

In this study, neonates with history of resuscitation at birth had longer recovery time as compared to those neonates without history of resuscitation at birth. The difference was statistically significant with a p-value of 0.0000.

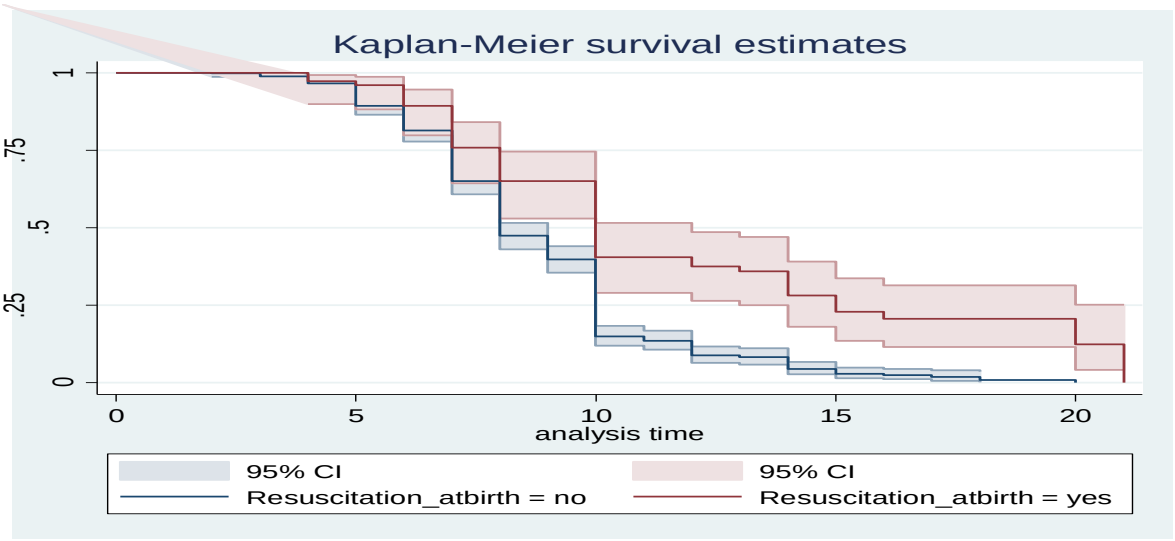


Figure 9: The Kaplan-Meier survival curve to compare the survival time of the category of neonates having resuscitation at birth in selected public Comprehensive specialized hospitals in SNNPRS, Ethiopia from January 1st, 2021- January 1st, 2023.

6.9. Log-rank estimate of recovery time among neonates with NS across predictors

As shown in the table below the log-rank test estimate between categories of different predictor or variables; those variables like; residence, place of delivery, intrapartum fever, resuscitation at birth, BCG vaccine, assisted with bag and mask and hypothermia were significantly different with p-value <0.05 as there is a significant difference among survival curves. The Kaplan Meier together with the log-rank test shows the effect of each predictor on the neonatal recovery with NS (table 8).

Table 8: Median recovery time and Log-rank test for equality of different categorical variables of neonates admitted with neonatal sepsis at public comprehensive specialized hospitals, SNNPRS, Ethiopia, 2023.

Variables	Category	Median recovery time	X^2	P-value
Residence	Urban	8(8,9)	4.41	0.0357
	Rural	9(8,10)		
Place of delivery	Home	10(9,14)	7.46	0.0063
	Health institution	8(8,9)		
Intrapartum fever	Yes	9(7,9)	6.07	0.0137
	No	8(8,9)		
ANC visit	No	10(6,)	12.1	0.0166
	One	10(9,10)		
	Two	9(8, 9)		
	Three	8(8, 9)		
	Four & above	8(8,9)		
EBFI	Yes	9(8,9)	3.17	0.0749
	No	8(8,9)		
Resuscitated at birth	Yes	10(10,12)	35	0.000
	No	8(8,9)		
BCG vaccine	Yes	8(8,9)	4.17	0.0411
	No	8(8,10)		
Oxygen supply	Yes	10(9,10)	13.33	0.000
	No	8(8,9)		
Fever at admission	Yes	9(8,10)	0.25	0.0152
	No	8(8,9)		
Birth weight	<2500gram	10(8,10)	17.02	0.0000
	>=2500gram	8(8,9)		
Respiratory distress	Yes	10(9,10)	44.071	0.0000
	No	7(7,8)		

6.7. Factor associated to neonatal sepsis recovery time

The Cox proportional hazard regression model was used to identify determinants of recovery of neonatal sepsis. Bivariate analysis was performed first using cox proportional hazard regression to identify which variable had an association with time to recovery from neonatal sepsis.

Those variables like; Twin pregnancy, intrapartum fever, having history of resuscitated at birth, BCG vaccination, sepsis type, Oxygen supply, having history of fever, respiratory distress, hypothermia, birth weight, 5^{th} minute APGAR score, frequency of anti-biotic change and place of delivery were statistically significant with a p-value ≤ 0.25 and candidate for multivariate cox regression model.

In a multivariable proportional hazard model; those variables like; Frequency of antibiotic change, resuscitated at birth, having history of fever and respiratory distress were remains independent determinants of recovery time among neonates with neonatal sepsis with (p value<0.05).

The multivariable analysis result shown that; the hazard of prolonged time to recovery of NS among neonates with fever was 18% delayed than its counterparts. Neonates with history of resuscitation at birth were delayed by 35% in time to recovery of NS as compared to neonates without history resuscitation at birth. Similarly, the time to recovery of NS among neonates with respiratory distress was prolonged by 29% as compared to its counterparts. The neonates who had no history of antibiotic change were 2 times shorter time to recovery from NS.

Table 9: Bivariate and multivariable Cox proportional hazard regression of neonates admitted with neonatal sepsis at public comprehensive specialized hospitals, SNNPRS, Ethiopia, 2023.

Variables	Category	CHR	P-value	AHR	P-vale
Place of delivery	Home	0.65(0.40,1.04)	0.07	0.71(0.44, 1.15)	1.171
	Health institution	1		1	
Twin pregnancy	Yes	0.74(0.54,1.03)	0.07	0.84(0.60, 1.17)	0.310
	No	1		1	
Intrapartum fever	Yes	1.31(0.98,1.74)	0.06	1.23(0.93, 1.65)	0.145
	No	1		1	
Resuscitation at	Yes	**0.60(0.45,0.79)**	**0.00**	**0.65(0.49, 0.87)**	**0.004***
birth	No	1		1	
BCG vaccine	Yes	1.17(0.99,1.40)	0.063	1.00(0.81, 1.24)	0.985
	No	1		1	
Sepsis type	EONS	0,89(.074,1.06)	0.21	0.96(0.77, 1.22)	0.792
	LONS	1		1	
Oxygen supply	Yes	0.79(0.66,0.96)	0.02	0.87(0.72, 1.06)	0.183
	No	1		1	
Fever during	Yes	**0.98(0.74,1.07)**	**0.22**	**0.82(0.67, 0.99)**	**0.046***
admission	No	1		1	
Respiratory	Yes	**0.67(0.56,0.79)**	**0.00**	**0.71(0.59, 0.85)**	**0.000***
distress	No	1		1	
Hypothermia	Yes	0.75(0.62,0.93)	0.01	0.83(0.65 1.05)	0.136
	No	1		1	
Birth weight	<2500	0.78(0.64,0.94)	0.01	0.89(0.71, 1.10)	0.299
	>2500	1		1	
5^{th} minute	<7	0.77(0.62,0.97)	0.03	0.88(0.70, 1.10)	0.272
APGAR score	>7	1		1	
Frequency of	No	**2.57(2.0, 3.30)**	**0.00**	**2.0(1.57, 2.63)**	**0.000***
antibiotic change	Once & above	1		1	

6.8. Test of proportional-hazards assumption

To use of fitted proportional hazard models, the proportional hazard assumption should be checked. As a result, in this study the Schoenfeld residuals proportional hazard assumption test was used for individual covariates as well as global tests. The proportional hazard assumption is not met if the P-Value is less than 0.05. In this study each covariate has P-Value > 0.05 and all covariates (Global test for Cox proportional hazard P-Value=0.1719 which is also > 0.05 well met the proportional hazard assumption as shown in (Table10).

Table10: Test of proportional hazard by Schoenfeld residuals for each predictor and global test.

Variables	**rho**	**chi2**	**Prob>chi2**
Place of delivery	-0.04517	1.08	0.2990
Intrapartum fever	0.07164	2.77	0.0961
Twin pregnancy	-0.05326	1.54	0.2146
Resuscitation at birth	0.06644	2.49	0.1147
Residence	-0.05576	1.69	0.1942
Respiratory distress	-0.02780	0.42	0.5155
Birth weight	-0.00697	0.02	0.8747
Fever during admission	-0.07834	3.36	0.0667
Place of delivery	-0.01771	0.18	0.6745
Gestational age	0.02536	0.38	0.5351
BCG vaccine	0.03903	0.91	0.3401
Sepsis type	0.03526	0.72	0.3948
Assisted with mask & bag	-0.06236	2.08	0.1490
Global test	17.63	13	0.1719

Notice: Rho is the correlation coefficient between the residuals and time

6.9. Testing overall fitness of the model

In this study goodness-of-fit (gof) was checked graphically using the Cox Snell residuals plot to check the assumption of the Cox proportional hazard model. For the residuals test, the hazard function follows 45º close to the baseline hazard, which indicates that the model was well-fitted . The jagged line with the reference line (Cox Snell residual line) follows the 45˚ line closely. Hence, the overall cox- regression model fits to the data (figure 8).

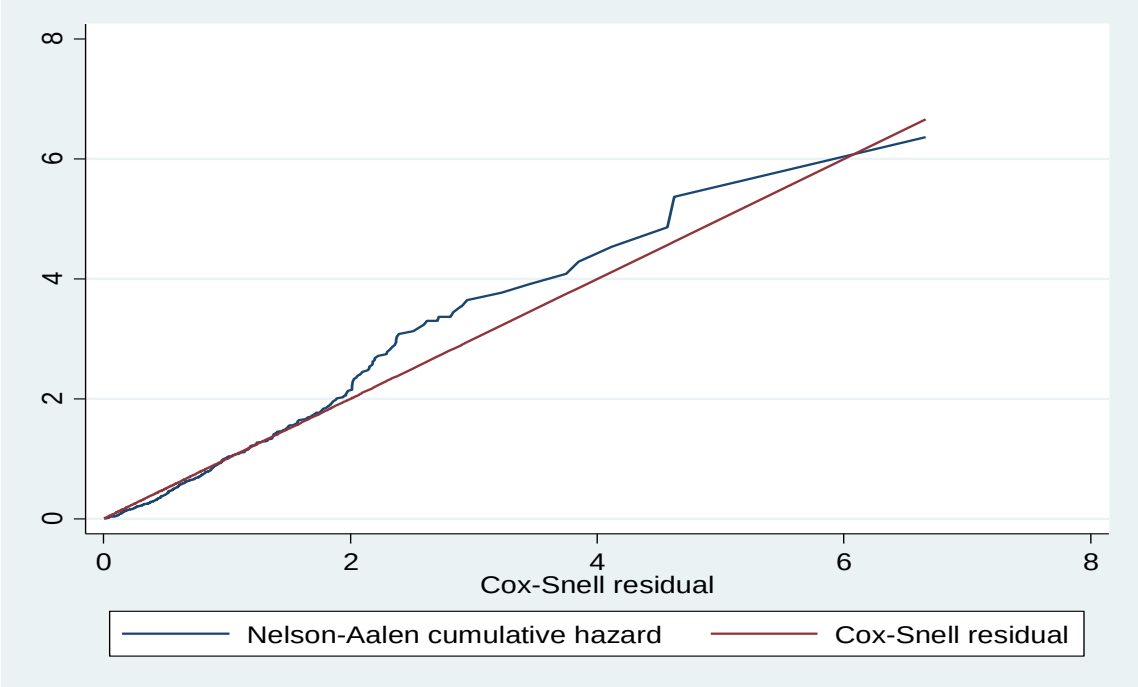


Figure8: Cox Snell residual test for proportional assumption of each covariant and overall Cox proportional hazard model.

7. Discussions

This study assessed the time to recovery of neonatal sepsis and determinant factors among neonates admitted in Public Comprehensive Specialized Hospitals of SNNPRS, Ethiopia. In this study, the neonates with sepsis were followed for a total of 5424-neonate day observations.

The result of this study show that the overall recovery time was 8 days (IQR; 7, 10).This result is in line with the previous study done in Addis Ababa which was reported as 8.92 days(70). And lower than the previous study conducted in Arbaminch and Brazil which was 12.74 and 19 days respectively(14, 34); The observed difference may be due to the variation in methodology (EONS was classified as 3 to 7 days) and study population (all neonates included). This may cause their survival time to be higher than the current study's median recovery time.

However this result was higher than the previous study conducted in Uganda and India which reports 5.5 and 5.4 days respectively (33, 35); the reason for this discrepancy might be due to difference in study design, sample size and age range of the participants they used (less than 4 month or birth to 120 days) which may help them for strength of their immunization and early recovery. The result of this study was also higher than the previous study done in Bahir Dar that reported as 6 days(70), Gondar 7 days (10) and Dire Dawa 7days(71). The possible reason might be due to; difference in model of analysis, number of neonates referred to other hospital which accounts 22.66% of admitted neonates and source population that the previous study (assesses recovery of all neonates admitted to NICU).

During the follow up period; recovery probability at the beginning, half and end of study was 99.84 %, 18.26 % and 1.98% respectively. This finding was supported by the previous study conducted in Gondar (10). The possible similarity may be due to almost similar sample size and model of analysis.

In this study the incidence rate of recovery was 9.86 per 100 neonate day of observation. This result is inconsistent with the study conducted in Gondar which was 10.78 per100 neonate days. The variation might be due to gestational age <37 weeks in the previous study was small in number than the current one, this may cause them to have increased rate of recovery (10).

In this study neonates with fever during admission were delayed by 18% in time to recovery of NS as compared to their counter parts. This finding was supported by previous study conducted in Nigeria(66) and Iraq (45). The reason may be due to the fact that; as the neonates have an infection, the body's temperature usually rises as it tries to fight off the host causing the infection as a result there is the exhaustion of immunity which leads to late recovery.

In this study the hazard of prolonged time to recovery of neonatal sepsis among neonates with respiratory distress were 29% less likely to recover fast as compared to those neonates without respiratory distress. This finding is in line with the study conducted in Nigeria(66). The possible reason for consistence may be due to similar age limit of the study participant. However this result was inconsistence with the study done in Bahir Dar Felege Hiwot Referral Hospital(72). The observed difference may be due to the variation in study design and model of analysis that the previous used logistic regression for outcome of neonate. The possible explanation is that; respiratory distress may leads to low gas exchange and increased physiological dead space, which causes multiple organ hypoxia and dysfunction; as a result neonates with such complication have prolonged hospital stay.

The time to recovery among neonates with resuscitation at birth is delayed by 35% from NS compared to their counterparts. This finding was supported by previous study done in Woldia and Dessie comprehensive specialized hospital (25), Tanzania(22) and Kaffa zone (67),. The possible fact may be due to the lumen of the peripheral airway of the newborn is thin and respiratory secretions are overflowing which could predispose to atelectasis. For the collapsed lungs, performing different procedures may cause for an entry point for microbial agents. And also resuscitation might be done with unsterile procedure, which could introduce microbes into the respiratory system of the neonate whose immune system is not well developed and unable to fight against other nosocomial infection and become risk for prolonged hospital admission.

In this study those neonates who had no history of antibiotic change were 2 times shorter time to recovery from NS than those neonates with history of one and above antibiotic change during their stays. This finding is inconsistence with the study done in Philadelphia (61). The observed difference may be due to small sample size (n=194) and age cut of point (<1year) on the pervious study.

This finding is also inconsistent with the previous study conducted in Nigeria (66) which report it as it has no effect on the patient outcome and recommended for further validation, this inconsistence may be due to difference in model of analysis that it was used. However this finding is supported by WHO guideline that recommends parenteral antibiotics treatment for a neonate having known risk of sepsis for no less than 2 days(8). This might be due to fear of antibiotic resistance to the host causing the infection.

8. Conclusion and Recommendation

8.1. Conclusion

In this study, the median time and rate of recovery was moderately acceptable as compared to the previous studies. With regard to determinants; having history of fever, frequency of antibiotic change, respiratory distress and resuscitation at birth were found statistically significant determinants of recovery among neonates admitted with neonatal sepsis.

8.2. Recommendation

Based on the findings of this study, the following recommendations have been forwarded with each respective body:-

To comprehensive specialized hospitals

- The hospitals directors shall encourage health care providers working in NICU to closely follow neonates with neonatal sepsis during their first 8 days of life especially for neonate with history of resuscitated at birth, fever and respiratory distress.
- Better to strengthen the regular training to update the knowledge of NICU staffs and the recovery audit system and
- Provide adequate treatment supplements for better improvement of neonatal sepsis outcome
- The medical director with health care providers of each SNNPRS should facilitate more research to find out additional precise predictors of recovery of neonatal sepsis

To Health professionals

- It is better to focus on the prevention, early diagnosis, and appropriate management of neonatal sepsis
- Minimize unnecessary hospital stay by treating fever and respiratory distress based on guidelines on time.
- Antibiotic change shall be change based on treatment guideline
- Use sterile procedure during resuscitation of neonates

To Future researchers

- Better to conduct using prospective cohort study that includes other variables such as parental, socio-demographic and economic characteristics.

9. Strengths and Limitations

9.1. Strengths

- The study area covers the SNNPRS public comprehensive specialized hospitals and the results in findings can be generalized.
- Large sample size was used comparing to the other study done in Ethiopia which increases generalization to population.
- Using a 2-year record which gives the more recent information for the current population

9.2. Limitations

- Since the study was retrospective and centered on secondary data, it did not take into account all possible determinants of the outcome variable, such as parental socio-demographic, socioeconomic, NICU status and environmental factors.

10. References

1. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. The lancet. 2017;390(10100).

2. Ethiopia Fmoho. Neonatal Intensive Care Unit (NICU) Training Participants' Manual, 2021. 2021.

3. UNICEF-Sd-Neonatal-Guidelines-report-2018.

4. Organization WH. Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions. 2020.

5. Stoll BJ, Adams-Chapman I, Kliegman RM, Behrman R, Jenson H, Stanton B. Nelson textbook of pediatrics. Nelson textbook of pediatrics. 2021.

6. Schrag SJ, Farley MM, Petit S, Reingold A, Weston EJ, Pondo T, et al. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. Pediatrics. 2016;138(6).

7. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. The lancet. 2017;390(10104).

8. FMoH. Final management protocol Sep 26 , 2021.

9. El-Din EMRS, El-Sokkary MMA, Bassiouny MR, Hassan R. Research Article Epidemiology of Neonatal Sepsis and Implicated Pathogens: A Study from Egypt. 2015.

10. Oumer M, Abebaw D, Tazebew A. Time to recovery of neonatal sepsis and determinant factors among neonates admitted in Public Hospitals of Central Gondar Zone, Northwest Ethiopia, 2021. PloS one. 2022;17(7):e0271997.

11. Derese T, Belay Y, Tariku Z. The Median Survival Recovery Time and Associated Factors Among Admitted Neonate in Intensive Care Units of Dire Dawa Public Hospitals, East Ethiopia. 2020.

12. Fjalstad JW, Esaiassen E, Juvet LK, van den Anker JN, Klingenberg C. Antibiotic therapy in neonates and impact on gut microbiota and antibiotic resistance development: a systematic review. Journal of Antimicrobial Chemotherapy. 2018;73(3).

13. Milton R, Gillespie D, Dyer C, Taiyari K, Carvalho MJ, Thomson K, et al. Neonatal sepsis and mortality in low-income and middle-income countries from a facility-based birth cohort: an international multisite prospective observational study. The Lancet Global Health. 2022;10(5):e661-e72.

14. Dessu S, Habte A, Melis T, Gebremedhin M. Survival Status and Predictors of Mortality among Newborns Admitted with Neonatal Sepsis at Public Hospitals in Ethiopia. International journal of pediatrics. 2020;2020:8327028.
15. Masanja PP, Kibusi SM, Mkhoi ML. Predictors of early onset neonatal sepsis among neonates in Dodoma, Tanzania: a case control study. Journal of tropical pediatrics. 2020;66(3).
16. Liang L, Kotadia N, English L, Kissoon N, Ansermino JM, Kabakyenga J, et al. Predictors of mortality in neonates and infants hospitalized with sepsis or serious infections in developing countries: a systematic review. Frontiers in pediatrics. 2018;6:277.
17. Fleischmann C, Reichert F, Cassini A, Horner R, Harder T, Markwart R, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. Archives of Disease in Childhood. 2021;106(8).
18. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. The Lancet Respiratory Medicine. 2018;6(3):223-30.
19. Labi A-K, Obeng-Nkrumah N, Bjerrum S, Enweronu-Laryea C, Newman MJ. Neonatal bloodstream infections in a Ghanaian Tertiary Hospital: Are the current antibiotic recommendations adequate? BMC infectious diseases. 2016;16(1):1-12.
20. Mah-Mungyeh E, Chiabi A, Tchokoteu FL, Nguefack S, Bogne JB, Siyou H, et al. Neonatal mortality in a referral hospital in Cameroon over a seven year period: trends, associated factors and causes. African health sciences. 2014;14(4).
21. Owusu BA, Lim A, Makaje N, Wobil P, SameAe A. Neonatal mortality at the neonatal unit: the situation at a teaching hospital in Ghana. African health sciences. 2018;18(2).
22. Jabiri A, Wella HL, Semiono A, Saria A, Protas J. Prevalence and factors associated with neonatal sepsis among neonates in Temeke and Mwananyamala Hospitals in Dar es Salaam, Tanzania. Tanzania Journal of Health Research. 2016;18(4).
23. Le Geyt J, Hauck S. G272 Epidemiological trends of neonatal sepsis in a county referral hospital in central Kenya. BMJ Publishing Group Ltd; 2016.
24. Medhat H, Khashana A. Incidence of neonatal infection in South Sinai, Egypt. International Journal of Infection. 2017;4(1).
25. EMDHS. The 2019 Ethiopia Mini Demographic and Health Survey, 2019.

26. Agnche Z, Yenus Yeshita H, Abdela Gonete K. Neonatal sepsis and its associated factors among neonates admitted to neonatal intensive care units in primary hospitals in central gondar zone, northwest ethiopia, 2019. Infection and drug resistance. 2020.
27. Getabelew A, Aman M, Fantaye E, Yeheyis T. Prevalence of Neonatal Sepsis and Associated Factors among Neonates in Neonatal Intensive Care Unit at Selected Governmental Hospitals in Shashemene Town, Oromia Regional State, Ethiopia, 2017. International journal of pediatrics. 2018;2018:7801272.
28. Bekele K, Bekele F, Edosa D, Mekonnen M, Benayew M. Magnitude and associated factors of neonatal sepsis among neonates admitted to neonatal intensive care unit of Northern oromia hospitals, Ethiopia: A multicenter cross-sectional study. Annals of Medicine and Surgery. 2022;78:103782.
29. Birrie E, Sisay E, Tibebu NS, Tefera BD, Zeleke M, Tefera Z. Neonatal sepsis and associated factors among newborns in Woldia and Dessie comprehensive specialized hospitals, North-East Ethiopia, 2021. Infection and drug resistance. 2022.
30. Mustefa A, Abera A, Aseffa A, Abathun T, Degefa N, Tadesse H. Prevalence of neonatal sepsis and associated factors amongst neonates admitted in arbaminch general hospital, arbaminch, southern Ethiopia, 2019. J Pediatr Neonatal Care. 2020;10(1):1-7.
31. Mersha A, Worku T, Shibiru S, Bante A, Molla A, Seifu G, et al. Neonatal sepsis and associated factors among newborns in hospitals of Wolaita Sodo Town, Southern Ethiopia. Research and reports in neonatology. 2019;9:1.
32. Orsido TT, Asseffa NA, Berheto TM. Predictors of Neonatal mortality in Neonatal intensive care unit at referral Hospital in Southern Ethiopia: a retrospective cohort study. BMC pregnancy and childbirth. 2019;19.
33. Singh P, Wadhwa N, Lodha R, Sommerfelt H, Aneja S, Natchu UCM, et al. Predictors of time to recovery in infants with probable serious bacterial infection. PloS one. 2015;10(4):e0124594.
34. Risso SdP, Nascimento LFC. Risk factors for neonatal death in neonatal intensive care unit according to survival analysis. Revista Brasileira de terapia intensiva. 2017;22.
35. Tumuhamye J, Sommerfelt H, Bwanga F, Ndeezi G, Mukunya D, Napyo A, et al. Neonatal sepsis at Mulago national referral hospital in Uganda: Etiology, antimicrobial resistance, associated factors and case fatality risk. PloS one. 2020;15(8):e0237085.

36. Clinical outcome and risk factors of neonatal sepsis among neonates in Felege Hiwot referral Hospital, Bahir Dar, Amhara Regional State, North West Ethiopia 2016: a retrospective chart review. 2017.

37. Dessu S, Habte A, Melis T, Gebremedhin M. Survival status and predictors of mortality among newborns admitted with neonatal sepsis at public hospitals in Ethiopia. International journal of pediatrics. 2020.

38. Sisay EA, Mengistu BL, Taye WA, Fentie AM, Yabeyu AB. Length of Hospital Stay and Its Predictors Among Neonatal Sepsis Patients: A Retrospective Follow-Up Study. International journal of general medicine. 2022.

39. Adjei G, Darteh EK, Nettey OEA, Doku DT. Neonatal mortality in the central districts of Ghana: analysis of community and composition factors. BMC public health. 2021;21(1):1-14.

40. Sabeeh Jumah D, Hassan K. Predictors of mortality outcome in neonatal sepsis. The Medical Journal of Basrah University. 20017;25(1):11-8.

41. Meshram RM, Gajimwar VS, Bhongade SD. Predictors of mortality in outborns with neonatal sepsis: A prospective observational study. Nigerian Postgraduate Medical Journal. 2019;26(4):216.

42. Alhassan AL. Determinants of mortality in Newborn with Sepsis condition using binary logistic model at the Tamale Teaching Hospital. Open Access Library Journal. 2019;6(05):1.

43. Berardi A, Sforza F, Baroni L, Spada C, Ambretti S, Biasucci G, et al. Epidemiology and complications of late-onset sepsis: an Italian area-based study. PloS one. 2019;14(11):e0225407.

44. Freitas F, Araujo A, Melo M, Romero G. Late-onset sepsis and mortality among neonates in a Brazilian Intensive Care Unit: a cohort study and survival analysis. Epidemiology & Infection. 2019;147.

45. ATRUSHI AM. The Profile of Neonatal Sepsis In Duhok City And Predictors of Mortality: A Prospective Case Series Study. Duhok Medical Journal. 2018;12(2):10-20.

46. Murthy S, Godinho MA, Guddattu V, Lewis LES, Nair NS. Risk factors of neonatal sepsis in India: A systematic review and meta-analysis. PloS one. 2019;14(4):e0215683.

47. Shobowale E, Ogunsola F, Oduyebo O, Ezeaka V. A study on the outcome of neonates with sepsis at the Lagos University Teaching Hospital. International Journal of Medicine and Biomedical Research. 2015;4(1):41-9.

48. Okube OT, Komen M. Prevalence and Predictors of Neonatal Sepsis among Neonates Admitted at the Newborn Unit of Kenyatta National Hospital, Nairobi, Kenya. Open Journal of Obstetrics and Gynecology. 2020;10(09).
49. Gebremedhin D, Berhe H, Gebrekirstos K. Risk factors for neonatal sepsis in public hospitals of Mekelle City, North Ethiopia, 2015: unmatched case control study. PloS one. 2016;11(5):e0154798.
50. Bulto GA, Fekene DB, Woldeyes BS, Debelo BT. Determinants of neonatal sepsis among neonates admitted to public hospitals in Central Ethiopia: unmatched case-control study. Global Pediatric Health. 2021;8:2333794X211026186.
51. Akalu TY, Gebremichael B, Desta KW, Aynalem YA, Shiferaw WS, Alamneh YM. Predictors of neonatal sepsis in public referral hospitals, Northwest Ethiopia: A case control study. PloS one. 2020;15(6):e0234472.
52. Alemu M, Ayana M, Abiy H, Minuye B, Alebachew W, Endalamaw A. Determinants of neonatal sepsis among neonates in the northwest part of Ethiopia: case-control study. Italian journal of pediatrics. 2019;45(1).
53. Erkihun K, Mesfin M, Direslegn M, Sultan H, Negussie B. Determinants of neonatal sepsis among neonates admitted in a neonatal intensive care unit at Jinka General Hospital, Southern Ethiopia. International Journal of Nursing and Midwifery. 2019;11(3):18-24.
54. Wale A, Chelkeba L, Wobie Y, Abebe A. Treatment Outcome and Associated Factors of Neonatal Sepsis at Mizan Tepi University Teaching Hospital, South West Ethiopia: A Prospective Observational Study. Pediatric health, medicine and therapeutics. 2021;12:467-79.
55. Endazanaw a. Treatment outcome of neonatal sepsis andcassociated factors among neonates admitted tocneonatal intensive care unit in public hospitals,caddis ababa, ethiopia, 2021.
56. Bohanon FJ, Nunez Lopez O, Adhikari D, Mehta HB, Rojas-Khalil Y, Bowen-Jallow KA, et al. Race, Income and Insurance Status Affect Neonatal Sepsis Mortality and Healthcare Resource Utilization. Pediatric Infectious Disease Journal. 2018;37(7):e178-e84.
57. Feleke AA, Abdella MY, W/Mariam AD. Determinants and Magnitude of Neonatal Sepsis at Hiwot Fana Comprehensive Specialized University Hospital, Harar, Ethiopia: A Cross-Sectional Study. medRxiv. 2021:2021.11. 04.21265874.

58. Abebia MT, Kibret GT, Belete MB, Asmare AG, Abate MT, Abebe SM, et al. Time to Death and Its Predictors Among Neonates Admitted With Neonatal Sepsis at Public Referral Hospitals of Bahir Dar City, Northwest Ethiopia, 2021: Retrospective Cohort Study. 2021.

59. Hsia Y, Lee BR, Versporten A, Yang Y, Bielicki J, Jackson C, et al. Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries. The Lancet Global Health. 2019;7(7):e861-e71.

60. Schlapbach LJ, van Rossum A, Carrol ED. Antibiotics for neonatal sepsis in low-income and middle-income countries—where to go from here? The Lancet Infectious Diseases. 2021;21(12):1617-8.

61. Schmatz M, Srinivasan L, Grundmeier RW, Elci OU, Weiss SL, Masino AJ, et al. Surviving sepsis in a referral neonatal intensive care unit: association between time to antibiotic administration and in-hospital outcomes. The Journal of Pediatrics. 2020;217:59-65. e1.

62. Al-Matary A, Al Sulaiman M, Al-Otaiby S, Qaraqei M, Al-Matary M. Association between the timing of antibiotics administration and outcome of neonatal sepsis. Journal of infection and public health. 2022;15(6):643-7.

63. Brook B, Harbeson DJ, Shannon CP, Cai B, He D, Ben-Othman R, et al. BCG vaccination–induced emergency granulopoiesis provides rapid protection from neonatal sepsis. Science Translational Medicine. 2020;12(542):eaax4517.

64. Fuchs A, Bielicki J, Mathur S, Sharland M, Van Den Anker J. Antibiotic use for sepsis in neonates and children: 2016 evidence update. WHO reviews. 2016.

65. Tan J, Kan J, Qiu G, Zhao D, Ren F, Luo Z, et al. Clinical prognosis in neonatal bacterial meningitis: the role of cerebrospinal fluid protein. PloS one. 2015;10(10):e0141620.

66. Dedeke I, Arowosegbe A, Shittu O, Ojo D, Akingbade O. Neonatal sepsis in a Nigerian tertiary hospital: clinical features, clinical outcome, aetiology and antibiotic susceptibility pattern. Southern African Journal of Infectious Diseases. 2017;32(4):127-31.

67. Melesse Belayneh1* GG, Alemaw Gebretsadik2. Determinants of Neonatal Sepsis Admitted In Neonatal Intensive Care Unit At Public Hospitals Of Kaffa Zone, South West Ethiopia, 2021.

68. Tadesse M. Time to Death and its Predictors Among Neonates Admitted with Neonatal Sepsis at Public Referal Hospitals of Bahir Dar City, Northwest Ethiopia,. 2021.

69. Corvaglia L, Martini S, editors. Feeding difficulties during the neonatal period. Italian Journal of Pediatrics; 2015: BioMed Central.
70. Sisay EA, Mengistu BL, Taye WA, Fentie AM, Yabeyu AB. Length of Hospital Stay and Its Predictors Among Neonatal Sepsis Patients: A Retrospective Follow-Up Study. International journal of general medicine. 2022.
71. The Median Survival Recovery Time and Associated Factors among Admitted Neonate in Intensive Care Units of Dire Dawa Public Hospitals, East Ethiopia 2019.
72. Tewabe T, Mohammed S, Tilahun Y, Melaku B, Fenta M, Dagnaw T, et al. Clinical outcome and risk factors of neonatal sepsis among neonates in Felege Hiwot referral Hospital, Bahir Dar, Amhara Regional State, North West Ethiopia 2016: a retrospective chart review. BMC research notes. 2017;10:1-7.

Annex I: Information sheet

Hello! My name is Elias Geneti; Currently I am a graduate student at Debre Brehan University, Asrat Woldeyes Health Sciences Campus, Department of pediatrics & child Health Nursing. Now I am interesting to conduct a study on the title:-Title of the research: Time to recovery of neonatal sepsis and determinant factors among neonate admitted to NICU at Public Comprehensive Specialized Hospitals, SNNPRS, Ethiopia, 2023.

Name of investigator: Elias Geneti

Sponsoring Organization:-Wachemo University Nigest Eleni Mohammed Memorial Comprehensive Specialized Hospital

Name of organization: Debre Brehan University Asrat Woldeyes Health Sciences Campus, School of Nursing and Midwifery, department of Pediatrics and Child Health Nursing.

Purpose of the study: To determine recovery time and its determinant factors among neonates admitted with neonatal sepsis admitted at NICU from 2020-2022.

Data collection time: From 1st April to 30th April, 2023 (for 15 days duration).

Study unit: Neonatal charts with a diagnosis of neonatal sepsis.

Risks: Since all data will be taken from medical chart, no any harm to patient. The name or any identification will not be recorded in the checklist. The confidentiality of all information taken from chart will be maintained.

Benefits: No direct benefits for those subjects whose documents will be reviewed. It is already passed. However, results will be used for policy makers and decision makers for designing appropriate measures to improve their recovery. So this study will benefit indirectly other new generations.

No name and other identification will be written in the checklist. If you have any questions about this study you may ask principal investigator Elias Geneti (MSc student in pediatrics & child health nursing at Debre Brehan University, Asrat Woldeyes health science campus

Principal investigator`s Phone number: +251921673354

E-mail: elogeneti@gmail.com

Annex II: Data collection checklist

Data collection checklist is prepared only for those variables found at neonatal chart. It incorporates socio demographic factor of mother & neonate, maternal factors, neonatal factors & clinical related factors

Part1: Socio demographic

S.no	Questions	Choice of responses
101	Age of the mother	……. in years
102	Place of residence	1. Urban 2. Rural
103	Sex of the neonate	1. Male 2. Female
104	Age of the neonate	…….age in days
Part 2: Maternal-related characteristics		
201	Place of delivery/birth	1. Home 2. Health institutions
202	Mode of delivery	1. Cesarean section 2. Spontaneous vaginal delivery 3. Forceps delivery
203	Number of ANC visits	1. No 2. One 3. Two 4. Three 5. Four and above
204	Twin pregnancy	1. Yes 2. No
205	Pregnancy-induced hypertension	1. Yes 2. No
206	Intra-partum fever	1. Yes 2. No
207	Diagnosed chorioamniotis	1. Yes 2. No
208	Duration after the rupture of membrane	……..hr

Part 3: Neonate related characteristics

301	Birth weight	_____Gm
302	Gestational age at birth	_____Weeks
303	Temperature at admission	_____0_C
304	Respiratory rate at admission	_____b/m
305	EBF initiated within one hour	1. Yes 2. No
306	First minute APGAR score	……
307	Fifth minute APGAR score	……..
308	Resuscitated at birth	1. Yes 2. No
309	New admission	1. Yes 2. No
310	Admission date	___dd____mm_____yyy,

Part 4: Medical treatment/Care related factors

401	Supply oxygen	1. Yes 2. No
	Medications/treatments	
402	Antibiotics given	1. Ampicillin + Gentamicin 2. Vancomycin + Ceftazidime 3. Ampicillin + Ceftriaxone 4. Vancomycin +Cefotaxime 5. Others specify……
403	Duration of treatment	……hours/days
404	BCG vaccination administration	1.Yes 2. No
405	Number of antibiotic switches/change	1.0 2.1x 3.2x

Part 5: Clinical features/presentation of neonates with sepsis

501	Have fever	1. Yes 2. No
502	Respiratory distress	1. Yes 2. No
503	Tachycardia	1. Yes 2. No
504	Poor feeding	1. Yes 2. No
505	Vomiting	1. Yes 2. No
506	Meconium Aspiration Syndrome	1. Yes 2. No
507	Hypothermia	1. Yes 2. No
508	Cyanosis	1. Yes 2. No
509	Jaundice	1. Yes 2. No
510	Sepsis type	1. EONS 2. LONS
511	Major co-morbidities	1. Yes 2. No
512	If yes which one	1.TB 2. HIV 3. CHD 4. Other, specify _____
513	Chest indrawing	1. Yes 2. No
	Specify other sign and symptom	……

6. Discharge and outcome status after admission

601	Discharged as	1. Recovered 2. Died 3. Defaulted/lost follow-up 4. Referred 5. Transferred/or not-recovered
602	Length/duration of hospital stay	…….Days
603	Discharge date	____dd_____mm_____yyy,

Annex III: **Multi co-linearity**

Variable	VIF	1/VIF
BCG vaccine |	1.67	0.598050
Age of Neonate	1.53	0.655007
Hypothermia	1.43	0.699542
Frist min APGAR	1.40	0.714612
Fifth min APGAR	1.39	0.719454
Number of ABX change	1.39	0.721155
Birth weight	1.30	0.769556
Place of delivery	1.26	0.791227
RDS	1.23	0.811548
EBFI	1.19	0.840539
Vomiting	1.17	0.853946
Fever	1.17	0.855676
Resuscitation at birth	1.17	0.857625
Mode of delivery	1.16	0.865324
Residence	1.14	0.874193
Frequency of ABX change	1.14	0.876254
New admission	1.13	0.882405
ABX given	1.13	0.885629
Oxygen supply	1.13	0.888758
Age of mother	1.12	0.890833
MAS	1.11	0.897759
Twin pregnancy	1.11	0.897848
Cyanosis	1.11	0.901035
Chest indrowing	1.10	0.906199
Co-morbidity	1.10	0.911241
Chorioamniotis	1.09	0.918188
Poor feeding	1.09	0.919955
Sex of neonate	1.07	0.933423
Intra partum fever	1.07	0.938341
Pregnancy induced HTN	1.06	0.942647
Jaundice	1.05	0.948111
Mean VIF	**1.20**	