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TIME TO RECOVERY AND ITS ASSOCIATED FACTORS AMONG PRETERM NEONATES WITH NECROTIZING ENTEROCOLITIS ADMITTED TO NEONATAL INTENSIVE CARE UNITE IN SELECTED HOSPITALS, ADDIS ABABA, ETHIOPIA, 2024

BY:

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A THESIS TO BE SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES OF ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCE, SCHOOL OF NURSING AND MIDWIFERY FOR PARTIAL-FULFILLMENT OF THE REQUIREMENTS FOR A MASTER OF SCIENCE IN NEONATAL NURSING.

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THE TIME TO RECOVERY AND ITS ASSOCIATED FACTORS AMONG PRETERM NEONATES WITH NECROTIZING ENTEROCOLITIS ADMITTED TO NICU IN SELECTED HOSPITALS, ADDIS ABABA, ETHIOPIA, 2024

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LIST OF ABBREVIATIONS AND ACRONYMS

AAU	Addis Ababa University
AGM	Ampicillin, Gentamicin, and Metronidazole
AHR	Adjusted hazard ratio
ANC	Antenatal care
BMV	Bag-mask ventilation
CBC	Complete blood count
CHR	Crude hazard ratio
CID	Combined immunodeficiency
CRP	C reactive protein
DM	Diabetic Mellitus
ELBW	Extremely low birth weight
FEF	Full enteral feeding
GMH	Gandhi Memorial Hospital
HMIS	Health management information system
I-FABP	Intestinal fatty acid-binding protein
IP	Intestinal perforation
LAMA	Left against medical advice
LBW	Low birth weight
MD	Mean difference
MV	Mechanical ventilator
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care units
NIRS	Near infrared spectroscopy
PPD	Persistent peritoneal drainage
PROM	Premature rupture of membrene
SPHMMC	St. Paul Millennium Medical College Specialized Teaching Hospital
TASH	Tikur Anbessa Specialized Hospital
TBGH	Tirunesh Beijing General Hospital
TFF	Time to full feeds

VIF	Variable inflation factor
VLBW	Very low birth weight
WBC	White blood cell
WHO	World Health Organization
Y12HMC	Yekatit 12 Hospital Medical College
ZMH	Zewditu Memorial Hospital

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ABSTRACT

Background: Necrotizing enterocolitis (NEC) is a complex multifactorial disease that results in ischemia, pneumatosis, necrosis, and perforation. It remains the leading cause of gastrointestinal disease-related mortality in preterm babies. However, there is a paucity of data regarding recovery time and associated factors. Thus, this study aimed to determine the time to recovery and associated factors among preterm neonates with NEC admitted to the NICU in selected public hospitals in Addis Ababa.

Methods: A retrospective study was conducted on 313 preterm neonates who were diagnosed with necrotizing enterocolitis and admitted to selected hospitals within the last ten years. Patient charts were selected using simple random sampling (lottery method). A data abstraction form was used to collect the data. STATA version 14.0 was used for the analysis. A Kaplan–Meier survival curve was generated to estimate the survival probabilities. A log-rank test was computed to compare the significant differences in survival probability at any time point between categories of covariates. The hazard ratio (HR) and 95% confidence interval (CI) were computed to determine the associations. According to the multivariate analysis, variables with a p value < 0.05 were considered to be statistically significant.

Results: Of the 313 preterm neonates with NEC, 52 (16.61%) recovered, and 261 (83.39%) were censored. The overall incidence of recovery time was 12.5 (95% CI: 0.01-0.02) per 1000 person-days. The median time to recovery from necrotizing enterocolitis among preterm neonates was 21 (IQR: 18–24) days. Predictors significantly associated with recovery time included birth weight of the neonate, steroid administration, PROM, and duration of antibiotics.

Conclusion and recommendation: The incidence rate of NEC was very low, and the overall median time to recover from NEC was high in the study area. Having an extremely low birth weight, not taking steroids, being born to a mother with no PROM, and taking antibiotics for more than fourteen days were proven to delay the time to recovery from NEC. Therefore, measures that increase the recovery rate and hasten the recovery time should be strengthened.

Keywords: Preterm neonate, necrotizing enterocolitis, time to recovery, associated factors, Ethiopia

Chapter 1

INTRODUCTION

1.1 Background

Necrotizing enterocolitis (NEC) is a complex multifactorial disease that results in ischemia, pneumatosis, necrosis, and perforation (1,2). Although hypoxia-ischemia is considered a major causal factor, other factors, such as microbial colonization, intestinal immaturity, microvascular imbalance, hereditary susceptibility, and highly immune-reactive mucosa, can also contribute to its development (2,3).

Preterm babies, defined as those born before 37 weeks of gestational age (4), are more often vulnerable to several acute and chronic illnesses, such as NEC (5). Globally, it is responsible for 14.84 million new-born deaths, with the highest incidence observed in Asia and sub-Saharan African countries (6).

The advent of surfactants in recent decades has improved the survival rate of extremely preterm newborns (7). NEC remains the leading cause of gastrointestinal (GI) disease-related mortality in preterm babies, affecting 5–12% of neonates born at a very low birth weight (VLBW; less than 1500 g) (8). A systematic review and meta-analysis of the global incidence of NEC revealed that 7 in 100 VLBW babies in the NICU are likely to develop NEC (9). The incidence of NEC is highest between the first and seventh days of life, although it can also occur in the second or third week (10,11).

The time to recovery was defined as the surrogate markers' return to baseline or normal values after the diagnosis of NEC (12). The time to full enteral feeding or the development of post-NEC complications can be used to assess whether the intestine is recovering (13). Preventing severe cases could improve patient outcomes and expenses, but the severity of NEC remains unknown (14). Therefore, studying the time to recovery and associated factors is relevant before the disease becomes complicated to improve the outcome. However, to the knowledge of the principal investigator, no study has been conducted on the time to recovery and its associated factors in patients with NEC in Ethiopia. Therefore, this study aimed to investigate the time to recovery and associated factors in preterm neonates with NEC.

1.2 Problem statement

Worldwide, neonatal intensive care units (NICUs) are home to many cases of serious neonatal diseases marked by ischemic intestinal necrosis, such as necrotizing enterocolitis (NEC) (15). NEC is a common gastrointestinal emergency that causes severe mortality (2,3) and morbidity, including intestinal failure and neurodevelopmental delay, in preterm neonates (1,14,16). Despite improvements in critical care and contemporary medicine, the occurrence of NEC has not diminished (17), and this condition remains challenging for neonatologists due to its unclear pathogenesis, ineffective treatment options, and poor hospitalization rates (3,8,14,18–20). Additionally, it impacts patient and family quality of life and increases therapy costs related to prolonged hospitalization (1).

Preventive strategies such as prenatal glucocorticoid administration, breastfeeding, the use of donor milk, and probiotic supplementation have been implemented, but NEC is still relatively common in most NICUs (2). Despite preventive strategies, preterm neonates with NEC require early intervention before the disease becomes complicated (21). According to recent studies, the survival rate of patients with NEC is gradually increasing as the quality of care in the critical care unit improves (18). The main obstacles to neonatal care in sub-Saharan African countries are inadequate facilities and a shortage of trained healthcare providers (22). In addition to the quality of care, factors associated with survival include the NEC stage and time of diagnosis (21,23). There is currently limited knowledge regarding the healing process of the intestine following NEC (13), and survival time can vary greatly among neonates, ranging from 3 to 97 days (12,24). The recovery time plays a significant role in decreasing the length of stay and therapy cost in NICUs for preterm neonates with NEC to recover (21). The financial burden of NEC is substantial, ranging from $500 million to $1 billion annually in the United States (25). If surgical intervention was needed, neonates diagnosed with NEC had hospital stays 60 days longer than unaffected neonates, and even without the need for surgery, their hospital stays were extended by more than 20 days (25).

Ethiopia is the country with the lowest survival of premature babies and the complication of prematurity such as NEC is the second (24.5%) commonest cause of under-five mortality (26). Prematurity and NEC are strongly correlated with early neonatal death in different contexts, including Ethiopia (27). In developing nations such as Ethiopia, the prognosis for patients with

NEC is poorly understood due to different conflicting results (23). However, research on NEC has been prioritized because it is difficult to eradicate (28,29). Currently, Ethiopia aims to reduce neonatal mortality by 21 per 1000 live births by 2024/2025, aligning with the Sustainable Development Goal (SDG 3), which focuses on reducing neonatal mortality to lower than 12 per 1000 live births by 2030 (30). To address this problem and increase survival, the government has implemented treatment plans and guidelines to improve care for premature neonates with conditions such as NEC (31). The insights gained from this study will provide healthcare providers with guidance on the optimal timing to enhance outcomes for preterm neonates with NEC. Additionally, understanding the factors impacting recovery time is pivotal for preventive measures, early interventions, and improving preterm neonatal care, ultimately aiming to reduce hospital stays and costs of care. However, to the best of our knowledge, there is limited research on this topic both nationally and globally. There is great variation in the recovery time from NEC based on different studies conducted abroad. In addition, no prior study has been performed on the time to recovery from NEC and its predictors in the study area. Therefore, this study aimed to investigate the time to recovery and associated factors among preterm neonates with NEC in public hospitals in Addis Ababa, Ethiopia.

1.3 Significance of the study

Research on the relationship between the time of recovery and prognostic factors is limited. This research has important implications for healthcare providers, parents, and families, as well as researchers and academics.

Overall, investigating the time to recovery and associated factors in preterm neonates with NEC has significant implications for improving patient care, supporting families, advancing medical knowledge, and promoting collaboration within the research community.

For healthcare providers, understanding the factors influencing recovery times can aid in treatment planning, the development of prognostic indicators, and quality improvement initiatives. Customized treatment plans can be created based on individual patient needs, and prognostic indicators can help predict outcomes and guide resource allocation.

Parents and families can benefit from information about recovery times and associated factors in several ways. Hence, this approach allows them to engage in informed decision-making, emotional support during the treatment process, and long-term planning for the child's healthcare needs in case of chronic sequelae.

Researchers and academicians will help as a baseline for conducting further studies on recovery times and associated factors. The findings can be used as input for treatment protocols and guideline developers to overview the existing conditions and develop best practices and guidelines to enhance patient care and improve outcomes accordingly.

Chapter 2

LITERATURE REVIEW

2.1 Introduction

Necrotizing enterocolitis (NEC) is a serious gastrointestinal condition that primarily affects premature neonates. The median time to recover from NEC can range from a few weeks to several months, depending on the severity of the condition and individual factors. Factors associated with recovery from NEC include sociodemographic characteristics such as gestational age and birth weight; maternal-related factors such as maternal age and antenatal complications; clinical-related factors such as NEC stage and onset; and diagnosis-related factors such as early identification and biomarker measurement. Understanding these factors can aid in predicting the severity of NEC, guiding treatment decisions, and improving survival rates through early diagnosis and intervention. Another major area of concern related to NEC is the long-term complications and outcomes for infants who survive the initial episode, including potential developmental delays, growth issues, and gastrointestinal problems.

2.2 Necrotizing Enterocolitis Classification

According to Bell's original staging strategy, NECs are classified into three stages: Bell's stage 1 (suspected but not confirmed NEC), Bell's stage 2 (confirmed pneumatosis intestinalis with or without portal venous gas), and Bell's stage 3 (advanced); these stages are characterized by hemodynamic instability, severe thrombocytopenia, disseminated intravascular coagulopathy, combined immunodeficiency (CID), peritonitis (IIA) and pneumoperitoneum (IIB) (10,32–34).

2.3 Factors Associated with Recovery from Necrotizing Enterocolitis

Sociodemographic characteristics

A study highlighted the significance of gestational age (in weeks) for both medical and surgical cases of NEC as factors influencing the time to full feeds (TFF) (35), and birth weight was also significantly associated with the survival of neonates with NEC (23). Moreover, a strong association was found between the sex (female) of neonates and survival in the context of NEC

(23). Conversely, a study performed at the National Institute of California, York University (NIUC) of Dr. Cipto Mangunkusumo Hospital revealed no significant differences in median survival between infants with a gestational age <32 weeks and those with a gestational age ≥32 or between those with a birth weight <1,000 grams and those with a birth weight ≥1,000 grams (36).

Maternal-related factors

A retrospective study conducted in the United States utilizing a composite scoring tool that included maternal age, parity, steroid administration, and the presence of antenatal complications (DM, hypertension, and chorioamnionitis) was used as a variable for early prediction of the severity of NEC in preterm infants, enabling physicians to make decisions regarding the appropriate timing of correct treatment (37). Similarly, based on a study aimed at predicting intestinal perforation related to NEC and investigating the predictive quality of variables, maternal age (>38 years) and maternal morbidity were among the critical variables for intestinal perforation prediction (38).

Clinical factors

The NEC stage is an important prognostic factor for a good outcome in patients with NEC (21). Similarly, one study revealed that the NEC stage significantly impacts neonatal survival, while other factors, such as sex, APGAR score, platelet count, and treatment type, do not (23). On the other hand, the median survival of patients with early-onset NEC was substantially lower than that of patients with late-onset NEC (36). Another study contended that a later onset of NEC is protective against the need for surgery, but an earlier onset of NEC, in combination with greater levels of C-reactive protein (CRP), indicates a greater risk (39). Additionally, factors influencing the time to full feeding (TFF) include intubation and positive pressure ventilation for both medical and surgical NEC (35,36).

Diagnosis-related factors

Findings from a retrospective, cross-sectional study conducted at Karachi's Ziauddin University Hospital indicate that early diagnosis of the clinical condition may improve survival rates (21). Furthermore, the normalization of radiologic sign like NIRS and identification of biomarkers such as I-FABP and intestinal alkaline phosphatase can indicate intestinal recovery, potentially

reducing mortality and morbidity during early diagnosis (33). Measuring citrulline-P in survivors within the first 24 hours following the start of NEC may indicate the rate of intestinal healing (40).

Based on the study aimed to identify the factors predisposing patients to the development of severe forms of NEC. Different laboratory values (C-reactive protein (CRP), white blood cell, and platelet count) were measured during the acute phase, and white blood cell and platelet counts were significantly different (39).

Treatment type-related factors

Treatment for Bell's stages I and II includes discontinuing enteral feedings, administering intravenous antibiotics, and providing supportive care via a variety of antimicrobial agents for 7 to 14 days (8,33). When "medical" care fails or there is intestinal rupture or necrosis (stage III), surgery is necessary to remove the necrotic part of the colon (33,41).

Compared to patients who need surgical intervention, those who undergo medicinal intervention for NEC have been demonstrated to have markedly greater success rates and lower rates of morbidity and death (16,21,24,42,43). Another study showed that patients who underwent surgery had a significantly lower gestational age and birth weight than did other patients (39). The mortality rate of VLBW infants with surgical NEC is between 50% and 72% (44). In the surgical management of NEC, laparotomy is preferred to peritoneal drainage (PPD) since patients receiving PPD alone have the greatest fatality rates (39,42). Furthermore, laparoscopically aided minimal-access techniques lead to a reduced risk of complications and full recovery in individuals with congenital abdominal cystic lesions (45). Similarly, primary anastomosis has been associated with a greater survival rate than stoma formation enterostomy, potentially leading to better outcomes for less sick children (46).

A study performed at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) revealed that surgical therapy was given to survivors more frequently and earlier than to nonsurvivors. However, compared to surgery for infants receiving medical care, surgery results in a noticeably greater death rate (43). When surgical intervention is necessary for severe NEC, the average duration of stay increases by 43 days, and there is a greater risk of morbidity (such as short bowel syndrome) and mortality (47).

According to recent observational data, infants with NEC who experience the greatest delay between diagnosis and surgery also appear to have the worst prognosis (48). Therefore, early intervention in infants, facilitated by timely access to pediatric surgical facilities, has been proven to enhance survival rates, presenting a promising opportunity for improved outcomes (21,49).

Drug-related factors

According to a study examining the connection between TFF and the duration of antibiotic therapy, there was a significant correlation between TFF and both surgical and medical NEC. It was concluded that longer antibiotic treatment durations were associated with prolonged hospital stays and intestinal recovery (35).

A study that evaluated how different antibiotic treatments affect NEC outcomes revealed that the efficacy of ampicillin, gentamicin, and metronidazole (AGM) was comparable to that of broader spectrum agents for all outcome measures. This finding suggested that the AGM regimen should still be regarded as appropriate for treating NEC, particularly in patients with medical diseases (50).

Feeding-related factors

According to recent studies, initiating enteral feeding early is associated with faster attainment of full enteral feeding and shorter hospital stays (33,41). Beginning enteral feedings <7 days following a diagnosis of NEC was associated with a markedly reduced incidence of both recurrent NEC and/or post-NEC stricture (51)**.**

There was little to no difference in the amount of time needed to complete full enteral feeding between two-hourly and three-hourly feeding, although this conclusion was not very definite (52). Additionally, another study showed that breastfeeding is beneficial for babies recovering from surgery in stage III NEC and that it is safe to begin feedings as soon as 96 hours after delivery; additionally, the process progresses more quickly (30 ml/kg/day), and bolus feed is used to help babies reach full feedings sooner (34).

Factors influencing the time to full feeds (TFF) include the use of breastmilk at 100 kcal/kg/d for both medical and surgical NEC (35). However, regular checking of gastric residue may

lengthen the time taken to achieve full enteral feeds (mean difference (MD) 3.92, 95% CI 2.06 to 5.77 days) (53).

2.4 Survival Rate of Patients with NEC

One study reported an overall cohort survival rate of 55.5% for infants with NEC (33). Other studies in Poland, India, Pakistan, and Indonesia reported survival rates of 79% (45), 87.27% (24), 72.4% (21), and 44.2% (23), respectively. However, a separate study revealed a lower survival rate of 27.27% among infants with NEC (36). Another investigation in India reported a postoperative survival rate of 46.15% (24).

The prevalent of NEC in our study area was 25.4% (54). According to studies conducted in Bahir Dar, the survival probability of infants with NEC was significantly different at different birth weight (94.78% for 1,500-2,500 g, 74.47% for 1,000-1,500 g, and 71.29% for birth weights <1,000 g) (10). Similarly, in another study performed in Bahir Dar, the survival rate of preterm neonates with NEC was 15% (26). Infants born at <32 weeks gestational age had a median survival of 27 days, whereas those born after ≥32 weeks had a median survival of 31 days (36). The median survival of infants with early-onset NEC was 27 days, that of infants with late-onset NEC was 28 days, and that of infants with birth weights <1,000 grams and ≥1,000 grams was 23 and 28 days, respectively (36).

2.5 Recovery Time from Necrotizing Enterocolitis

The median recovery time for patients with NEC varied according to the severity of the condition, according to research performed in Colombia; mild patients recovered in 3 days, moderate patients recovered in 4 days, and severe patients recovered in 9 days (12). The length of stay in the NICU varies according to the stage of NEC, lasting 37–53 days in Stage 1, 49–57 days in Stage 2, and 63–81 days in Stage 3 (24). Moreover, it took an average of 97 days for enterostomy reversal following primary laparotomy (24).

According to meta-analysis done across three studies the overall mean days to recover was between 8 and 11 days (52) and based on a study in Italy it was 17.2 ± 8.2 days (33), and based on a study performed in the Netherlands, the median time to recover after NEC was 20 (IQR: 16-30) days (55). The median time to recover (IQR) in other comparable studies was 24.5 (14,

55) days for surgical NEC patients and 11 (7, 24) days for medical NEC patients (35). Additionally, the total enteral feed group's time to recover (9.571± 1.458 days) was shorter than that of the expressed breast milk or minimum enteral feed supplemented groups (10.833 ± 1.655 days) (56).

2.6 Conceptual framework

The conceptual framework of this study shows the relationships of the dependent variable (time to recovery) with the independent variables. The conceptual framework to guide this study is adapted from different studies (8,10,12,16,21,23,24,26,33–56).

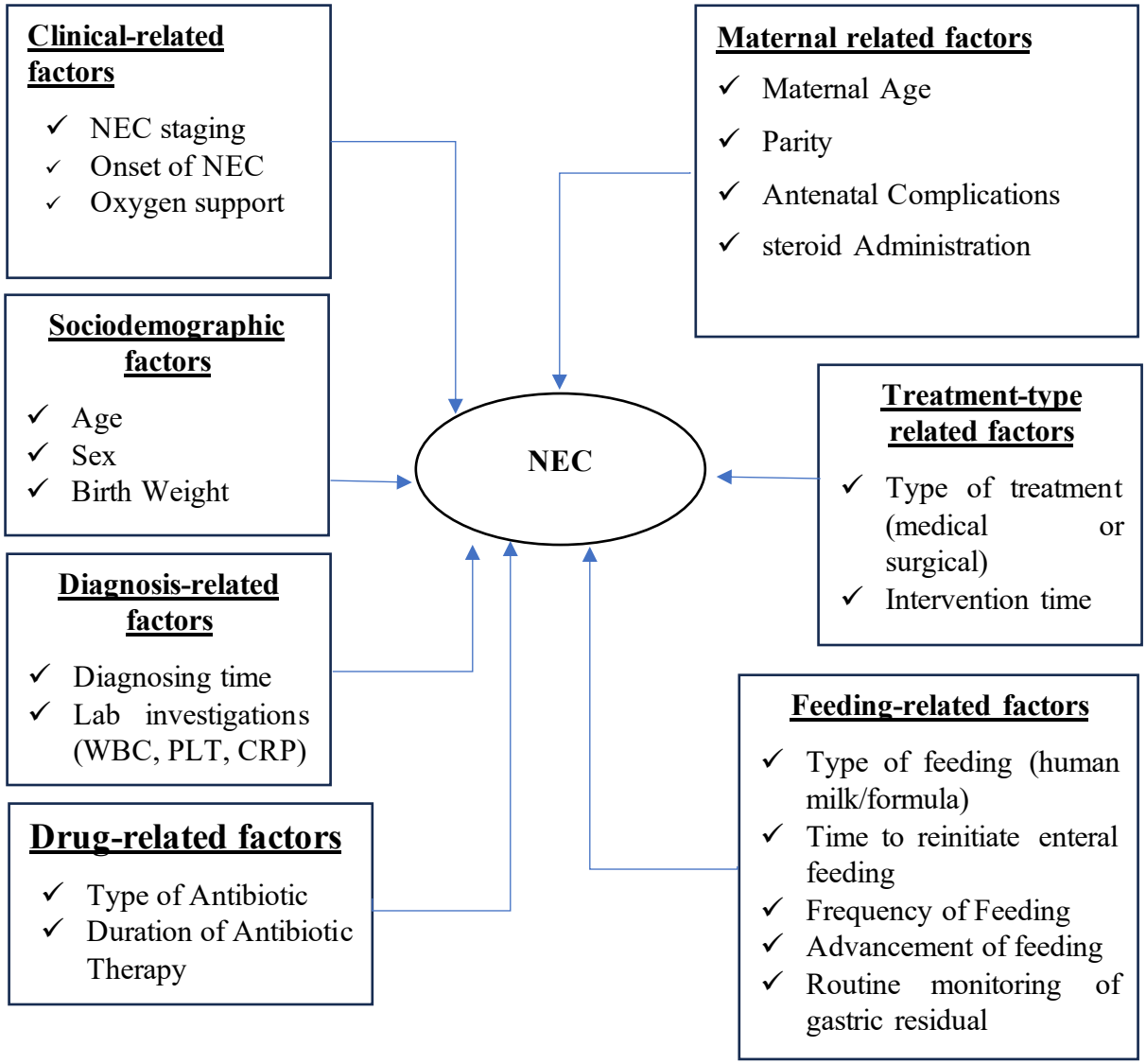

Figure 1: Conceptual framework for NEC.

Chapter 3

OBJECTIVE

3.1 General objective

The main aim of this study was to assess the time to recovery and associated factors among preterm neonates with NEC admitted to the NICU in selected public hospitals in Addis Ababa, Ethiopia, 2024.

3.2 Specific objectives

1. To determine the time to recovery among preterm neonates with a diagnosis of NEC admitted to the NICU in selected public hospitals in Addis Ababa, Ethiopia, in 2024.
2. To identify the factors associated with the time to recovery among preterm neonates with necrotizing enterocolitis admitted to the NICU in selected public hospitals in Addis Ababa, Ethiopia, in 2024.

Chapter 4

METHODS AND MATERIALS

4.1 Study Area and Period

The study was conducted in six randomly selected public hospitals in Addis Ababa, Ethiopia, from February 19 to March 19, 2024. Addis Ababa is the capital city of Ethiopia, with a population was estimated to be around 5,00,6000 people in 2021, This capital city holds 527 km of area in Ethiopia (57).

The city is divided into 11 subcities with 116 woredas at an altitude of 7,546 feet (2,300 meters). Addis Ababa has more than fifty-two hospitals, six of which are owned by the Addis Ababa City Health Bureau, five by the federal government, 3 by NGOs, 3 by the Defense Force and Police, and 35 by private owners.

The study was conducted at Tikur Anbessa Specialized Hospital (TASH), St. Paul Hospital Millennium Medical College (SPHMMC), Zewditu Memorial Hospital (ZMH), Gandhi Memorial Hospital (GMH), Yekatit 12 Hospital Medical College (Y12HMC), and Tirunesh Beijing General Hospital (TBGH), which were selected randomly for the study.

Tikur anbessa specialized hospital is one of tertiary hospital in the country and 800 beds hospital and currently 800 nurses working and approximately 370,000–400,000 patients per year. (TASH human resource office 2021). Zewditu memorial hospital is a teaching and general hospital with 175 beds and 280 nurses. Gandi memorial and Tiruneh Beijing hospital has 450 and 400 clinical and non-clinical staffs respectively. Yekatit 12 hospital is 272 bed hospital with 480 nurses. And St. Peter's specialized hospital is 271 bed hospital and 267 staff nurses (Human resource office documents 2021) (57).

4.2 Study design

An institution-based retrospective cohort study was conducted.

4.3 Source population

All preterm neonates admitted to the NICU in public hospitals in Addis Ababa

4.4 Study population

All preterm neonates who were diagnosed with NEC during admission or during the course of therapy at the six selected public hospitals in Addis Ababa from January 1, 2014, to December 31, 2023, were included.

4.5 Inclusion and exclusion criteria

4.5.1 Inclusion criteria

All medical records of preterm neonates with an NEC diagnosis admitted to the selected hospitals during the defined period.

4.5.2 Exclusion criteria

Preterm neonates with an NEC diagnosis whose medical records had incomplete information about major variables (date of diagnosis or discharge, date of reaching full enteral feeding, and outcome status) or whose medical records were missing at the time of data collection were excluded. Preterm neonate with congenital anomality which affect the gastrointestinal system were also excluded.

4.6 Sample size determination

By using a single proportion formula, the total sample size was estimated as follows:

$$n \frac{(Z_{\alpha/2})^2\, p\,(1-p)}{(d)^2}$$

where n = the required sample size and p = the prevalence of the outcome variable (p=25.4%), as obtained from a cross-sectional study in selected public hospitals in Addis Ababa on the prevalence of necrotizing enterocolitis and associated factors among enteral-fed preterm and low-birth-weight neonates (54). d = margin of error (level of precision), taking 0.05. $Z_{\alpha/2}$ = the corresponding Z score of 95% CI = (1.96)

$$n = \frac{(1.96)^2\,(0.254)\,(1-0.254)}{(0.05)^2} = \mathbf{292}$$

The sample size was also calculated by STATA version 14.0 statistical software. The sample size was computed for each covariable that was significantly associated in the previous study (23,36) by using hazard ratios and the following assumptions: significance level=0.05, power=80%, and allocation ratio=1. Then, the final sample size was determined by comparing the single proportion sampling result with the largest sample size from the predictor factors (see Table 1) (59).

Table 1: Sample size determination for predictors of recovery from NEC among preterm neonates admitted to public hospitals from January 1, 2014, to December 31, 2023, GC.

variables	Hazard ratio	Sample size	Reference
Sex	3.1	17	(23)
NEC staging	0.44	28	(23)
Birth weight	1.65	67	(36)
Gestational age	1.54	88	(36)
Onset of NEC	0.45	29	(36)
Intubation	1.75	54	(36)
CPAP	1.27	**279**	(36)

Finally, after the sample sizes of the single proportion sampling (n=**292**) and covariate CPAP (n=**279**) were compared, the largest sample size **(n=292)** was used for the study.

A correction formula was used since the total population size was **9360 (i.e., n/N ≤ 0.05)**.

$$n = \frac{n_0}{\left(1 + \frac{n_0}{N}\right)}$$

where n is the corrected sample size, n_0 = sample size calculated early (n=292), and N = total number of populations (n=9360) in the study area.

Thus, the sample size determined after using the correction formula was **284**. After adding the 10% no-response rate, the total sample size became **313**.

4.7 Sampling procedures

Six (50%) out of 12 public hospitals were randomly selected by the lottery method for the study to make the sample representative. These hospitals included Tikur Anbessa Specialized Teaching Hospital, St. Paul Millennium Medical College Specialized Teaching Hospital,

Zewditu Memorial Hospital, Gandhi Memorial Hospital, Yekatit 12 Medical College Hospital, and Tirunesh Beijing General Hospital.

A period of ten consecutive years, from January 1, 2014, to December 31, 2023, was included. Starting from the most recent month, backward simple random sampling and the lottery method were used to check the medical records of all preterm neonates with different complications in the selected hospitals until the required sample size (313 preterm neonates with NEC) was obtained. After that, the medical records of preterm neonates who were diagnosed with NEC and who fulfilled the inclusion criteria were isolated and included.

During the ten years, the total number of preterm neonates with NEC admitted to the selected hospitals was nine thousand three hundred sixty (9360).

The total sample size will be proportionally allocated based on N (TASH, N=2,040; SPHMMC, N=1,800; ZMH, N= 1,440; Y12HM, N=1,320; GMH, N=1,680; and TBGH, N=1,080).

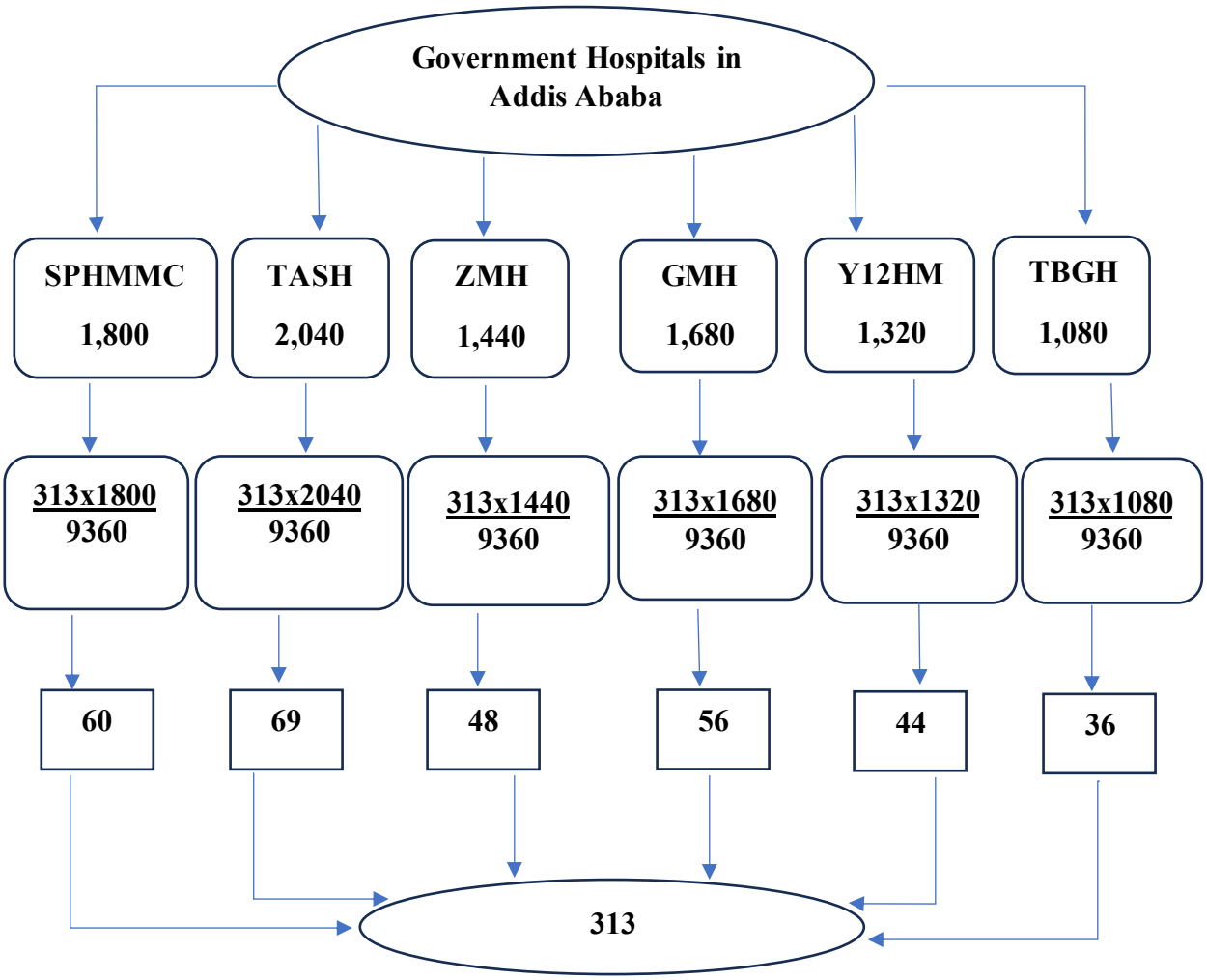

Figure 2: Schematic representation of the sampling procedures used in the study.

4.8 Variables

4.8.1 Dependent variable

Time to recovery from NEC.

4.8.2 Independent variables

Sociodemographic characteristics: Age, sex, and birth weight.

Maternal factors included maternal age, parity, steroid administration, and the presence of antenatal complications such as diabetes mellitus, hypertension, and chorioamnionitis.

Clinical characteristics: Clinical stage, onset of NEC, and oxygen support.

Diagnostic-related factors: Time to diagnose NEC and laboratory investigations, such as the WBC, platelet count, and CRP level.

Treatment-related factors: Type of treatment (medical or surgical) and intervention time.

The feeding-related factors included type of feeding (human milk/formula), time to reinitiate enteral feeding, frequency of feeding, advancement of feeding, and routine monitoring of gastric residue.

Drug-related factors: Type and duration of antibiotic therapy.

4.9 Operational definitions

Censored: refers to preterm neonates with an NEC diagnosis who were lost to follow-up (either died, left against medical advice, or were referred) before their recovery.

Early-onset NEC: onset of NEC in preterm neonates within <14 days of age (36)

Event refers to the recovery of preterm neonates from NEC during the study period.

Full Enteral Feeding (FEF): defined the tolerance of preterm neonates to enteral feeding at 150 mL/kg/day for at least 24 h (13).

Late-onset NEC refers to the onset of NEC in preterm neonates that occurs at ≥14 days of age (36)

Medical NEC: a preterm neonate diagnosed with Bell's stage 1 and Bell's stage 2 NEC (34).

Necrotizing enterocolitis cases: A medical diagnosis of neonatal NEC was given by a physician in the medical records.

Necrotizing enterocolitis: Necrotizing enterocolitis is a condition diagnosed by clinical or radiographic findings and classified according to the modified Bell criteria (10)

Recovered: The time at which full enteral feeding was maintained (13) or recovery was confirmed by the physician and documented as recovery from NEC.

Time to recovery refers to the time of preterm neonates from the time of diagnosis of NEC to the date of recovery.

Surgical NEC: a preterm neonate diagnosed with Bell's stage 3 NEC (34).

4.10 Data collection tool and procedure

4.10.1 Data collection tool

The data abstraction form was adapted from previous studies conducted in Indonesia (23) and different articles (8,10,12,16,21,23,24,26,33–56). Then, an appropriate data extraction format was prepared in English to extract all the relevant variables to meet the study objectives from patient charts. The data were extracted based on the study objectives and consisted of five parts: sociodemographic, maternal, clinical, diagnostic, and treatment-related information.

4.10.2 Data collection procedure

All available information in patient records was checked. The time from the diagnosis of NEC was the starting point for retrospective follow-up, and the endpoints were the date of recovery, the date of loss to follow-up, medical advice or the date of death. All preterm medical records of patients admitted to the six selected hospitals from January 1, 2014, to December 31, 2023, were retrieved from the HMIS registration book. The records of all study participants were selected according to the eligibility criteria.

Two BSc nurses for supervision and six BSc nurses for data collection were recruited. Half a day of training was provided to the data collectors and supervisors regarding the significance of

the study and the methods of the data collection process. The supervisors monitored the quality and completeness of the data collection.

4.11 Data Quality Assurance

To ensure the quality of the data, supervisors and data collectors were trained on how and what information they should collect from the targeted data sources. To check the accuracy and validity of the tool, experts were consulted. Before data collection, a data extraction form was tested on 17 (5%) medical charts at Ras Desta Hospital to ensure that the data abstraction format agreed with the needs of the study. Then, some modifications to the questionnaire were made after the pretest. The completeness of the collected data was checked onsite daily during data collection, and prompt feedback was given by the supervisors and the principal investigator. During data management, storage, cleaning, and review, all the completed data collection forms were checked for completeness and accuracy. The principal investigator examined consistency by selecting cards at random and comparing their similarities.

4.12 Data processing and analysis

The collected data were exported to IBM SPSS version 25, and analysis was performed using STATA version 14.0 statistical software. Before analysis, the data were cleaned and edited. The characteristics of the continuous data are described by the mean and standard deviation. Categorical data were calculated using frequency distributions. To calculate recovery time, days were used as a time scale. The median was computed following a review of the data's distribution. To estimate the probabilities of recovery over time, a life table was constructed. Kaplan-Meier survival curves were generated to estimate and compare the differences in survival probability among different categories of covariates. In the Kaplan-Meier survival curve, one survival function curve located under another indicates that the lower curve group has a lower survival status than the upper curve group or has a less desirable survival probability than the upper curve group. Furthermore, the difference was described statistically by the log-rank test. The log-rank test was used to test the null hypothesis that there is no difference between the categories of covariates in terms of the probability of recovery at any time point, and for a log-rank p value < 0.05, the null hypothesis was rejected.

The Cox proportional hazard regression model was used to analyze the associations between independent and outcome variables. Bivariate analysis was performed for all variables, and p <0.25 was selected for multivariate analysis. Before multivariate analysis, multicollinearity was tested using the VIF command to determine the variable inflation factor. Then, proportional hazard assumptions were checked using the Schoenfeld residual test (global test). Additionally, the fit of the Cox proportional hazard model to the data was checked using Cox-Snell residuals. In multivariate analysis, any statistical test with $p < 0.05$ was considered to indicate statistical significance. Associations were subsequently summarized using an adjusted hazard ratio, and statistical significance was defined at a significance level of 0.05. The results are presented as hazard ratios (HRs), 95% CIs, and $p < 0.05$.

4.12.1 Ethical considerations

Ethical approval was obtained from the research ethics committee (REC) of the School of Nursing and Midwifery of Addis Ababa University. After the approval of the proposal, the letter was obtained from the School of Nursing and Midwifery to the selected hospitals, and then a written permission letter to access the patient's charts was obtained from each institution. All the information collected from patient charts was kept strictly confidential and was not revealed to any person other than the principal investigator.

Chapter 5

RESULTS

5.1 Sociodemographic characteristics of the neonate

The study included records of preterm neonates who were diagnosed with NEC and admitted for ten consecutive years (January 1, 2014, to December 31, 2023). In this study, the medical records of a total of 313 hospitalized preterm neonates with NEC were reviewed. Approximately one hundred sixty-seven (53.35%) were female, 130 (41.35%) were in the 34-36 gestational age group, and 133 (42.49%) were between 1,500 and 2.499 grams (LBW). Among those, 29 (9.27%), 19 (6.07%), and 25 (7.99%) recoveries were observed in each category, respectively. The mean gestational age and birth weight were 32.98 (SD ±1.59) weeks and 1497.5 (SD ±236.96) grams, respectively (see Table 2).

Table 2: Sociodemographic characteristics of the preterm neonate with necrotizing enterocolitis Admitted from Jan 1, 2014, to Dec 31, 2023, at public hospitals in Addis Ababa, Ethiopia.

Variables	Category	Frequency (%)	Status	
			Recovered (%)	Censored (%)
Gestational Age (week)	28-31	70(22.36)	12(3.83)	58(18.53)
	32-33	113(36.10)	21(6.71)	92(29.39)
	34-36	130(41.53)	19 (6.07)	111(35.46)
Total			**52(16.61)**	**261(83.39)**
Sex	Male	146(46.65)	23(7.35)	123(39.3)
	Female	167(53.35)	29(9.27)	138(44.09)
Total			**52(16.6)**	**261(83.39)**
Birth weight (gram)	1,500-2,499	133 (42.49)	25(7.99)	108(34.50)
	1,001-1,499	130(41.53)	24(7.67)	106(33.87)
	≤1000	50(15.97)	3(0.96)	47(15.02)
Total			**52(16.6)**	**261(83.39)**

5.2 Risk factors

Maternal-related factors

Among all comorbidities, hypertension was present in 58 (18.53%) of mothers, followed by chorioamnionitis and DM (51 [16.29%] and 23 [7.35%], respectively. One hundred forty-seven (46.96%) mothers were between the ages of 25 and 29 years, 157 (50.16%) were primipara, 161 (51.44%) did not take steroids, and 163 (52.08%) had no ANC complications. The mean maternal age was 28.90 (SD ±4.28) years. Also, thirty four (10.86%) neonates with no maternal complications were recovered from their illness (see Table 3).

Table 3: Maternal-related factors of preterm neonate with necrotizing enterocolitis Admitted from Jan 1, 2014, to Dec 31, 2023, at public hospitals in Addis Ababa, Ethiopia.

Variables	Category	Frequency (%)	Status	
			Recovered (%)	Censored (%)
Maternal age (year)	18-28	159 (50.80)	23(7.35)	136(43.45)
	29-39	154(49.20)	29(9.27)	125(39.94)
Parity	Primipara	157(50.16)	28(8.95)	129(41.21)
	Multipara	156(49.84)	24(7.67)	132(42.17)
Steroid administration	Yes	152 (48.56)	47(15.02)	105(33.55)
	No	161(51.44)	5(1.60)	156(49.84)
ANC complication*	Yes	150(47.92)	18(5.75)	132(42.17)
	No	163(52.08)	34(10.86)	129(41.21)
Diabetes Mellitus	Yes	23(7.35)	4(1.28)	19(6.07)
	No	290(92.65)	48(15.34)	242(77.32)
Hypertension	Yes	58(18.53)	7(2.24)	51(16.29)
	No	255(81.47)	45(14.38)	210(67.09)
Chorioamnionitis	Yes	51(16.29)	7(2.24)	44(14.06)
	No	262(83.71)	45(14.38)	217(69.33)
PROM	Yes	7(2.24)	3(0.96)	4(1.28)
	No	306(97.76)	49(15.65)	257(82.11)
Anemia	Yes	7(1.96)	1(0.32)	6(1.92)
	No	306(98.06)	51(16.29)	255(81.47)

*ANC complications: include Diabetes Mellitus, Hypertension, Chorioamnionitis, PROM, and Anemia

Clinical-related Factors

The majority of the preterm neonates diagnosed with NEC (246, 78.59%) were suspected cases (stage 1). Two hundred sixty-nine (85.94%) NECs occurred before the age of 14 days. Among the reviewed records of preterm neonates, 287 (91.69%) had an APGAR score ≥ 7 at the 5th minute. All preterm neonates were administered CPAP since all the participants were preterm and all recovered neonates received intranasal oxygen. The neonates who were resuscitated (BMV) and used a mechanical ventilator (MV) as an oxygen source had a low recovery rate from their illness (see Table 4).

Table 4: Clinical-related factors of preterm neonate with necrotizing enterocolitis admitted from Jan 1, 2014, to Dec 31, 2023, at public hospitals in Addis Ababa, Ethiopia.

Clinically Related Factors	Categories	Frequency (%)	Status	
			Recovered (%)	Censored (%)
NEC stage	Stage 1	246(78.59)	38(12.14)	208(66.45)
	Stage 2	52(16.61)	11(3.51)	41(13.10)
	Stage 3	15(4.79)	3(0.96)	12(3.83)
Onset of NEC	≥14	44(14.06)	7(2.24)	37(11.82)
	<14	269(85.94)	45(14.38)	224(71.57)
Asphyxia (5th minute APGAR)	Yes	26(8.31)	4(1.28)	22(7.03)
	No	287(91.69)	48(15.34)	239(76.36)
Intra Nasal Oxygen	Yes	121(38.66)	52(16.61)	69(22.05)
	No	192(61.34)	0(0)	192(61.34)
CPAP	Yes	313(100)	52(16.61)	261(83.39)
BMV	Yes	26(8.31)	4(1.28)	22(7.03)
	No	287(91.69)	48(15.34)	239(76.36)
MV	Yes	27(8.63)	3(0.96)	24(7.67)
	No	286(91.37)	49(15.65)	237(75.72)

Note: Intra Nasal Oxygen, CPAP, BMV, and MV are methods of oxygen administration

Diagnosis-related factors

Analysis of basic laboratory markers revealed that 121 (38.66%) of the study population exhibited leukopenia with WBC counts less than 5,000/mm^3. Furthermore, thrombocytopenia (platelet count less than 150,000/µl) was observed in 142 (45.37%) patients in the study cohort. Almost half of the participants, 154 (49.20%), were positive, and the remaining 159 (50.80%) had a negative CRP test (see Table 5).

Table 5: Diagnosis-related factors of preterm neonate with necrotizing enterocolitis admitted from Jan 1, 2014, to Dec 31, 2023, at public hospitals in Addis Ababa, Ethiopia.

Diagnosis-related factors	Categories	Frequency (%)	Status	
			Recovered (%)	Censored (%)
WBC count	<5,000/mm^3	121(38.66)	24(7.67)	97(30.99)
	5,000-30,000/mm^3	81(25.88)	12(3.83)	69(22.04)
	>30,000/mm^3	111(35.46)	16(5.11)	95(30.35)
CRP	Positive	154(49.20)	24(7.67)	130(41.53)
	Negative	159(50.80)	28(8.95)	131(41.85)
Platelet Count	>350,000/µl	98(31.31)	13(4.15)	85(27.16)
	150,000-350,000/µl	73(23.32)	15(4.79)	58(18.53)
	<150,000/µl	142(45.37)	24(7.67)	118(37.70)

Treatment-related factors

Among all preterm neonates with NEC who were treated in the NICU, 298 (95.21%) were treated by medical management, 13 (4.15%) received primary peritoneal drainage, and 2 (0.64%) received laparotomy. Among the sixty-nine (22.04%) preterm neonates with NEC who began feeding, sixty-six (95.65%) were fed breast milk from their mothers. The mean time of starting feeding was 3.8 days (SD ±1.67), and the majority of the participants (38; 55.07%) were feeding every six-hour interval, with a daily average advancement of 6.8 ml/day (SD ±2.5). The feeding residuals were not routinely monitored among 294 (93.93%) preterm neonates with NEC, 49 (15.65%) of whom recovered among all 52 recovered preterm neonates.

Patients were treated with ampicillin 259 (82.75%), gentamicin 187 (59.74%), cefotaxime 144 (46.01%), meropenem 149 (47.60%) or vancomycin 102 (32.59%). Among all preterm neonates with NEC, the majority of preterm neonates who received ampicillin, gentamicin, or metronidazole recovered from their illness. The mean duration of antibiotic treatment was 14.21 days (SD ±5.97) (see Table 6).

Table 6: Treatment-related factors of preterm neonate with necrotizing enterocolitis admitted from Jan 1, 2014, to Dec 31, 2023, at public hospitals in Addis Ababa, Ethiopia.

Treatment-related factors	Categories	Frequency (%)	Status	
			Recovered (%)	Censored (%)
Management options	Medical	298(95.21)	49(15.65)	249(79.55)
	Surgical	15(4.79)	3(0.96)	12(3.83)
Peritoneal drainage	Yes	13(4.15)	3(0.96)	10(3.19)
	No	300(95.85)	49(15.65)	251(80.19)
Laparotomy	Yes	2(0.64)	0(0)	2(0.64)
	No	311(99.36)	52(16.61)	259(82.75)
Feeding started	Yes	69(22.04)	52(16.61)	17(5.43)
	No	244(77.96)	0(0)	244(77.96)
Feeding start date	<3.8	34 (49.28)	24(34.78)	10(14.49)
	>3.8	35 (50.72)	28(40.58)	7(10.14)
Milk type	Breast Milk	66(95.65)	50(72.46)	16(23.19)
	Formula Milk	3(4.35)	2(2.90)	1(1.45)
Feeding interval	3 hourlies	5(7.25)	3(4.35)	2(2.90)
	4 hourlies	4(5.80)	3(4.35)	1(1.45)
	6 hourlies	38(55.07)	28(40.58)	10(14.49)
	8 hourlies	22(31.88)	18(26.09)	4(5.80)
Advancement (ml/day)	<6.8	34(49.28)	26(37.68)	8(11.59)
	>6.8	35(50.72)	26(37.68)	9(13.04)
Routine Residual checked	Yes	19(6.07)	3(0.96)	16(5.11)
	No	294(93.93)	49(15.65)	245(78.27)
Ampicillin	Yes	259(82.75)	46(14.70)	213(68.05)
	No	54(17.25)	6(1.92)	48(15.34)
Gentamycin	Yes	187(59.74)	40(12.78)	147(46.96)
	No	126(40.26)	12(3.83)	114(36.42)
Metronidazole	Yes	200(63.90)	33(10.54)	167(53.35)
	No	113(36.10)	19(6.07)	94(30.03)
Cefotaxime	Yes	144(46.01)	20(6.39)	124(39.62)
	No	169(53.99)	32(10.22)	137(43.77)
Meropenem	Yes	149(47.60)	15(4.79)	134(42.81)
	No	164(52.40)	37(11.82)	127(40.58)
Vancomycin	Yes	102(32.59)	8(2.56)	94(30.03)
	No	211(67.41)	44(14.06)	167(53.35)
Duration of antibiotics	< 14.21	163 (52.08)	7(2.24)	156(49.84)
	>14.21	150 (47.92)	45(14.38)	105(33.55)

5.3 Survival status and incidence of preterm neonates on time to recovery

A total of 313 preterm neonates were followed for 4157 person-days. The median follow-up time was 13 days, with minimum and maximum follow-up durations of 5 and 25 days, respectively. The median survival time was 21 (IQR: 18–24) days. The cumulative probability of recovery starting at 13 days (97.65%) was 95% CI: 0.94-0.99. The overall incidence of recovery time was 12.5 (95% CI: 0.01-0.02) per 1000 person-days. Among the 313 preterm neonates with NEC, 52 (16.61%) recovered, and 261 (83.39%) were censored (Died, left against medical advice (LAMA), and referred) (Figure 3).

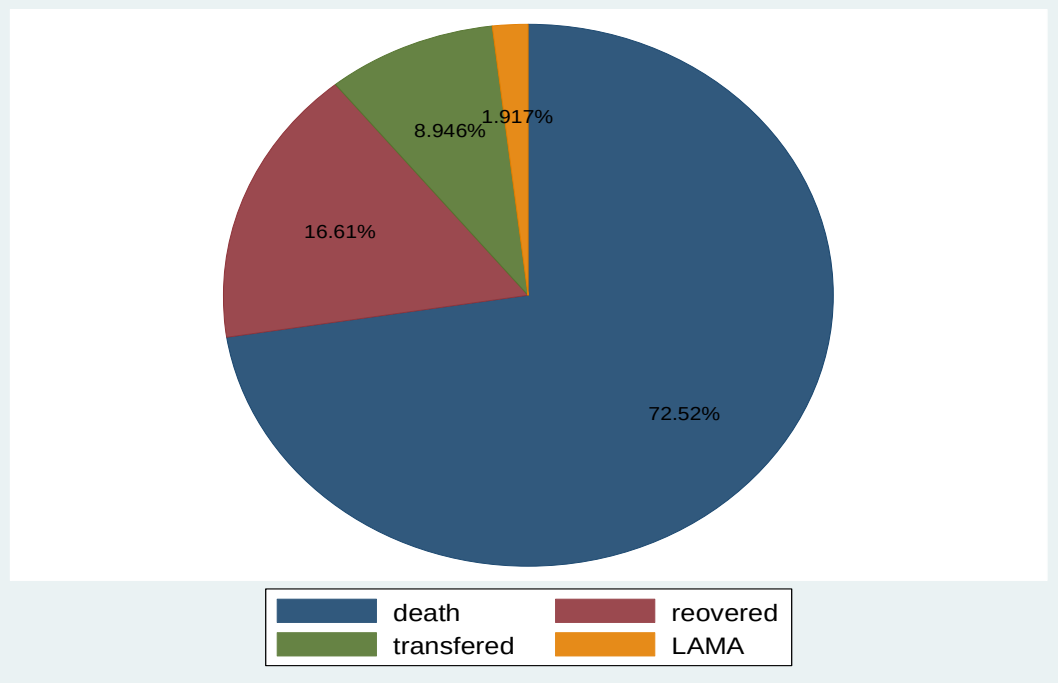

Figure 3: Overall outcomes of preterm neonates with necrotizing enterocolitis admitted from January 1, 2014, to December 31, 2020, at public hospitals in Addis Ababa.

Using the Life Table estimator of cumulative survival function, 97% (95% CI: 0.93– 0.98) of neonatal recovery occurred within a 10-15 day period of follow-up (see Table 7).

Table 7: Overall Lifetime table

Interval		Beg. Total	Deaths	Lost	Survival	Std. Error	[95% Conf. Int.]
5	10	313	0	91	1.00	0.00	. .
10	15	222	6	84	0.97	0.01	0.93 - 0.98
15	20	132	30	72	0.66	0.05	0.56 - 0.75
20	25	30	15	13	0.24	0.07	0.12 - 0.38
25	30	2	1	1	0.08	0.09	0.002 - 0.37

5.4 Comparisons of survival functions according to different categorical variables

The overall median time to recovery from necrotizing enterocolitis was 21 days (IQR: 18-24, SD ± 0.79, 95% CI: 20-24). The birth weight of low-birth-weight neonates had a median recovery period of 20 days, while very low- and extremely low-birth-weight neonates had recovery times of 21 and 25 days, respectively. On the other hand, the median time to recovery did not vary between the sexes. In terms of ANC complications, neonates born to mothers with complications had a median recovery time of 21 days. However, neonates born to mothers without complications had a median recovery time of 20 days (IQR 17-24). Preterm neonates born to mothers with PROM had a median recovery time of 20 days, compared to 21 days for those born to mothers without PROM. There was a difference in the median recovery time among patients with platelet counts <150,000/µl, ≥150,000–350,000/µl, and >350,000/µl at admission (22,19 and 24 days, respectively). Preterm neonates whose onset of NEC was >14 days had a prolonged median recovery time of 22 days (IQR: 19-24) compared to that of the other group (20 days) (IQR: 18-25). Similarly, the median recovery times for medically treated preterm neonates were 20 days (IQR: 18-25) and 24 days (IQR: 19-24) for surgically treated patients. Additionally, the median time to recover from NEC patients who consumed formula milk was 20 days (IQR: 20-24), whereas for those who consumed breast milk, it was 17 days (IQR: 16-20) (see Appendix C).

The log-rank test showed a statistically significant difference in the probability of recovery of preterm neonates with NEC among covariates of intranasal oxygen administration, steroid administration, meropenem, vancomycin, and duration of antibiotics. This difference was statistically significant, with a p-value < 0.05 (see Table 8).

Table 8: Median survival time and log-rank test for NEC recovery among different covariates in selected governmental hospitals of Addis Ababa, Ethiopia from January 1, 2014, to December 31, 2023. (N=313)

Variables	**Category**	**Median recovery time (IQR)**	**Log-rank x^2 value**	**p value**
Steroid	Yes	20(17-23)	20.06	< . 001***
	No	-		
Intra nasal oxygen	Yes	19(17-21)	49.26	< .001***
	No	-		
Meropenem	Yes	25(19-25)	8.42	.004**
	No	20(17-23)		
Vancomycin	Yes	24	3.87	.049*
	No	20(17-24)		
Duration of antibiotics	< 14.21	-	18.63	< .001***
	>14.21	20(17-21)		

Note: *** = p value < 0.001, ** = p value < 0.01, * = p value < 0.05

The overall Kaplan–Meier estimates revealed that the probability of survival of preterm neonates admitted with NEC was high on the first day of admission and decreased as the follow-up time increased (Figure 4). In this study, the overall median survival time of admitted preterm neonates with NEC was 21 (IQR: 18–24) days. The highest (97.65%) survival probability occurred within the thirteen-day follow-up period. Moreover, the cumulative survival probabilities at 15, 20, and 25 days were 91.62%, 47.64%, and 6.59%, respectively.

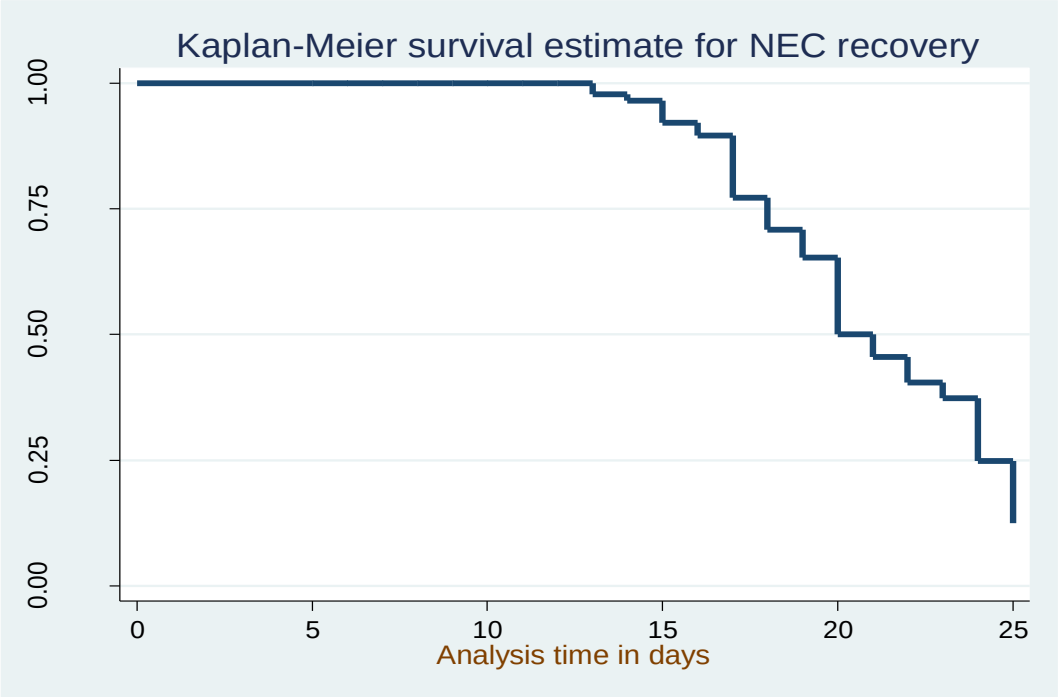

Figure 4: Overall Kaplan–Meier survival estimate of recovery time among preterm neonates with NEC admitted to governmental hospitals, 2014–2023, Addis Ababa, Ethiopia.

Based on Kaplan–Meier survival estimates, preterm neonates with NEC treated with intranasal oxygen, meropenem, or vancomycin; born to mothers who took steroids; and born to neonates on antibiotics for a period extending 14 days had a low chance of survival compared to their counterparts who had a median recovery of 19, 25, 24, 20 or 20 days, respectively (Figures 5–8).

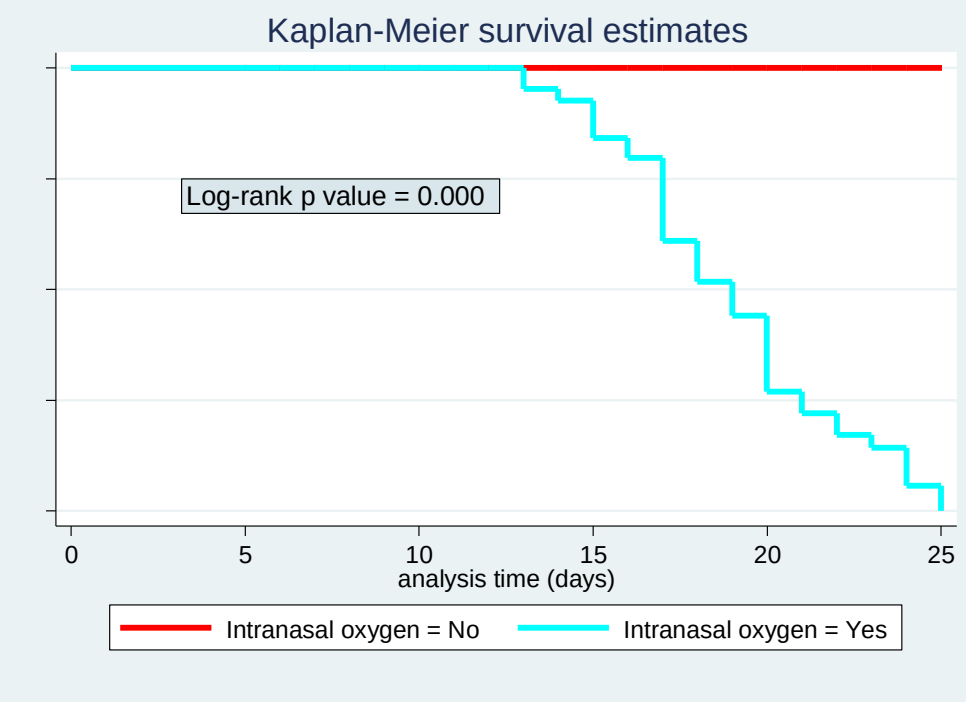

Figure 5: Kaplan–Meier survival curves and log-rank tests for time to recovery and intranasal oxygen for preterm neonates with NEC admitted to the NICU.

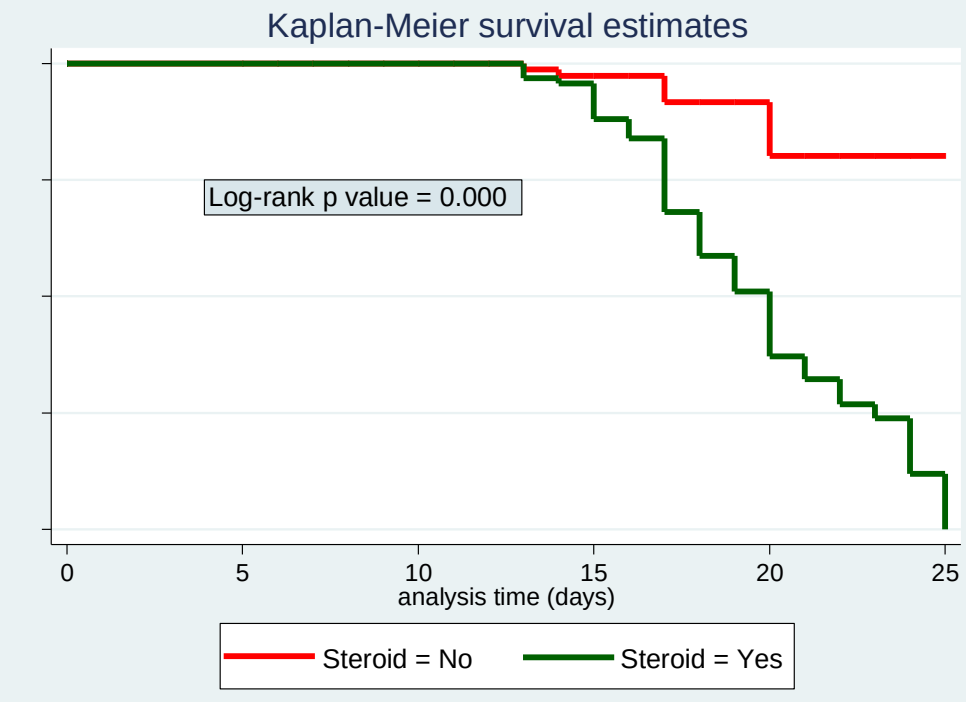

Figure 6: Kaplan–Meier survival curves and log-rank tests for time to recovery and steroid administration for preterm neonates with NEC admitted to the NICU.

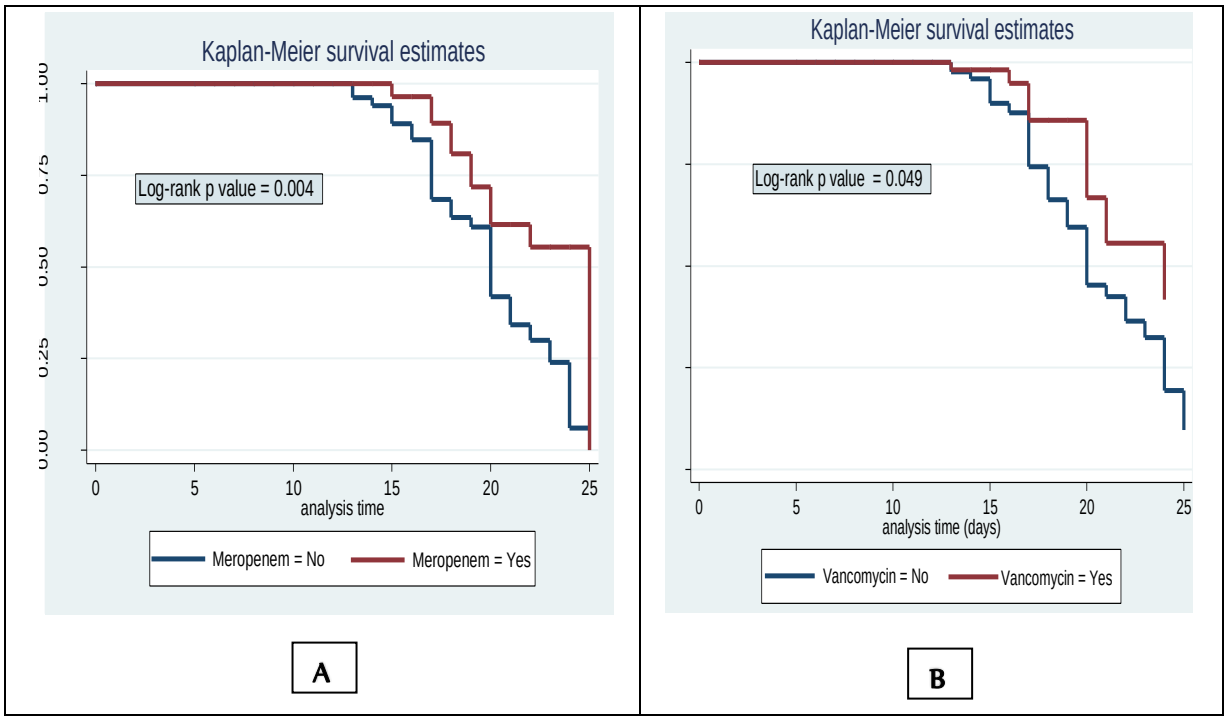

Figure 7: Kaplan–Meier survival curves and log-rank tests for time to recovery and meropenem (A) and vancomycin (B) for preterm neonates with NEC admitted to the NICU.

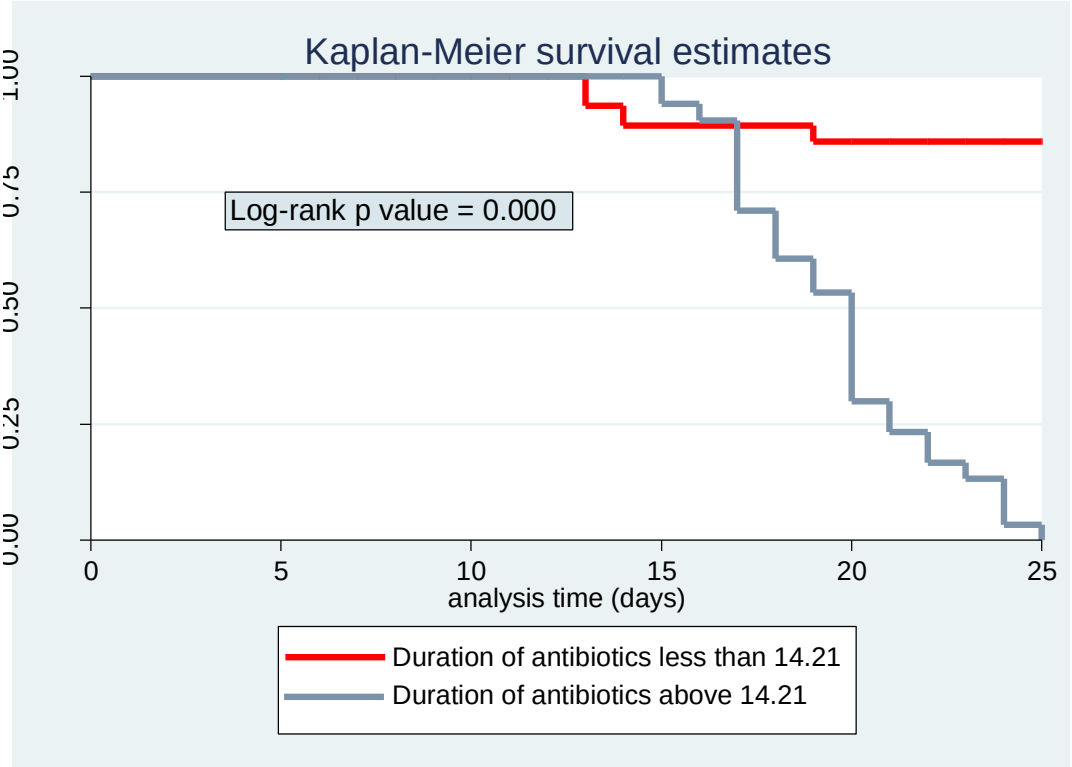

Figure 8: Kaplan–Meier survival curves and log-rank tests for time to recovery and duration of antibiotic treatment for preterm neonates with NEC admitted to the NICU.

5.5 Proportional hazard assumption test

The proportional hazard assumption test by the Schoenfeld residual revealed that the p value of the rho statistic for all covariates was above 0.05, and the global test p value was 0.87. This means that the Cox proportional hazard assumption is satisfied since the p value is greater than 0.05 (see Table 9).

Table 9: The global goodness of fit test of the Cox proportional hazard assumption

Predictors	**Rho**	**chi2**	**Df**	**Prob>chi2**
Birth weight	0.24	3.16	1	0.08
ANC complication	-0.07	0.33	1	0.56
Hypertension	-0.007	0.00	1	0.96
PROM	0.09	0.00	1	0.95
Anemia	0.03	0.05	1	0.82
Steroid administration	0.12	1.09	1	0.29
NEC stage	0.19	2.51	1	0.11
WBC Count	-0.13	1.06	1	0.30
Gentamycin	-0.09	0.7	1	0.40
Cefotaxime	-0.08	0.43	1	0.51
Meropenem	-0.18	1.89	1	0.17
Vancomycin	0.13	0.86	1	0.35
Feeding interval	0.19	2.42	1	0.12
Duration of antibiotics	0.22	1.85	1	0.17
Global test		12.24	19	0.87

5.6 The goodness of fit of the Cox regression model

The goodness of fit of the Cox regression model was assessed using a Cox-Snell residual plot. Analysis of the plot revealed that the residuals aligned closely with the reference line (within a 45-degree alignment), indicating a strong fit between the model and the data **(**see Figure 8**).**

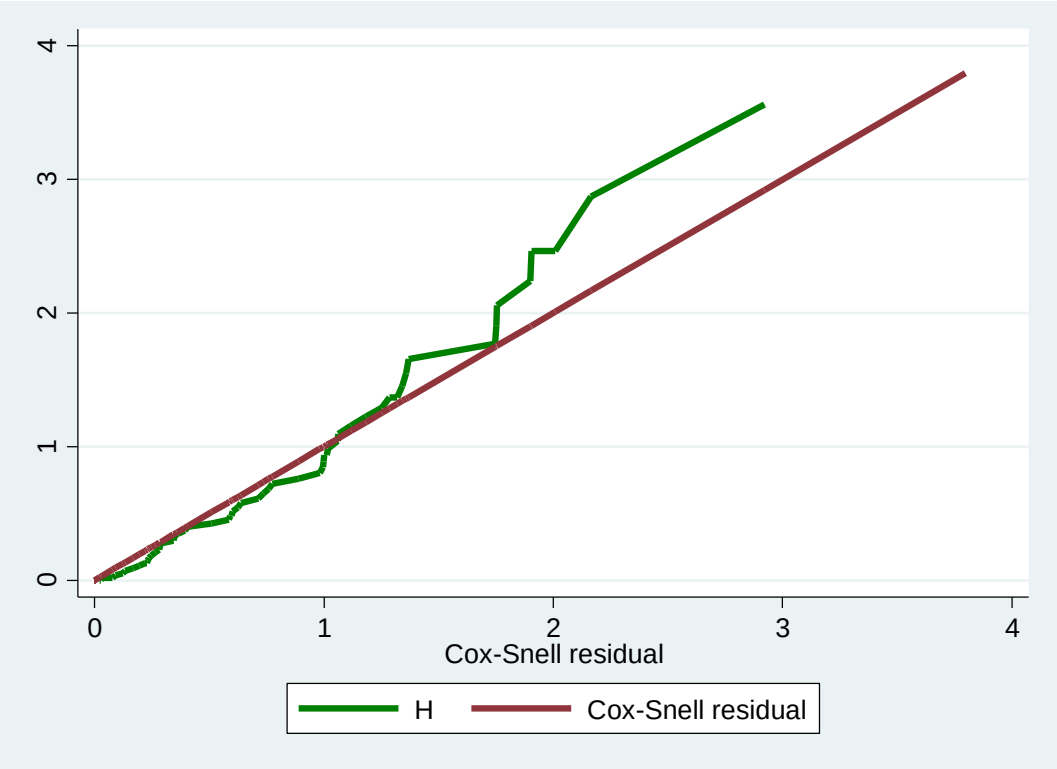

Figure 9: Cox-Snell residual plot to test the goodness of fit of the Cox regression model.

5.7 Determinants of Time to Recovery from Necrotizing Enterocolitis

The Cox proportional hazard regression model was used to determine the predictors of time to recovery from NEC. According to the bivariable Cox regression analysis, determinants such as the birth weight of the neonate, steroid administration, stage of NEC, WBC count, feeding interval, ANC complications (hypertension, PROM, and anemia), antibiotics (gentamycin, cefotaxime, meropenem, and vancomycin) and duration of antibiotics were associated with time to recovery, with p values less than 0.25. Before multivariate analysis, multicollinearity was tested using the variable inflation factor (VIF). The mean variance inflation factor (VIF) was 1.29, which indicates that there is no multicollinearity since multicollinearity was considered for a mean VIF > 5 (see Appendix D).

After multivariate Cox regression analysis, the variables birth weight of the neonate, steroid administration, PROM, and duration of antibiotics were found to be significant determinants of the time to recovery from NEC, with p values less than 0.05 and 95% CIs.

From socio-demographic factors, birth weight was significantly associated with time to recovery from NEC. Being an extremely low birth weight neonate will decrease the risk of recovery from NEC by a factor of 0.134 compared to the low-birth-weight preterm neonate (AHR; 0.134, 95% CI: 0.027-0.66). The study also looked at different maternal-related factors. The hazard of recovery time from NEC was 5-fold increased among preterm neonates born from PROM mothers than the reverse group (AHR; 5.21, 95% CI: 1.12-24.34). Again, the p-value for maternal steroid administration is 0.003, indicating a significant relationship between steroid administration and risk of recovery. Moreover, the duration of antibiotics was significantly associated with the time to recovery from NEC. The risk of recovery was 97.7% lower for preterm neonates who took antibiotics for more than 14 days than for those who took them for less than 14 days (AHR; 0.023, 95% CI: 0.005-0.1) (see Table 11 and Appendix E).

Table 10: Multivariable Cox Proportional Regression Analysis of determinant factors for time to recovery from necrotizing enterocolitis among preterm neonates Admitted at Addis Ababa Public Hospitals, Addis Ababa, Ethiopia from 2014 to 2023.

Variables	Category	Recovery status		CHR (95%CI)	AHR (95%CI)	p value
		Recovered (n %)	Censored (n %)			
Birth weight	LBW	25(7.99%)	108(34.50%)	1	1	-
	VLBW	24(7.67%)	106(33.87%)	0.64(0.36-1.13	0.47(0.22-1.009)	.053
	ELBW	3(0.96%)	47(15.02%)	0.17(0.053-0.58)	**0.134(0.027-0.66)**	**.014***
PROM	Yes	3(0.96%)	4(1.28%)	2.55(0.79-8.26)	**5.21(1.12-24.34)**	**.036***
	No	49(15.65%)	257(82.11%)	1	1	-
Steroid administration	Yes	47(15.02%)	105(33.55%)	1		-
	No	5(1.60%)	156(49.84%)	0.09(0.035-0.227)	**0.14(0.038-0.51)**	**.003****
Duration of antibiotics	< 14.21	7(2.24%)	156(49.84%)	1	1	-
	> 14.21	45(14.38%)	105(33.55%)	0.54(0.24-1.23)	**0.023(0.005-0.1)**	**< .001*****

a) *** = p value < 0.001, ** = p value < 0.01, * = p value < 0.05

b) 1=considered as reference category

c) CHR = Crude hazard ratio. AHR = Adjusted hazard ratio, CI = confidence interval

Chapter 6

DISCUSSION

This study aimed to determine the time to recovery from necrotizing enterocolitis and identify its associated factors among preterm neonates admitted to study hospitals within the study period. The birth weight of the neonate, steroid administration, PROM, and duration of antibiotics were found to be significant determinants of the time to recovery from NEC. The overall incidence of recovery in the study was 12.5 per 1000 person-days of risk time, and 16.6% of patients recovered. This finding is lower than those of other studies in Poland (79%), India (87.27%), Pakistan (72.4%), Italy (55.5%), and Indonesia (44.2%), which reported higher rates of survival (21,23,24,33,45). However, this percentage was slightly greater than that in a study conducted in Bahir Dar, Ethiopia, where the survival rate was reported to be 15% (26).

The overall median recovery time from NEC was 21 days (IQR: 18–24). This finding is in line with studies conducted in the Netherlands, where the median time to recovery after NEC was 20 (IQR: 16-30) days (55), This may be due to similarity in Participant characteristics. In contrast, this finding showed a longer recovery time than that of a previous study performed in Colombia, which revealed that mild patients recovered in 3 days, moderate patients recovered in 4 days, and severe patients recovered in 9 days (12). Based on another study in Italy, clinical cures were achieved at a mean time of 17.2 ± 8.2 days (33). Additionally, this study showed a shorter recovery time than did the prospective study conducted among 639 preterm neonates in Indonesia because infants born at <32 weeks gestational age had a median survival of 27 days, whereas those born after ≥32 weeks had a median survival of 31 days (36). The difference may be attributed to variations in participant classifications, central tendency measures, study design, and sample size. Disparities in treatment and care practices, treatment protocols, and socioeconomic status can all be considered potential causes of the variation in the recovery rate and duration of NEC. Recent advancements in diagnostic techniques, therapeutic alternatives, and technology likely play a significant role in improving recovery outcomes. These advancements include early detection approaches, improved treatment protocols involving antibiotics, probiotics, and surgical treatments, tailored care plans, improved nutritional assistance, and minimally invasive surgical methods. The identified variations are also influenced by patient characteristics, disease severity, treatment procedures, healthcare

infrastructure, study timing, and environmental factors. Methodological variations in study design and data collection methods, as well as differences in healthcare practices and cultural beliefs, further contribute to discrepancies in findings.

The findings of this study revealed that as birth weight decreases, the time to recover from NEC is delayed. This finding is in agreement with previous studies (23,35,36,39), which concluded that a decrease in gestational age is linked to prolonged recovery time and poor outcomes. Compared with other neonates, ELBW neonates recover from NEC more slowly due to several factors, including their immature immune system's difficulty in battling infection and inflammation, their limited supply of vital nutrients for tissue repair, their impaired intestinal function impeding healing, their increased risk of complications such as sepsis and stricture, and their overall fragile physiological state (23). Due to these vulnerabilities, ELBW babies have a longer recovery time than babies with higher birth weights and are more vulnerable to the consequences of NEC.

Preterm neonates born from mothers with PROM took less time to recover compared to their counterparts. This can be attributed to several clinical reasons, including close prenatal monitoring, potential treatments for the mother to lower the risk of infection, less exposure to intrauterine infections (60), timely birth leading to decreased exposure to intrauterine infections, and more likely to give birth in facilities equipped with specialized neonatal care. These factors can contribute to early identification, timely intervention, and improved NEC care, which will eventually help these neonate's outcomes.

This result also showed that not taking steroids was associated with a longer recovery time than taking steroids. In a retrospective cohort study of critically ill newborns, exposure to prenatal steroids at GA 22 6/7 weeks or less was associated with increased survival rates and illness-free survival (61). This suggests that early administration of prenatal steroids to pregnant mothers with suspected disease may improve the health of the newborn.

With respect to antibiotic treatment, individuals who received 14 or more days of antibiotic treatment had a 97.7% longer recovery period. Similarly, in a study in the United States, infants with both medical and surgical NEC who received longer courses of antibiotics took more time to recover (35). However, in another study, there was no difference based on antibiotic duration (12).

6.1 Strengths and Limitations of the Study

6.1.1 Strengths of the Study

Based on the researcher knowledge, this study is the first in Ethiopia to examine the time to recovery and its associated factors among preterm neonates with NEC. The strengths of this study are based on its study design, the use of multiple healthcare settings, and the use of an adequate sample size, which increases the generalizability of the findings. Additionally, this study provides insight for researchers, especially for prospective follow-up studies.

6.1.2 Limitations of the Study

Despite the above possible strengths, the retrospective nature of the study poses certain limitations. Relying on retrospective data may hinder the exploration of additional factors, particularly parental sociodemographic, socioeconomic, and environmental characteristics, which could be potential predictors influencing recovery time from NEC.

Chapter 7

CONCLUSION AND RECOMMENDATION

7.1 Conclusion

The incidence rate of recovery for preterm neonates with NEC was low, and the median recovery time was high in the study area, with birth weight, maternal steroid administration, PROM, and duration of antibiotics being significant determinants of recovery time. This research provides guidance for the optimal timing of interventions to improve outcomes for preterm neonates with NEC. However, the retrospective nature of the data limits the exploration of additional factors that could affect the recovery time. Therefore, further prospective studies are recommended, and measures that increase the recovery rate and hasten the recovery time should be strengthened.

7.2 Recommendations

To health providers

Preterm neonates, especially extremely low birth weight neonates and those born to mothers with PROM who do not receive steroids require special attention and tailored treatment plans to improve outcomes. Healthcare professionals should carefully monitor the duration of antibiotic treatment for preterm neonates with NEC. Specialized care, close monitoring, and individualized treatments are crucial for supporting recovery and improving outcomes in this vulnerable population. Additionally, early administration of prenatal steroids to mothers has positive effects on the health of the newborn.

To future researchers

Further research is needed to address the limitations of the current study on recovery time from NEC and improve the completeness of the data. Prospective studies with larger sample sizes and longer follow-up periods are recommended. These studies should also incorporate important predictors of recovery, such as parental sociodemographic, socioeconomic, and environmental characteristics. Additionally, further research is needed to determine the optimal duration of antibiotic therapy for preterm neonates with NEC to improve outcomes and reduce the time to achieve full feeding.

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APPENDIX

Appendix A: Information Sheet

Greetings:

My name is _____, I am a data collector for the research entitled "Time to recovery and associated factors among preterm neonates with necrotizing enterocolitis admitted to the NICU in selected public hospitals, Addis Ababa, Ethiopia", which was carried out by Juhar Seid, an MSc student of neonatal nursing at Adis Ababa University, College of Health Sciences, School of Nursing and Midwifery.

Title: Time to recovery and associated factors among preterm neonates with necrotizing enterocolitis admitted to the NICU in selected public hospitals, Addis Ababa, Ethiopia, 2024.

Principal investigator: Juhar Seid Hamza

Name of the organization: Addis Ababa University, College of Health Sciences, School of Nursing and Midwifery.

Purpose of the Research Project: The main aim of this research was to determine the time to recovery from necrotizing enterocolitis and its associated factors among preterm neonates who were admitted to the neonatal intensive unit in public hospitals in Addis Ababa, Ethiopia.

Procedure: To achieve the above objective, information necessary for the study was collected from the HMIS registration book of neonates.

Risk and/or discomfort: Since the study was conducted by taking appropriate information from medical records, there was no harm to the patient. The name or any other identifying information was not recorded on the questionnaire, and all the information taken from the chart was kept strictly confidential and in a safe place. The information retrieved was only used for study purposes.

Benefits: This research had no direct benefit for those whose document/record was included in this research. However, the indirect benefit of the research for the participants and other clients in the program is clear. This is because if program planners were preparing a predicted plan, there would be a benefit for clients in the program of receiving appropriate care and treatment

services. Overall, this research has had a paramount direct benefit for healthcare planners and managers, especially for those involved in planning and managing neonatal health problems**.**

Person to contact: This research paper was reviewed and approved **by the School of Nursing and Midwifery, Addis Ababa University IRB Committee**, and permission was obtained from the Neonatal Nursing Department of all selected hospitals. If you have any queries regarding the research paper, you can contact the research committee through the principal investigator's address below.

Juhar Seid**:** Addis Ababa University, College of Health Science, School of Nursing and Midwifery, Department of Neonatal Nursing: Principal Investigator

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Appendix B: Data extraction form

This tool is prepared for data collection from the medical records of neonates who were admitted to the NICU in selected public hospitals in Addis Ababa. The checklist has five sections to collect all important information for this study. All this information will be retrieved from individual patient cards without mentioning the names of the clients.

Data collection date----------month----------Year----------

Name of the Hospital ----------

Name of data collector---------- signature----------

Name of supervisor----------signature----------

Code no.----------

Part-I Sociodemographic characteristics of the neonates

S. n	Variables	Categories/response	Answer code	Skip
1.1	Gestational age of the neonate	---------- weeks		
1.2	Sex	1. Male 2. Female		
1.3	Birth weight	---------- gram		

Part II Maternal-related factors

S. n	Variables	Response	Answer code	Skip
2.1	Age of the mother	---------- years.		
2.2	Parity	1. Primipara 2. Multipara 3. Grand multiparous		
2.3	Steroid administration	1. Yes 2. No		
2.4	Any ANC complication	1. yes 2. No		
2.5	If yes, specify it	1. Diabetes 2. Hypertension 3. Chorioamnionitis 4. Other----------		

Part III- Clinical-related factors

S. n	Questions	Variable/response	Answer code	Skip
3.1	What was the Bell stage of NEC?	1. stage I 2. stage II 3. stage III		
3.2	Onset of NEC	1. < 14 days 2. ≥ 14 days		
3.3	Asphyxia (5th minutes APGAR score)	1. Yes (<7) 2. No (≥7)		
3.4	Was the baby supported by oxygen?	1. Yes 2. No		
3.5	If yes, what type of oxygen-delivering system was used?	1. INO_2 2. BMV 3. CPAP 4. MV		

IV. Diagnosis-related factors

S. n	Question	Variable/response	Answer code	Skip
4.1	Time of diagnosis	----------		
4.2	WBC count on the day of diagnosis	1. < 5,000/mm^3 2. 5,000-30,000/mm^3 3. > 30,000/mm^3		
4.3	CRP on the day of diagnosis	1. Positive 2. Negative		
4.4	Platelet count on the day of diagnosis	1. >350,000/µl 2. ≥150,000–350,000/µl 3. <150,000/µl		

Part VI- Treatment-related factors

S. n	Question	Variable/response	Answer code	Skip
5.1	What management option was given for neonates?	1. Medical 2. Surgical		
5.2	If surgery was done what type of surgery was done?	1. Laparotomy 2. peritoneal drainage 3. Other----------		
5.3	Does the neonate start feeding?	1. yes 2. No		
5.4	If yes, when does the newborn initiate/reinitiate feeding after NEC?	_____Hour/day		

5.5	What type of feeding was given?	1. Breast milk 2. Formula milk 3. Mixed		
5.6	What is the time interval for enteral feeding?	---------- Hourly		
5.7	How much daily feeding advancement?	_____ml/kg/day		
5.8	Was gastric residual being checked before feeding routinely?	1. Yes 2. No		
5.9	Does the neonate reach full enteral feeding?	1. Yes 2. No		
5.10	If yes, when the neonates reach full enteral feeding	_____days		
5.11	Which antibiotic was given?	----------		
5.12	How long the antibiotics was given?	_____days		
5.13	Survival status of the newborn after NEC	1. Recovered 2. Died 3. Referred 4. LAMA		
5.14	Time of outcome occurrence	---------- days		

Appendix C: Median survival time and log-rank test for NEC recovery among different covariates.

Variables	Category	Median recovery time (IQR)	Log-rank x^2 value	p value
Gestational age	Late Preterm	20	0.32	0.85
	Moderate preterm	22(17-25)		
	Very preterm	21(17-24)		
Sex	Male	20(18-23)	0.14	0.70
	Female	20(18-25)		
Birth weight	LBW	20	4.65	0.09
	VLBW	21(18-24)		
	ELBW	25(19-25)		
Maternal age	18-28	20(19-20)	1.61	0.66
	29-39	20(18-25)		
Parity	Primipara	20(18-24)	0.13	0.72
	Multipara	22(18-24)		
ANC complication	Yes	21	0.02	0.89
	No	20(17-24)		
DM	Yes	18	1.58	0.20
	No	21(18-25)		
Hypertension	Yes	20	0.07	0.79
	No	21(18-24)		
Chorioamnionitis	Yes	24	0.00	0.95
	No	20(18-25)		
PROM	Yes	20	1.41	0.24
	No	21(18-25)		
Anemia	Yes	15	1.51	0.22
	No	21(18-24)		
Steroid administration	Yes	20(17-23)	20.06	0. 000***
	No	-		
Stage of NEC	Stage 1	21(18-25)	1.19	0.55
	Stage 2	20		
	Stage 3	24(19-24)		
Onset of NEC	< 14 days	20(18-25)	0.00	0.98
	≥14 days	22(19-24)		
Asphyxia	Yes	-	0.10	0.75
	No	21(18-24)		
Intra nasal oxygen	Yes	19(17-21)	49.26	0.000***
	No	-		
BMV	Yes	-	0.10	0.75
	No	21(18-24)		
MV	Yes	24	1.71	0.19
	No	20(18-24)		

WBC count	< 5,000/mm^3	20(18-24)	0.72	0.69
	5– 30,000 mm^3	23		
	> 30,000/µl	20(18-24)		
CRP	Positive	20(19-24)	0.00	0.96
	Negative	21(18-25)		
Platelet	>350,000/µl	24	2.40	0.30
	≥150,000–350,000/µl	19(18-21)		
	<150,000/µl	22(19-25)		
Management	Medical	20(18-25)	0.04	0.84
	Surgical	24(19-24)		
Feeding start date	<3.8	18(16-20)	0.33	0.57
	>3.8	17(16-20)		
Type of feeding	Breast milk	17(16-20)	1.27	0.26
	Formula milk	20(20-24)		
Feeding interval	3 hourlies	19(14-21)	0.24	0.97
	4 hourlies	17(17-24)		
	6 hourlies	17(16-20)		
	8 hourlies	18(17-20)		
Advancement	< 6.8	17(16-20)	1.16	0.28
	>6.8	18(16-21)		
Residual	Yes	24(17-24)	0.07	0.79
	No	20(18-25)		
Ampicillin	Yes	21(18-25)	0.02	0.88
	No	20(19-24)		
Gentamycin	Yes	20(17-24)	1.44	0.23
	No	20(19-25)		
Metronidazole	Yes	20(18-25)	0.03	0.87
	No	22		
Cefotaxime	Yes	22(19-25)	3.13	0.08
	No	20(17-24)		
Meropenem	Yes	25(19-25)	8.42	0.004**
	No	20(17-23)		
Vancomycin	Yes	24	3.87	0.049*
	No	20(17-24)		
Duration of antibiotics	< 14.21	-	18.63	0.000***
	>14.21	20(17-21)		

Note: *** = p value < 0.001, ** = p value < 0.01, * = p value < 0.05

Appendix D: Multicollinearity test

Variable	VIF	1/VIF
Steroid administration	1.44	0.694228
Feeding interval	1.38	0.724510
Hypertension	1.36	0.732797
Meropenem	1.35	0.742687
Vancomycin	1.34	0.747955
Stage of NEC	1.32	0.758798
Duration of antibiotics	1.31	0.765736
ANC complication	1.29	0.775504
WBC count	1.26	0.794817
PROM	1.24	0.809542
Cefotaxime	1.21	0.827527
Gentamycin	1.14	0.878617
Anemia	1.12	0.893805
Mean VIF	**1.29**	

Appendix E: Multivariable Cox Proportional Regression Analysis

Variables	Category	Recovery status		CHR (95%CI)	AHR (95%CI)	p value
		Recovered (n (%))	Censored (n (%))			
Birth weight	LBW	25(7.99)	108(34.50)	1	1	-
	VLBW	24(7.67)	106(33.87)	0.64(0.36-1.13	0.47(0.22-1.009)	0.053
	ELBW	3(0.96)	47(15.02)	0.17(0.053-0.58)	**0.134(0.027-0.66)**	**0.014***
ANC complication	Yes	18(5.75)	132(42.17)	1	1	-
	No	34(10.86)	129(41.21)	1.86(1.05-3.29)	1.32(0.59-2.9)	0.495
Hypertension	Yes	7(2.24)	51(16.29)	1	1	-
	No	45(14.38)	210(67.09)	1.74(0.78-3.87)	1.01(0.33-3.06)	0.983
PROM	Yes	3(0.96)	4(1.28)	2.55(0.79-8.26)	**5.21(1.12-24.34)**	**0.036***
	No	49(15.65)	257(82.11)	1	1	-
Anemia	Yes	1(0.32)	6(1.92)	1	1	-
	No	51(16.29)	255(81.47)	0.14(0.018-1.09)	0.145(0.015 1.43)	0.098
Steroid administration	Yes	47(15.02)	105(33.55)	1		-
	No	5(1.60)	156(49.84)	0.09(0.035-0.227)	**0.14(0.038-0.51)**	**0.003****
NEC stage	Stage 1	38(12.14)	208(66.45)	0.46(0.14-1.5)	0.66(0.13-3.34)	0.622
	Stage 2	11(3.51)	41(13.10)	0.65(0.18-2.33)	0.94(0.18-4.9)	0.942
	Stage 3	3(0.96)	12(3.83)	1	1	-
WBC Count	< 5,000/mm^3	24(7.67)	97(30.99)	1	1	-
	5–30,000/mm^3	12(3.83)	69(22.04)	0.64(0.32-1.28)	1.323618(0.58-3.00)	0.503
	> 30,000/mm^3	16(5.11)	95(30.35)	0.59(0.31-1.11)	0.5994589(0.28-1.25)	0.174
Gentamycin	Yes	40(12.78)	147(46.96)	1.63(0.86-3.12)	0.89(0.37-2.18)	0.815
	No	12(3.83)	114(36.42)	1	1	-
Cefotaxime	Yes	20(6.39)	124(39.62)	0.71(0.4-1.25)	0.7(0.33-1.52)	0.380
	No	32(10.22)	137(43.77	1	1	-

			)			
Meropenem	Yes	15(4.79)	134(42.81)	0.67(0.37-1.23)	1.32(0.57-3.06)	0.508
	No	37(11.82)	127(40.58)	1	1	-
Vancomycin	Yes	8(2.56)	94(30.03)	0.4(0.188-0.85)	0.62(0.23-1.7)	0.355
	No	44(14.06)	167(53.35)	1	1	-
Feeding interval	3 hourlies	3(4.35)	2(2.90)	1	1	-
	4 hourlies	3(4.35)	1(1.45)	1.66(0.33-8.29)	0.59(0.08 4.07)	0.591
	6 hourlies	28(40.58)	10(14.49)	2.28(0.69-7.55)	0.49(0.1-2.38)	0.383
	8 hourlies	18(26.09)	4(5.80)	2.05(0.599-7.03)	0.43(0.08-2.26)	0.320
Duration of antibiotics	< 14.21	7(2.24)	156(49.84)	1	1	-
	> 14.21	45(14.38)	105(33.55)	0.54(0.24-1.23)	**0.023(0.005-0.1)**	**0.000*** **

a) *** = p value < 0.001, ** = p value < 0.01, * = p value < 0.05

b) 1=considered the reference category

c) CHR = Crude hazard ratio. AHR = Adjusted hazard ratio, CI = confidence interval