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Derivation And Validation Of A Predictive Nomogram for Mortality Among Neonates With Necrotizing Enterocolitis In Tertiary care Hospitals At Bahir Dar City , Bahir Dar, Ethiopia:

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BAHAR DAR UNIVERSITY

COLLEGE OF MEDICINE AND HEALTH SIENCES

SCHOOL OF PUBLIC HEALTH

DEPARTEMENT OF EPIDEMIOLOGY AND BIOSTATISTICS

DERIVATION AND VALIDATION OF A PREDICTIVE NOMOGRAM FOR MORTALITY AMONG NEONATES WITH NECROTIZING ENTEROCOLITIS IN TERTIARY CARE HOSPITALS AT BAHIR DAR CITY, BAHIR DAR ETHIOPIA

BY: Belaynew Zemed

A RESEARCH THESIS TO BE SUBMITTED TO THE DEPARTMENT OF EPIDEMIOLOGY AND BIOSTATISTICS, SCHOOL OF PUBLIC HEALTH, COLLEGE OF MEDICINE AND HEALTH SCIENCE, BAHIR DAR UNIVERISTY IN PARTIAL FULFLLMENT OF THE REQUAREMENTS FOR THE DEGREE OF MASTER IN EPIDEMIOLOGY

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BAHAR DAR UNIVERSITY

COLLEGE OF MEDICINE AND HEALTH SIENCES

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PROSPECTIVE FOLLOW UP STUDY

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Study area	Tibebe Ghion comprehensive specialized hospital and Felege Hiwot comprehensive specialized Hospital, Bahirdar, Ethiopia

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Acronyms and abbreviations

CHD congenital heart disease

FHCSH Felege Hiwot comprehensive specialized hospital

GI gastrointestinal

GIT gastrointestinal tract

IUGR intra uterine growth restriction

NEC necrotizing enterocolitis

NICU neonatal intensive care unit

NRP_NEC none rapidly progressive necrotizing enterocolitis

PDA patent ductus arteriosus

ROC receiver operating curve

RP_NEC rapidly progressive necrotizing enterocolitis

SD standard Deviation

TGCSH Tibebe Ghion comprehensive specialized hospital

VLBW very low birth weight

Table of content

Contents

Acknowledgement ii

Acronyms and abbreviations iii

Table of content iv

Lists of tables vi

List of figures vii

1. Introduction 10

1.1. Background: 10

1.2. Statement of the problem 11

1.3. Significance of the study 12

2. Literature review 14

2.1. Mortality rate of necrotizing enterocolitis 14

2.2. Predictors of mortality in necrotizing enterocolitis 15

2.2.1. Sociodemographic predictors of NEC mortality 15

2.2.2. Neonatal clinical profiles predicting NEC mortality 16

2.2.3. Treatment related predictors of NEC mortality 17

Conceptual framework 19

3. Study objective 20

3.1. General objective 20

3.2. Specific objectives 20

4. Methods and materials 21

4.1. Study area 21

4.2. Study design and period 21

4.3. Population 21

4.3.1. Source population 21

4.3.2. Study population 21

4.4. Inclusion and exclusion criteria 21

4.5. Sample size determination 22

4.6. Sampling procedure 22

4.7. Study variables 22

4.8. Operational Definitions 23

4.9. Measurement 23
4.10. Data collection procedure 24
4.11. Data processing and analysis 24
4.12. Data quality control 24
4.13. Ethical consideration 25
5. Results 26
5.1. Maternal demographics and obstetric characteristics 26
5.2. Demographic and Clinical Characteristics of Neonates with NEC 27
5.3. Treatment related factors 28
5.4. NEC Mortality 30
5.5. Model Development 30
5.6. Nomogram Derivation 37
5.7. Mortality Risk classification 38
5.8. Decision curve analysis 39
6. Discussion 40
7. Conclusion 44
8. Recommendation 45
9. References 46
10. Annexes 49
10.1. Annex 1: Assent form (patient ID_____) 49
10.2. Annex 2: Data collection tool (structured questionnaire and check list) 51
10.3. Annex 3: Assurance of Investigator 54

Lists of tables

Table 5.1: Sociodemographic and obstetric characteristics of mothers of neonates diagnosed with NEC admitted at TGCSH and FHCSH, 2024

Table 5.2: Demographic and clinical characteristics of neonates with NEC admitted to TGCSH and FHCSH, 2024

Table 5.3: Treatment related factors among neonates With NEC admitted to TGCSH and FHCSH, 2024

Table 5.4: Multivariable binary logistic regression analysis, original model

Table 5.5: Multivariable binary logistic regression analysis, final (Nomogram) model

Table 5.6: model performance at different probability threshold cut points

Table 5.7: performance metrics of the nomogram following bootstrapping with 1000 bootstrap samples

Table 5.8: Risk classification of neonatal mortality in neonates with NEC using nomogram

List of figures

Fig.1: Conceptual framework showing determinant factors of NEC among neonates admitted to tertiary hospitals at Bahir Dar city

Fig.2: AUC for mortality prediction, original model

Fig.3: density plot for mortality prediction, Original model

Fig.4: The calibration plot evaluated the alignment between predicted probabilities and observed outcomes for the original model

Fig.5: AUC for mortality prediction nomogram, final model

Fig.6: density plot for mortality prediction nomogram, final model

Fig.7: The calibration plot evaluated the alignment between predicted probabilities and observed outcomes for the final model

Fig.8: calibration curve of the NEC mortality predictive model after bootstrapping with 1000 resamples

Fig.9: Nomogram developed for the prediction of mortality in neonates with NEC admitted at tertiary Hospitals in Bahir Dar city, 2024

Fig.10: A decision curve plot showing standardized net benefit (y-axis) against threshold probability with corresponding cost–benefit ratios (x-axis)

Abstract

Background: Necrotizing Enterocolitis (NEC) is a serious gastrointestinal condition primarily affecting preterm neonates, with mortality rates remaining unacceptably high despite advancements in neonatal care. In low-resource settings, such as Ethiopia, some local studies report a mortality rate as high as 82%. However, there is a lack of research on the predictive factors for NEC mortality, and existing studies show highly variable results. This highlights the need for a context-specific predictive model that can improve early risk assessment and guide clinical decision-making. Developing such a model in Ethiopia could help address the gap in current research and improve outcomes for neonates suffering from NEC.

Objective: To derivate and validate a predictive nomogram for mortality among neonates with necrotizing enterocolitis in tertiary care hospitals at Bahir Dar city, July to December, 2024

Methods: An institution-based prospective follow-up study was conducted at tertiary care hospitals in Bahir Dar city from July to December 2024, with a sample size of 251. Data were collected using a structured questionnaire from mothers of neonates admitted with necrotizing enterocolitis and a checklist from patient charts, then entered into EpiData version 4.6, and exported to statistical package for social sciences (SPSS) for data cleaning. Finally data were exported to R software for analysis and nomogram development. Descriptive data analysis techniques, including frequency, percentages, and mean, were used to summarize the characteristics of the study population and selection of variables for logistic regression. Binary logistic regression was performed to identify predictors for neonatal mortality due to Necrotizing enterocolitis. β-Coefficients with their 95% confidence level were used to evaluate the impact of each predictor on mortality. The Receiver operating characteristics curve (ROC) and calibration curves were drawn to show model performances. Statistical significance was determined at a p-value of less than 0.05 with a 95% confidence interval. Bootstrap technique was used to validate our model, and findings were evaluated against the original model. Finally, nomogram was developed to visually represent the effect of each predictor.

Results: A total of 251 cases of necrotizing enterocolitis were included in the study. Preterm accounted for 78%; with a mean gestational age of 34 weeks, and 84% of neonates were low birth weight. The mortality rate was found to be 51% and the predictors include; Site of delivery(outborn) , Gestational age, onset in the first 3 days of life, Delayed 1st feeding , Abdominal wall erythema, stage III Necrotizing Enterocolitis , Severe thrombocytopenia, Clinical deterioration, presence of Hospital Acquired infection . The original model achieved an AUC of 96.5% (95% CI: 94.3, 98.2), with a sensitivity of 88.3% (95% CI: 81.4, 93.3) and specificity of 90.2% (95% CI: 83.6, 94.9) at an optimal cutoff point 0.615, resulting in an overall accuracy of 89.2% (95% CI: 84.7, 92.8). The calibration test showed a p-value of 0.086. The nomogram model

demonstrated an AUC of 95.9% (95% CI: 94.2, 98.2) and, at an optimal cutoff point 0.630, a sensitivity of 87.5% (95% CI: 80.5, 92.7), specificity of 91% (95% CI: 84.6, 95.5), and an overall accuracy of 89.3% (95% CI: 84.7, 92.8), with a model fitness test p-value of 0.293.

Conclusion and recommendation: Neonatal mortality from necrotizing enterocolitis (NEC) in this study is high. Site of delivery, gestational age, time of first feeding, abdominal wall erythema, staging, disease onset, clinical deterioration, severe thrombocytopenia and hospital-acquired infections were found to be key predictors. Healthcare facilities should focus on early diagnosis, reducing feeding delays, and improving infection control and future researchers on external validation of the model and explore the role of surgical intervention in improving outcomes.

Key words: Necrotizing Enterocolitis, Nomogram, Ethiopia

1. Introduction

1.1. Background:

Necrotizing enterocolitis (NEC) is the most common life-threatening emergency of the gastrointestinal tract (GIT) in the newborn period; predominantly affecting preterm neonates. Approximately 90% of the cases occur in newborns less than 32 weeks of gestation, and there is an inverse relationship between gestational age and NEC incidence (1-3). It is characterized by ischemic necrosis of the intestinal mucosa, severe inflammation, bacterial invasion of the bowel wall, which can lead to systemic sepsis, multiorgan failure and death in severe cases (4).

Globally, the incidence of NEC varies across different healthcare setups and ranges from 5% to 15% among neonates with birth weights under 1500 g, with mortality rates of 20–30% for medically managed cases and up to 50% for those requiring surgery (5-7). Premature and low birth weight neonates are particularly vulnerable, with increasing incidence and case fatality rates as birth weight and gestational age decreases (4, 8, 9). In Ethiopia, the reported prevalence of NEC varies significantly between 2% and 25%, reflecting inconsistencies across studies and it's pooled in hospital mortality rate is as high as 70% (10-13).

The cause and pathogenesis of NEC remains unclear but is thought to be multifactorial which includes increased production of nitric oxide, expression of Toll-like receptor 4, intestinal ischemia and reduced activity of intestinal stem cells (6, 14, 15). Key risk factors include Prematurity, low birth weight, formula feeding, intestinal dysbiosis,(16) and maternal factors such chorioamnionitis. Additional fetal and neonatal contributors include genetic predisposition, intra-uterine growth restriction, hypoxia and patent ductus Arteriosus (PDA) (3, 17-19).

Diagnosis of NEC relies on clinical, radiographic and laboratory data. Initial symptoms include feeding intolerance, abdominal distension, and bloody stools; often accompanied by signs of sepsis (5, 20, 21). Plain abdominal radiographs provide confirmation through findings such as pneumatosis intestinalis in early stages (Bell stage II) and pneumoperitoneum in advanced cases (Bell stage III) (21, 22).

Management depends on disease severity and includes supportive, medical therapy, or surgery (21). Preventive strategies such as antenatal care, use of antenatal steroids, avoid formula feeding in preterm newborns, probiotic use, hypoxia management and aggressive treatment of infection (6, 23). However, NEC remains a major contributor to mortality and long-term complications in resource-limited settings. Survivors often face prolonged hospitalization and complications such as intestinal obstruction, liver failure, short bowel syndrome, and neurodevelopmental deficits (24, 25).

1.2. Statement of the problem

Although neonatal care has significantly improved survival rates in high-resource settings, necrotizing enterocolitis (NEC) continues to be a major global health challenge (7, 26). Mortality and complication rates remain alarmingly high, particularly in low-resource settings where access to specialized care is limited (9, 24). The acute phase of NEC has profound social, emotional, and economic consequences for families, while its long-term outcomes include an increased risk of neurodevelopmental impairments, particularly among infants requiring surgical intervention (25, 27, 28). In high-income countries, NEC accounts for approximately 20% of annual NICU costs. This financial burden is likely even greater in low-income settings, which face higher rates of prematurity and fewer healthcare resources.

Mortality from NEC remains disproportionately high in resource constrained settings, and survivors often suffer from severe complications and prolonged hospital stays (9, 10, 29). This discrepancy in mortality is due to high burden of premature delivery, very low birth weight, neonatal sepsis, perinatal asphyxia, severe disease at diagnosis, and inadequate access to timely and effective care in low income countries (30, 31). Infants who recover from disease require prolonged hospitalization due to complications, such as intestinal obstruction from stricture and adhesion, liver failure due to a prolonged requirement for total parenteral nutrition, short bowel syndrome with intestinal failure and associated nutritional deficiencies, and associated defects in neurologic development (24, 25, 32, 33).

Globally, the mortality rate of neonates with NEC is significantly associated with gestational age and birth weight. Studies have shown that NEC also has long-term consequences, including poor neurodevelopmental outcomes, particularly for infants with advanced disease (34). In addition to its significant medical impact, NEC causes a substantial economic burden on healthcare systems, accounting for approximately 20% of annual NICU costs in high-income countries. This burden is likely higher in LMICs, where the incidence and complications of NEC is expected to be high as a result of inadequate prenatal care, limited access to specialized neonatal intensive care units, and a higher prevalence of premature births due to factors like malnutrition and infectious diseases (35).

In Ethiopia, neonatal mortality due to NEC varies widely, ranging from 45% to 89%, an unacceptably high rate caused by poor healthcare infrastructure, inadequate prenatal and neonatal care, and a high prevalence of low birth weight (9, 13, 16, 36). Despite this significant burden, there is a limited understanding of the outcomes and prognostic factors of NEC in resource-limited settings, emphasizing the urgent need for further research to inform effective interventions.

Previous studies have reported inconsistent prevalence rates of NEC in Ethiopia, ranging from 2% to 25% (10, 11). Furthermore, there is a scarcity of data regarding the predictors of NEC outcome, highlighting a significant gap in understanding the burden and prognosis of the disease in the country. Factors such as inadequate prenatal care, low birth weight, sepsis, and perinatal asphyxia contribute to the high incidence and mortality rates of NEC in these settings (9, 10, 37). The lack of data and predictive tools tailored to Ethiopia and similar resource-restricted settings affects identification of high-risk neonates and implement timely interventions.

In Low income Countries, the burden of NEC is further exacerbated by scarcity of diagnostic tools and delayed recognition of the disease. Developing a predictive model, such as a nomogram, to determine the prognosis of neonates with NEC tailored to the local context could improve risk stratification, guide clinical decision-making, and optimize resource allocation, ultimately reducing mortality and morbidity associated with NEC in this setting. Additionally, such advancements could have long-term economic benefits by improving population health and productivity. This study aims to contribute significantly to scientific research by providing valuable insights into the nature of NEC, its outcomes, and the key predictors in resource-limited neonatal care settings.

By identifying neonates at the highest risk of mortality, healthcare providers can prioritize interventions to improve outcomes. This study seeks to address the existing knowledge gap by determining the incidence of mortality and prognostic factors for NEC in tertiary care hospitals in Bahir Dar, Ethiopia. The findings are expected to contribute in enhancing neonatal care and reducing the burden of NEC related mortality in the study areas and in similar resource-limited settings.

1.3. Significance of the study

First, by providing an overview of the mortality burden and identifying the predictors of NEC mortality in Ethiopia, this study is expected to fill the gap in neonatal health research. It also gave us valuable insights into the local context, where healthcare infrastructure and resources are limited.

Secondly, the findings of this study are also expected to guide healthcare providers in identifying high-risk neonates and implementing timely and targeted interventions. By understanding the key factors associated with NEC outcomes, clinicians can make evidence-based decisions to improve neonatal care.

Thirdly, the study also has generated good data that help to develop a nomogram tailored to the facilities and other resource-constrained settings. This predictive tool will help clinicians to assess the prognosis of neonates with NEC and prioritize care for those at higher risk of mortality.

Fourth, the study's results will inform policymakers about the burden of NEC and the importance of investing in neonatal care. It will help prioritize resource allocation, advocate for improved prenatal and neonatal care services, and encourage the development of national strategies to reduce NEC-related mortality.

Fifth, by highlighting predictors to poor outcomes in neonates with NEC, the study will contribute to the design of interventions aimed at improving survival rates and reduce the emotional and financial burden on families.

Finally, the findings will have broader implications for other low- and middle-income countries with similar healthcare challenges, serving as a reference for addressing NEC in resource-limited environments.

2. Literature review

2.1. Mortality rate of necrotizing enterocolitis

In a retrospective cross-sectional study on the survival and factors associated with the mortality of preterm neonates admitted to Felege Hiwot Comprehensive Specialized Hospital in Bahir Dar, Ethiopia, in 2020, NEC accounted for 33% of preterm mortality, with an overall mortality rate of 82% among NEC patients(16).

A systematic review and meta-analysis of 12 studies from various Ethiopian hospitals reported a pooled in-hospital mortality rate of 70% among neonates with necrotizing enterocolitis(13).

A retrospective study on the outcomes and prognostic factors for survival of neonates with Necrotizing Enterocolitis (NEC) at Universitas Gadjah Mada/Dr. Sardjito Hospital in Yogyakarta, Indonesia, conducted from January 2014 to December 2019, included 52 neonates diagnosed with NEC. The study found that the overall survival rate was 44.2% (33).

A retrospective study in china from 1,167 NEC cases found a 41.7% mortality rate for stage 2 and 3 NEC. In VLBW infants, SGA (OR 5.02) and stage 3 NEC (OR 8.09) were major risk factors. In LBW infants (1500-2499 g), sepsis (OR 2.59) and stage 3 NEC (OR 5.37) significantly increased mortality risk (38).

A single-center retrospective follow-up study conducted at Nicolaus Copernicus University in Torun, Poland, analyzed the clinical course, infections, treatment, and outcomes of 76 infants with Necrotizing Enterocolitis (NEC) hospitalized over a period of 6 years found that the survival rate in the cohort was 79%.

In a retrospective observational study conducted at a tertiary neonatal unit in South Africa, which aimed to describe the maternal, obstetric, and neonatal characteristics and survival to hospital discharge in very low birth weight (VLBW) babies with Necrotizing Enterocolitis (NEC), data was collected from 2,111 VLBW and preterm babies admitted between January 2013 and December 2017. The study found that the mortality rate in babies with NEC was 49.1% and the following factors were identified as significantly associated with mortality, Surgery for NEC ($P = 0.01$), Mechanical ventilation ($P < 0.001$), Late onset sepsis ($P = 0.018$) (29).

A five-year retrospective study in a resource-limited NICU in Cape Town reported a 52% 30-day NEC mortality rate, with 35% of survivors having neurodevelopmental abnormalities. An adverse composite outcome (mortality or abnormal neurodevelopment) affected 63% of cases. Key mortality risk factors included SGA, shock, metabolic acidosis, inotrope use, and delayed feeding post-surgery (>9 days). The

study highlighted significant NEC-related mortality and long-term challenges in resource-limited settings (24).

A retrospective, cross-sectional study conducted at Ziauddin University Hospital, Karachi, Pakistan, aimed to evaluate the frequency, associated factors, and outcomes of Necrotizing Enterocolitis (NEC) in preterm infants from December 1, 2020, to December 1, 2022, found a prevalence of NEC of 7.1% and an overall mortality rate of 32.7%. Key associated factors for mortality were thrombocytopenia, hypotension, formula feeding, positive blood cultures, and invasive ventilation, with a p-value of 0.01(8).

Retrospective review of infants with confirmed (Bell stage II or III) NEC treated in Great Ormond Street Hospital, London, United Kingdom during January 2002 to December 2010 with the aim of comparing characteristics of survivors and non survivors found the overall mortality to be 32%, the highest mortality was in infants with pan-intestinal disease (86%) (39).

A prospective study of a cohort of 110 preterm neonates with gestational age <36 weeks and weight <1600 g infants diagnosed to have NEC were followed for 90 days at Ashish Hospital and Research Centre, Jabalpur, Madhya Pradesh, India between January 2015 and December 2017 to see 90-day survival rate and risk factors for mortality. The study showed that the overall 90-day survival rate was 87.27% (96/110), and the post-operative survival rate was 46.15% (12/26). The age of gestation, weight, and extent of the disease were the main risk factor for mortality (28).

A retrospective study conducted in Tunisia aimed to identify predictive factors for mortality in neonates with Necrotizing Enterocolitis (NEC) between January 1, 2010, and March 31, 2022, found an overall survival rate of 47%. Factors associated with mortality were gestational age <32 weeks (OR 2.5), five-minute Apgar score <8 (OR 3.621), birth weight <1,500 g (OR 4.136), platelet count <50,000/mm³ (OR 2.5), Bell's stage 3 NEC (OR 2.496), and sepsis during hospitalization (OR 5.971) (9).

2.2. Predictors of mortality in necrotizing enterocolitis

2.2.1. Sociodemographic predictors of NEC mortality

A retrospective follow up study to assess effect of Deregionalized Care on Mortality in Very Low-Birth-Weight Infants With Necrotizing Enterocolitis in NICUs in California from 2005 to 2011 to assess mortality rates among a population-based sample of 30 566 VLBW infants, 1879 with necrotizing enterocolitis, according to the level of care and VLBW case volume at the hospital of birth showed that Outcomes for VLBW infants continue to be suboptimal when they are not born into high-level, high-volume centers(40).

In a prospective, observational study conducted at six university children's hospitals in USA in 2008 from 455 neonates analyzed, 192 (42%) progressed to severe disease, and 263 (58%) advanced to full feedings without operation. Teenaged mother, having never received enteral feeding before diagnosis, and receiving cardiac compressions and/or resuscitative drugs at the time of delivery, Gram negative and Gram positive bacteremia, abdominal wall discoloration, radiographic findings of portal venous gas and of pneumatosis intestinalis, metabolic acidosis on day of diagnosis, male gender and birth weight <1000 g were found to be independent predictors of disease progression (41).

2.2.2. Neonatal clinical profiles predicting NEC mortality

A prospective cohort study in Jabalpur, India (2015–2017) followed 110 preterm neonates with NEC for 90 days. The mean gestational age was 32.4 weeks, and NEC onset occurred at 13 days. Sepsis was the most common complication (88.18%). Postoperative survival was low (46.15%), with complications like wound infection (73.07%) and intestinal stricture (34.61%). The overall 90-day survival rate was 87.27%. Gestational age, weight, and disease extent were key mortality risk factors, with Stage 3 NEC linked to high morbidity and mortality (28).

A six-year retrospective study in Poland analyzed 76 NEC cases, reporting a 79% survival rate. Surgical intervention was required in 56 infants (53 laparotomies, 3 peritoneal drains), while 20 received conservative treatment. Key risk factors for poor outcomes included gut perforation, infection, abdominal wall erythema, and acute kidney injury (42).

A retrospective study of 1,167 NEC cases from 95 NICUs in China found that in VLBW infants, small for gestational age (OR: 5.02) and stage 3 NEC (OR: 8.09) were key mortality risk factors. In moderate LBW infants (1500-2499 g), sepsis (OR: 2.59) and stage 3 NEC (OR: 5.37) significantly increased mortality risk (38).

A retrospective study on neonates with NEC in Indonesia, found an overall survival rate of 44.2%. NEC staging and birth weight were significantly associated with survival, while sex, Apgar score, platelet count, and treatment type were not. Multivariate analysis revealed that sex (HR = 3.10) and NEC staging (HR = 0.44) were strong predictors of survival (32).

A retrospective study of neonates with Bell stage II or III NEC at Texas Children's Hospital (1997-2001) examined whether severe thrombocytopenia predicts outcomes. Infants were divided into two groups: those with severe thrombocytopenia (platelet count <100,000/mm^3) and those without. Results showed that infants in the thrombocytopenia group were more premature (28.0±4.1 vs. 30.0±4.2 weeks) and more likely to

require laparotomy for gangrenous bowel (adjusted OR 16.33). Severe thrombocytopenia was also a predictor of mortality (adjusted OR 6.39) and NEC-related gastrointestinal complications (adjusted OR 5.47) (43).

A retrospective multicenter analysis from three Swiss hospitals on risk factors for mortality in preterm infants with NEC included 157 premature children with confirmed NEC between January 2007 and October 2018. The study found that low 1st and 5th minute Apgar scores, low hemoglobin concentration (Hgb), and high lactate levels were associated with NEC severity and mortality. Severe NEC was linked to congenital heart disease (OR 2.6) and patent ductus arteriosus (PDA — OR 3.3), while death was strongly associated with the presence of PDA (OR 5.5) (44).

A retrospective analysis of neonates with NEC admitted to the NICU in Cape Town, South Africa, from January 2014 to December 2018 aimed to assess 30-day mortality, neurodevelopmental outcomes, and composite outcomes in a resource-limited setting. The study included 135 neonates and found a 52% 30-day mortality rate. Neurodevelopmental abnormalities and adverse composite outcomes occurred in 35% and 63% of survivors, respectively. Factors such as small for gestational age, shock, metabolic acidosis, inotrope requirement, and delayed first feed (>9 days post-surgery) were associated with increased mortality and adverse outcomes (24).

A retrospective study in China (2015–2020), found that neutropenia at NEC onset was associated with adverse outcomes (HR 3.48) and lower survival probability (χ^2 10.63). The presence of thrombocytopenia along with neutropenia at NEC onset increased the predictive value for severe surgical NEC and higher mortality (45).

A retrospective case-control cohort study performed at Chengdu Women's and Children's Central Hospital, Chengdu, China from total of 163 Infants diagnosed with confirmed NEC to assess risk factors for necrotizing enterocolitis associated mortality showed; from univariate analysis; gestational age, birth weight, 5-min Apgar score, leukopenia, thrombocytopenia, highest C-reaction protein (CRP) value and the necrotic range of intestine to be associated with an increased risk of mortality and from multivariable logistic regression model, thrombocytopenia found to be a risk factor for NEC associated mortality (46).

2.2.3. Treatment related predictors of NEC mortality

A review of medical records from 214 neonates with NEC in Indonesia (2016–2021), identified prognostic factors for clinical deterioration. Late-onset NEC, history of blood transfusion, thrombocytopenia, and elevated CRP were significantly associated with deterioration in univariate analysis. Multivariate analysis

revealed that late onset (after 10.5 days) and elevated CRP (≥4.5 mg/L) were strongly linked to clinical deterioration, with odds ratios of 3.25 and 3.53, respectively (47).

A retrospective review of 205 infants with confirmed NEC at Great Ormond Street Hospital, London (2002–2010), compared survivors and non-survivors. Of the 205 infants, 35 (17%) were medically managed and 170 (83%) underwent surgery. The overall mortality rate was 32%, with the highest mortality observed in infants with pan-intestinal disease (86%). Mortality remained significant in less severe forms (multifocal 39%; focal disease 21%). The most common cause of death was multiorgan dysfunction, and nearly half of the non-survivors had care withdrawn (39).

A retrospective study at a tertiary neonatal unit in South Africa examined the characteristics and survival outcomes of preterm VLBW babies with NEC from 2,111 VLBW admissions (January 2013–December 2017). Of these, 173 (8%) were diagnosed with NEC. Factors associated with NEC included HIV exposure, late-onset sepsis, respiratory support, surfactant administration, and blood transfusion. Surgery was performed in 48 (27.7%) of the NEC cases, and the mortality rate was 49.1%. Deaths were associated with surgery, mechanical ventilation, and late-onset sepsis (29).

A retrospective study in China assessed predictive factors for rapid progression of NEC in preterm neonates (December 2015–April 2019). Among 216 preterm neonates with NEC, 64 had rapidly progressive NEC (RP-NEC) and 152 had non-rapidly progressive NEC (nRP-NEC). The mortality rate for RP-NEC was 32.8%, compared to 3.28% for nRP-NEC. Independent risk factors for RP-NEC included male sex, portal venous gas, neutrophils $<2.0 \times 10^9$ /L, and pH <7.3. A predictive model based on these factors showed an area under the curve of 0.801, with 83% specificity and 66% sensitivity (48).

Conceptual framework

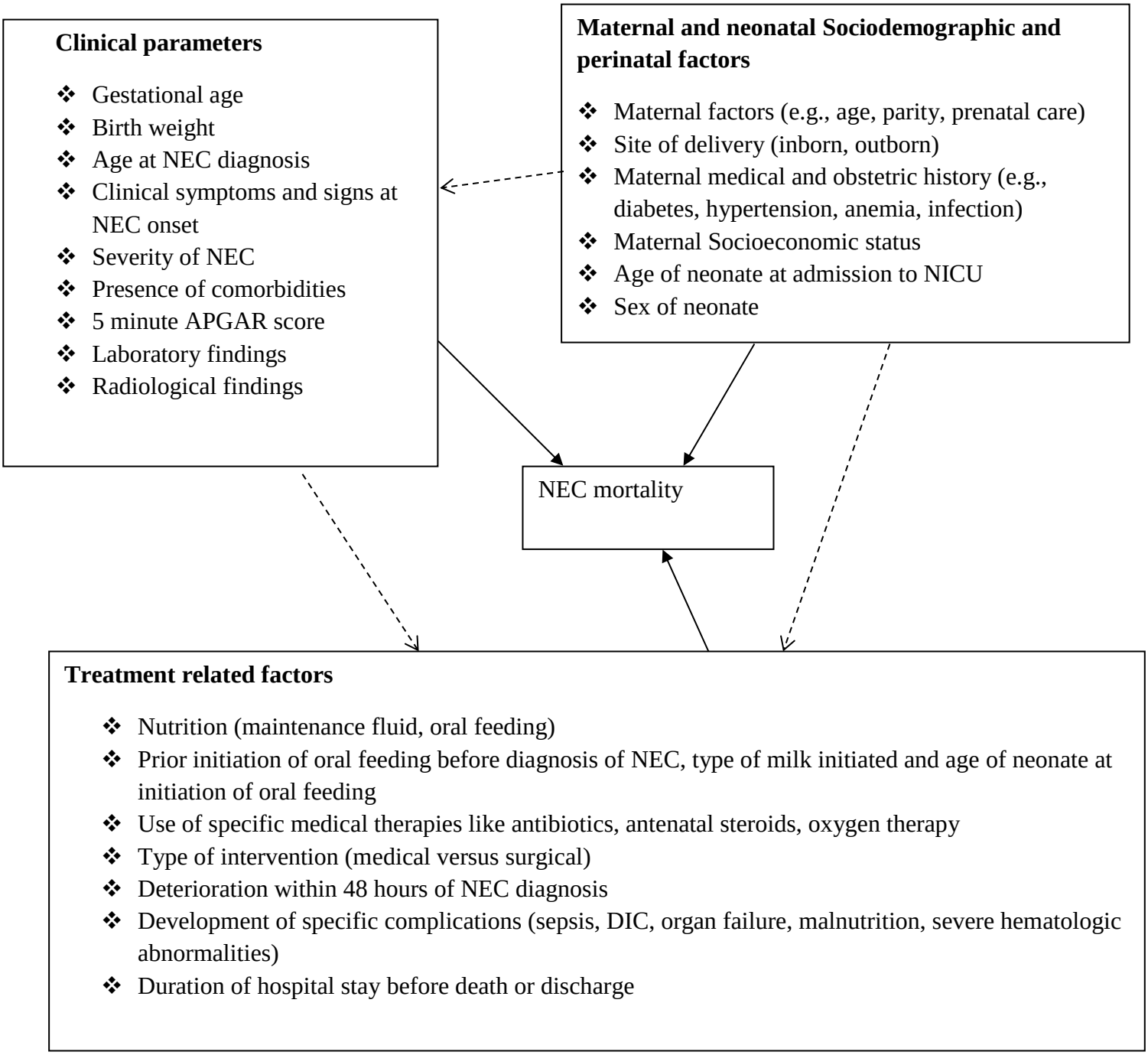


Fig.1: conceptual framework showing determinant factors of NEC mortality among neonates admitted to TGSH and FHCSH neonatal intensive care units,based on litreature review

3. Study objective

3.1. General objective

To Derivate and validate a nomogram to predict mortality among neonates with necrotizing enterocolitis admitted to neonatal intensive care unit in tertiary hospitals at Bahir Dar city, northwest Ethiopia, 2024.

3.2. Specific objectives

To determine mortality rate among neonates admitted with necrotizing enterocolitis

To identify prognostic determinants of mortality among neonates with necrotizing enterocolitis

To develop a nomogram for prediction of mortality among neonates with NEC in the study facilities

4. Methods and materials

4.1. Study area

The study was conducted at two tertiary hospitals in Bahir Dar city; Tibebe Ghion and Felege Hiwot comprehensive specialized Hospitals which are among few tertiary hospitals in the region and collectively serve a population of more than 7,500,000 within their catchment area. Along with other pediatrics and child health services both hospitals have been giving neonatal intensive care unit service with comparable setup and human resource. However, specialized pediatric cardiac and pediatric surgical services are exclusively available at Tibebe Ghion comprehensive Specialized Hospital. Hence, patients requiring these subspecialty services are being referred to Tibebe Ghion comprehensive Specialized Hospital. Unlike other services, neonatal intensive care service is not being provided by private health institutions. As a result there is a high tendency of referring newborns both from other government hospitals and private institutions to these hospitals for better neonatal care.

4.2. Study design and period

An institution-based prospective follow-up study was conducted at two tertiary hospitals in Bahir Dar city from July to December 2024. The study, designed as a prognostic investigation, aimed to assess the "incidence of mortality from necrotizing enterocolitis in neonates during hospitalization as a function of multiple prognostic determinants at Tibebe Ghion and Felege Hiwot Comprehensive Specialized Hospitals."

4.3. Population

4.3.1. Source population

All neonates admitted to NICU of tertiary hospitals at Bahir Dar city and diagnosed with NEC

4.3.2. Study population

All neonates admitted to the NICU of tertiary hospitals at Bahir Dar city and diagnosed with NEC during the study period

4.4. Inclusion and exclusion criteria

Inclusion criteria:

All neonates diagnosed with NEC, either upon admission or during the hospital course.

Exclusion criteria:

Neonates with known major congenital GI anomalies

Neonates transferred from other health institutions with incomplete medical documentation

4.5. Sample size determination

Based on recommendations from experts and using the rule of thumb method for determining sample size in prognostic studies, the sample size for this study was calculated. The rule suggests having at least 10-20 samples per variable. Since 20 variables were included for regression analysis based on the literature review, the sample size was initially calculated as: N=n×10 Where; N = sample size to be calculated, n = number of predictors, which is 20; Thus, the calculation is: N=20×10=200; to account for a 10% non-response rate, the final sample size is adjusted as: 200+ (200×0.10)=220, Therefore, the minimum sample size for this study was set at **220**.

4.6. Sampling procedure

Due to small number of cases, all patients diagnosed with the disease during the study period were included in the sample. A total of 147 cases were included from Tibebe Ghion Specialized Hospital (TGCSH) and 104 cases from Felege Hiwot Comprehensive Specialized Hospital (FHCSH).

4.7. Study variables

Prognostic outcome: NEC mortality, the final outcome of the patient specified based on the current admission and categorized as either **death** or **survival**. This outcome was determined at the time of discharge or death during the course of the current hospital admission.

Prognostic Determinants:

Demographic and perinatal factors; includes, maternal characteristics (age, parity, and prenatal care), site of delivery (inborn or outborn), maternal medical and obstetric complications (diabetes, hypertension, anemia, and cardiac disease), parental socioeconomic status and sex and age of neonate at admission.

Neonatal clinical profile; includes, gestational age, birth weight, age at NEC diagnosis, clinical symptoms and signs (abdominal distension, abdominal wall erythema, vomiting or gastric residuals, gastrointestinal bleeding, apnea, and hypothermia), severity of NEC based on modified Bell's staging, presence of comorbidities (respiratory distress syndrome, sepsis, hypoglycemia, hypothermia, perinatal asphyxia, and congenital heart disease) , laboratory findings (white blood cell count, platelet count, hematocrit, blood culture results, and organ function tests), radiological findings (pneumatosis intestinalis, portal venous gas, and peritoneal abscess collection).

Treatment-related factors; include nutrition, mode of feeding, initiation of oral feeding before NEC diagnosis, type of milk initiated, neonate's age at initiation of feeding, use of specific medical therapies

(antibiotics, antenatal steroids, and oxygen therapy), surgical interventions, clinical deterioration within 48 hours of diagnosis, the development of specific complications (sepsis, disseminated intravascular coagulation (DIC), organ failure, malnutrition, and severe hematologic abnormalities), duration of hospital stay.

4.8. Operational Definitions

Necrotizing enterocolitis: a clinical condition diagnosed using modified Bell's clinical staging criteria based on clinical symptoms, physical signs, imaging findings and laboratory results and includes stage II and stage III

Stage II (proven NEC): characterized by abdominal signs, such as increased gastric residuals, abdominal distention, vomiting, and heme-positive stool or coffee ground vomitus, absent bowel sounds with or without imaging findings like intestinal dilation, ileus, ascites and pneumatosis intestinalis

Stage III (Advanced NEC): characterized by Signs of stage II plus hypotension, bradycardia, severe apnea, and signs of peritonitis (abdominal distention and marked tenderness) with or without abdominal imaging findings like pneumoperitoneum and gas in the biliary tree and laboratory signs include neutropenia and disseminated intravascular coagulation (DIC).

Acute kidney injury in neonate: serum creatinine >1.5 mg/dl after 24 hrs of life

Severe thrombocytopenia: platelet count <50,000

Hospital acquired sepsis: infections occurred after 48 hours of admission to NICU and diagnosed based on physicians assessment using clinical criteria such as fever, tachycardia, respiratory distress, white blood cell abnormality and failure to breast feed with or without positive blood culture.

Clinical deterioration within 48 hours: significant worsening of neonate's clinical condition within 48 hours of diagnosis characterized by progression in staging (Stage II to Stage III), worsening of baseline clinical parameters or death.

Delayed feeding: initial feeding delayed beyond 48 hours of postnatal age

NEC onset: categorized as onset within 3 days and after 3 days

4.9. Measurement

The outcome variable, newborn survival after necrotizing enterocolitis was assessed by checklist and it was categorized as death or survival. The independent variables were interpreted based on their association with the outcome. Gestational was measured in completed weeks, based on last menstrual period or early ultrasound. Birth weight was measured in grams using a calibrated scale. Age at diagnosis of NEC was recorded in postnatal days at the time of NEC diagnosis. The stage of NEC was classified as Stage II or

Stage III using the modified Bell's clinical staging criteria. Lastly, the age at initiation of oral feeding was recorded in postnatal days.

4.10. Data collection procedure

Data were collected using a structured questionnaire and checklist. The structured questionnaire was used to gather information on the Sociodemographic characteristics of mothers and newborns from mothers of neonates diagnosed with necrotizing enterocolitis (NEC). The structured checklist was used to collect data on the clinical profile of the newborns, including laboratory results, treatment-related parameters, hospital course, and outcomes. Baseline information on the demographic and perinatal factors of the mothers and newborns was collected through the questionnaire. Clinical details, including laboratory results, treatment parameters, disease progression, NEC-related complications, and survival status, were recorded using the checklist. Data collectors were neonatal nurses working in the NICUs of the respective hospitals.

4.11. Data processing and analysis

After collection, data were entered in Epi- data version 4.6 then exported to SPSS for cleaning and R software for regression analysis, and nomogram development and validation. Missing data were managed with multiple imputation method. Descriptive statistics like frequency, proportions, mean and standard deviation were computed. Based on review of existing literature and descriptive analysis potential predictors of mortality for NEC were selected and predictive model was developed using binary logistic regression to explore the effects of several predictors on mortality of neonates with NEC. First Univariable binary logistic regression was performed then variables with P value less than 0.2 were taken for multivariate binary logistic regression. P-value of less than 0.05 at 95% confidence interval was taken to determine statistical significance in the multivariable analysis. Model accuracy was checked using discrimination metrics (ROC, and area under the curve) and model calibration using Hosmer and Lemenshow p-value and calibration plot. Internal validation (model performance) was ensured by conducting bootstrapping technique. Finally a nomogram was developed from the predictive model. Multicolinearity test using variable inflation factor and correlation metrics were performed to know the independent effect of each predictor.

4.12. Data quality control

Structured check list and questionnaire were used for data collection. The check list and questionnaire were reviewed by principal research advisors and necessary comments were incorporated to ensure validity. A pretest was conducted at Adisalem Hospital to assess the tools' effectiveness. Before data collection, training was given for both data collectors and supervisor by the principal investigator. Following data collection

each day, the checklist and questionnaire were reviewed for completeness by the supervisors and principal investigator, with necessary feedback provided to the data collectors to ensure accuracy and completeness.

4.13. Ethical consideration

This study was approved by Ethical review committee of the college of medicine and health sciences, Bahir Dar University, with the reference number RDD/2043/2024, dated 06/06/2024. Permission was also obtained from the respective hospitals where data collection took place. Data were collected without interfering with the management of the patients. Written assent was taken from each participant to ensure their willingness in the participation of data collection. All information collected through the questionnaire and check list was kept confidential to maintain the privacy and rights of the participants.

5. Results

5.1. Maternal demographics and obstetric characteristics

A total of 251 mothers of neonates were included in this cohort to gather basic information that could influence various neonatal characteristics. The mothers' ages ranged from 18 to 42 years, with a mean age of 29.52 years (SD = 5.99). Most mothers, 146 (58.2%) were aged 25–34 years, while mothers of age less than 20 years accounted only 2.8% and 35 years and older accounted 27.5%. Majority of mothers (72.1%) were multipara indicating that nearly three-fourths had experienced more than one delivery.

Urban residents represented, 161(64.1%) of the mothers and most mothers, 229 (91.2%), attended at least one antenatal care (ANC) follow-up. Regarding educational status, 63 (25.1%) of the mothers were illiterate and 57 (22.7%) had degree or higher qualification. Housewives made up the largest mother's occupational comprising, 100 (41%) of the mothers followed by government employees, 87 (34.7%).

Nearly half of the mothers, 129 (51.4%), gave birth at the site of the study facility, while the remaining 122 (48.6%) gave birth at external locations. Obstetric or medical complications were reported by 101 (40.2%) of the mothers and about, 99 (39.4%) of the mothers were given antenatal steroids for fetal lung maturity.

Table 5.1: Sociodemographic and obstetric characteristics of mothers of neonates diagnosed with NEC admitted at TGCSH and FHCSH, 2024

Maternal Sociodemographic and obstetric characteristics	Category	Frequency	Percent
Age of mother	<20 years	7	2.8
	20-24 years	29	11.6
	25-34 years	146	58.2
	>=35 years	69	27.5
Parity	Primipara	70	27.9
	Multipara	181	72.1
Maternal Residence	Urban	161	64.1
	Rural	90	35.9
ANC follow up	Yes	229	91.2
	No	22	8.8
Maternal educational status	Illiterate	63	25.1
	Primary	54	21.5
	Secondary	46	18.3
	Diploma	25	10

	Degree and above	57	22.7
	Missing	6	2.4
Maternal occupation	House wife	100	41
	Government employ	87	34.7
	Merchant	49	19.5
	Missing	15	4.8
Site of Delivery	Inborn	129	51.4
	Outborn	122	48.6
Maternal obstetric and medical complications	Yes	101	40.2
	No	150	59.8
Use of antenatal steroid	Yes	99	39.4
	No	152	60.6

5.2. Demographic and Clinical Characteristics of Neonates with NEC

Age of neonates' at admission ranged from 1 to 16 days, with a mean of 2.27 days (SD: 2.523). Majority of neonates, 196 (78.1%) were preterm, with gestational ages ranging from 28 to 41 weeks, and a mean gestational age of 34 weeks (SD: 3.342). Their birth weights ranged from 900 to 3600 grams, with a mean of 1759.06 grams (SD: 591.31). A significant proportion (84.1%) of neonates were classified as low birth weight (<2500 grams).

Age of neonates at NEC diagnosis ranged from 2 to 18 days, with a mean of 4.8 days (SD: 2.298). Nearly one- third of neonates, 73 (29.1%) were diagnosed within the first 3 days of life. All Neonates with NEC had one or more comorbidities, with neonatal sepsis being the most prevalent, affecting 94.8% of cases. Other common conditions included respiratory distress syndrome (54.6%), hypothermia (38.6%), jaundice (35.5%), and small-for-gestational-age (SGA) (30.7%). Less frequent comorbidities included perinatal asphyxia (13.1%), hypoglycemia (12.7%), and congenital heart disease (3.6%).

The most common clinical presentations were abdominal distension and vomiting or gastric residuals, both observed in all cases (100%). Other common symptoms were gastrointestinal bleeding (49.8%), abdominal wall erythema (25.9%) and apnea (17.9%). Hematologic abnormalities were present in 71.3% of neonates; thrombocytopenia being the most common; affecting 68.9% of cases. Based on the modified Bell's clinical

staging criteria, 78.5% of neonates were classified as in stage II and the remaining, 16.7% were categorized as stage III.

Table 5.2: Demographic and clinical characteristics of neonates with NEC admitted to TGCSH and FHCSH, 2024

Neonatal Demographic and clinical characteristics	Category	Frequency	Percent
Sex of neonate	Male	138	55
	Female	113	45
Gestational Age in weeks	<37 weeks	196	78.1
	>=37 weeks	55	21.9
Birth Weight in Grams	<2500	211	84.1
	>=2500	40	15.9
Age of neonate at NEC diagnosis in days	<= 3 days	73	29.1
	> 4 days	178	70.9
Comorbidities	Jaundice	89	35.5
	Perinatal Asphyxia	33	13.1
	Hypoglycemia	32	12.7
	Hypothermia	97	38.6
	Neonatal sepsis	238	94.8
	Respiratory distress syndrome	137	54.6
	Congenital heart Disease	9	3.6
	SGA	77	30.7
Clinical presentation	Abdominal distension	251	100.0
	Abdominal wall erythema	65	25.9
	Gastrointestinal bleeding	125	49.8
	Vomiting/gastric residual	251	100.0
	Hypothermia	50	19.8
	Increased work of breathing	63	25.1
	Apnea	46	18.3
Hematologic abnormality	Thrombocytopenia	173	68.9
	Neutropenia	39	15.5
	Anemia	58	23.1
	Pancytopenia	25	10
NEC clinical staging	stage II	209	83.3
	stage III	42	16.7

5.3. Treatment related factors

The majority of neonates, 239 (95.2%), had initiated enteral feeding prior to their NEC diagnosis. Among them, 88.7% were fed breast milk, while 11.3% received formula. The age at first feeding ranged from 1 to

11 days, with a mean of 2.65 days (SD: 1.6). Among all neonates, 158 (62.9%) had a delay in initiating their first enteral feeding beyond the first 48 hours of life. All neonates in the cohort were managed medically, with no surgical interventions reported. Prior antibiotic treatment was administered to 95.2% of neonates before their NEC diagnosis. Clinical deterioration within 48 hours of Dx occurred in 47% of neonates. Complications occurred in 67.3% of cases. The most frequent complication was hospital-acquired infections, affecting 47.4% of neonates, severe thrombocytopenia in 45.4% of cases, while neonatal malnutrition and organ failure were less common, occurring in 9.6% and 9.2% of cases, respectively. The duration of hospital stay ranged from 2 to 38 days, with a mean of 13.8 days (SD: 7.8) (mean duration for deaths=10.9 days and for survivors=21.4 days)

Table 5.3: Treatment related factors among neonates With NEC admitted to TGCSH and FHCSH, 2024

Treatment related factors	Category	Frequency	Percent
Initiation of feeding before Dx of NEC	Yes	239	95.2
	No	12	4.8
Type of milk given for those who started feeding prior to NEC Dx	Breast milk	212	88.7
	Formula	27	11.3
Delayed first feeding	Yes	158	62.9
	No	93	37.1
Presence of Hospital Acquired Infection (HAI)	Yes	119	47.4
	No	132	52.6
Use of prior antibiotics before Dx of NEC	Yes	239	95.2
	No	12	4.8
Abdominal X-ray done	Yes	32	12.7
	No	219	87.3
Type of intervention	Medical	251	100.0
	Surgical	0	0
Clinical Deterioration within 48 hrs	Yes	118	47
	No	133	53
Presence of complications	Yes	169	67.3
	No	82	32.7
Common Complications	Organ failure	23	9.2
	malnutrition	24	9.6
	HAI	113	45
	Severe hematologic abnormality	114	45.4
	DIC	67	26.7

**Since patients could have more than one complication, the total frequency exceeds the overall sample size*

5.4. NEC Mortality

The outcomes of neonates diagnosed with NEC revealed a near-equal distribution between mortality and recovery. From total cohort of neonates with NEC in the study period, 51% (128 cases) were died due to NEC and its complications, while 49% (123 cases) improved and were subsequently discharged.

5.5. Model Development

Bivarible logistic regression was used to select candidate prognostic determinants for multivariable logistic regression model. Accordingly, the Bivariable logistic regression was performed between site of delivery, sex, gestational age, birth weight, SGA, age at NEC diagnosis, abdominal wall erythema, Bell's clinical staging, apnea, and clinical deterioration within 48 hours, use of antenatal steroids, time of initial feeding, type of milk used, perinatal asphyxia, hospital-acquired sepsis, AKI, thrombocytopenia, neutropenia, type of management with NEC. A p-value of 0.2 was used as a cut-off point to declare association for the Bivariable analysis and export the variables into multivariable logistic regression model. Although gestational age had a high p-value (0.503), it was included in the multivariable logistic regression due to its universal significance in predicting NEC mortality. A total of 12 variables (site of delivery, Gestational age, Being SGA, Abdominal wall erythema, Apnea, staging, thrombocytopenia, clinical deterioration, AKI, HAI, age at NEC Dx, and delayed first feeding beyond 48hrs) were included in the multivariable logistic regression analysis.

Table 5.4: Multivariable binary logistic regression analysis (n =251), original model

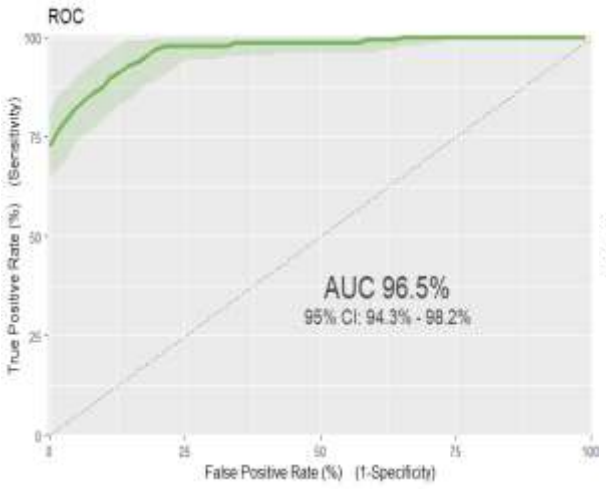
Sr.no	Predictors	Univariable logistic Regression		Multivariable logistic Regression	
		β(95%CI)	p-value	β(95%CI)	p-value
1	Site of delivery(outborn)	0.37(-0.13 ,0.87)	0.144	1.35(0.34, 2.46)	**0.012***
2	Gestational age	-0.03(-0.10, 0.05)	0.503	-0.16 (-0.31, -0.01)	**0.037***
3	Being SGA(yes)	0.67(0.12, 1.22)	0.018	-1.00(-2.14, 0.05)	0.073
4	Age at NEC Dx(<= 3days)	1.11(0.54, 1.71)	<0.001	2.89(1.69, 4.31)	**<0.001****
5	Delayed 1st feeding beyond 48 hrs	1.25(0.72, 1.81)	<0.001	2.26(1.16, 3.51)	**<0.001****
6	Abdominal wall erythema(yes)	0.84 (0.26, 1.43)	0.005	1.42(0.28, 2.63)	**0.017****
7	Apnea (yes)	1.21(0.52, 1.96)	<0.001	0.56(-0.92, 2.12)	0.465
8	Bell's stage(stage-III)	2.26 (1.37, 3.36)	<0.001	1.59(0.28, 3.10)	**0.025 ***
9	Severe thrombocytopenia (yes)	2.46(1.88, 3.08)	<0.001	2.32(1.27, 3.50)	**<0.001****
10	Clinical deterioration within 48 hrs	3.15(2.51, 3.84)	<0.001	2.64(1.59, 3.80)	**<0.001****
11	Acute kidney injury(AKI)	1.35(0.39, 2.49)	0.009	1.53(-0.23, 3.43)	0.101
12	Hospital Acquired infection(HAI)	2.72(2.11, 3.37)	<0.001	1.82(0.74, 2.95)	**0.001****

B=> Coefficient of predictors in the regression model

The multivariable logistic regression analysis identified nine significant prognostic factors for NEC mortality: site of delivery, gestational age, abdominal wall erythema, Bell's clinical staging, severe thrombocytopenia, clinical deterioration, hospital-acquired infection (HAI), age at NEC diagnosis, and delayed first feeding beyond 48 hours. Based on these significant variables and their corresponding B-coefficients, the following predictive model is generated:

Logit (NEC mortality) = -0.68 + 1.35 (Site of delivery (outborn)) −0.16 (Gestational age) + 2.89 (Age at NEC Dx ≤ 3 days) +2.26 (Delayed first feeding beyond 48 hrs) + 1.42(Abdominal wall erythema) +1.59 (stage III) + 2.32(Severe thrombocytopenia) + 2.64(Clinical deterioration within 48 hrs) + 1.82(HAI)

The AUC of the original model was 96.5% (95% CI: 94.3, 98.2), as shown in the ROC curve below (Fig.5.2). This indicates excellent discriminative ability of the model in predicting mortality of neonates from NEC. At the optimal cutoff point of 0.615(youden's index=0.79), the model demonstrated a sensitivity of 88.3 % (95% CI: 81.4, 93.3) and specificity of 90.2% (95% CI: 83.6, 94.9) in predicting NEC mortality. The positive predictive value (PPV) was 90.4% (95% CI: 83.8, 94.6), and the negative predictive value (NPV) was 88.1% (95% CI: 81.1, 93.7) with an overall accuracy of 89.2% (95% CI: 84.7, 92.8). With the specified optimal cutoff value the model misclassified 15 neonates as death, who actually improved and were discharged, and 12 neonates as improved, who actually died; resulting in an overall misclassification rate of 10.76%. The calibration curve as shown below (Fig.4) and hosmer and Lemenshow model fitness p-value of 0.086 for the original model (with polynomial degree 2) indicates no significant difference between the observed and predicted probabilities of mortality, thus demonstrating good calibration of the model. The prediction density plot further evaluated the model's performance. It effectively identified positive cases as the predicted probability approached 1 and negative cases as the probability approached 0.



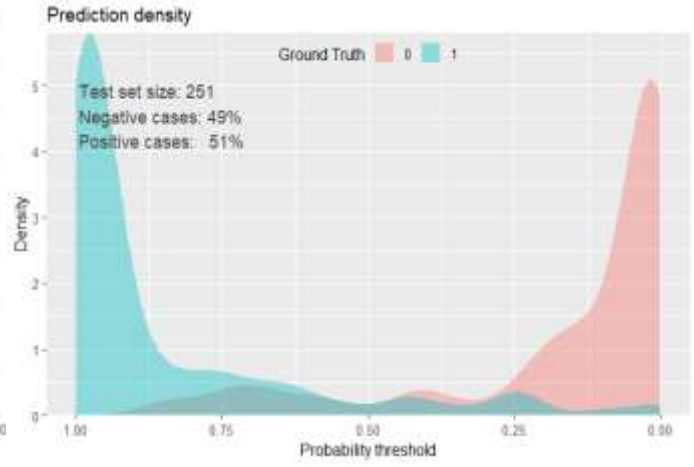


***Fig.2**: AUC for mortality prediction nomogram* ***Fig.3**: density plot for mortality prediction nomogram, Original model*

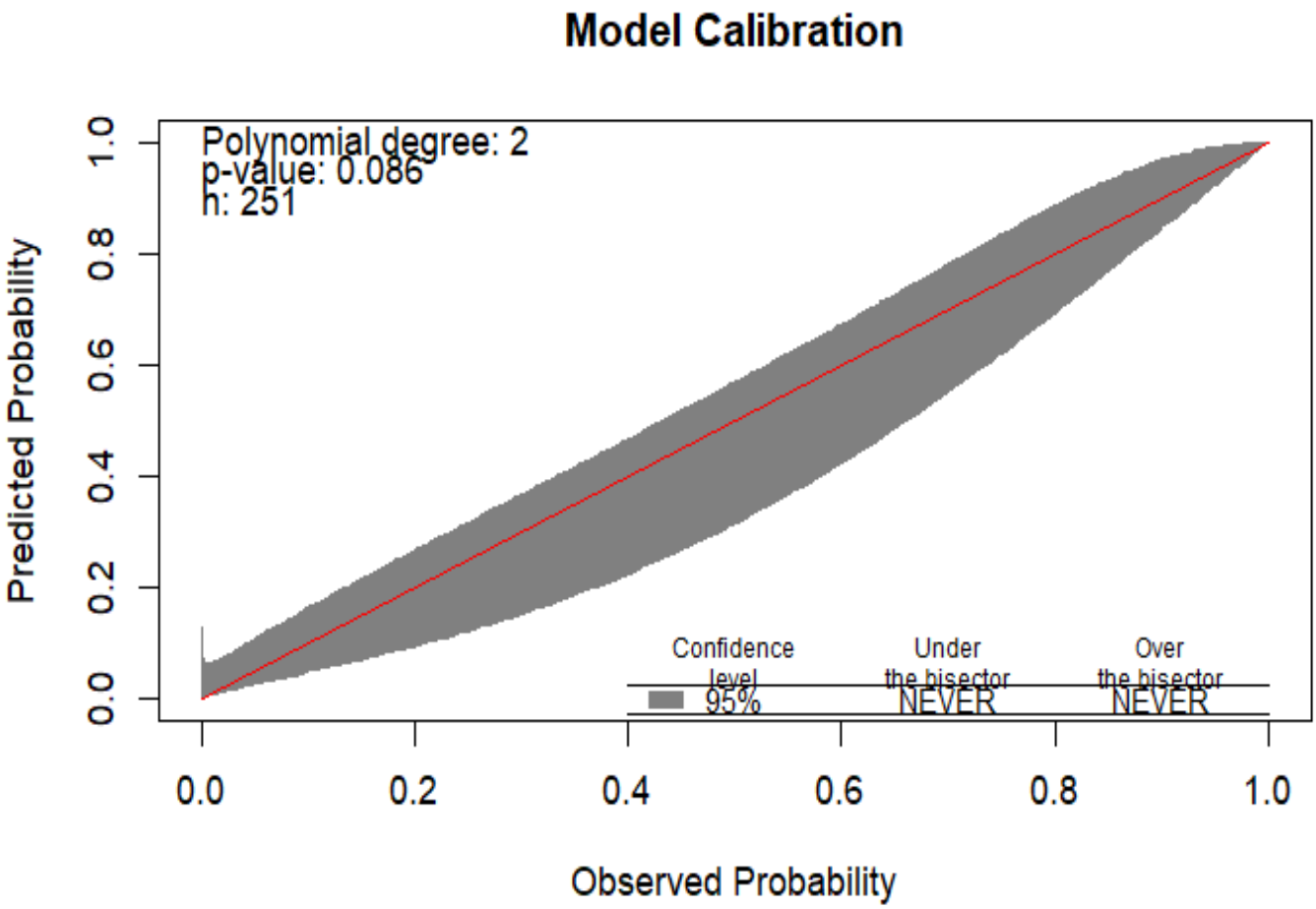


Fig.4*: The calibration plot evaluated the alignment between predicted probabilities and observed outcomes for the model. The x-axis represents the observed probabilities, while the y-axis represents the predicted probabilities. The red diagonal line (bisector) represents perfect calibration, where predicted probabilities match observed probabilities exactly. The model's predictions, represented by the gray confidence band (95% confidence interval), closely follow the red diagonal line, indicating good agreement between predictions and outcomes across the probability spectrum. The p-value of 0.086 (using a polynomial of degree 2) further suggests no statistically significant deviation from perfect calibration.*

Using significant variables from the original logistic regression model; namely site of delivery, Gestational age, Abdominal wall erythema, Bell's clinical staging, thrombocytopenia, clinical deterioration, HAI, age at NEC Dx, and delayed first feeding beyond 48hrs; A new regression model was developed, from which a nomogram was derived for practical individualized risk assessment. This tool simplifies complex regression results to visually represent the contribution of each predictor to the probability of NEC mortality for individual cases.

Table 5.5: Logistic Regression Analysis of Significant Predictors for Nomogram Development to predict NEC mortality, final model (nomogram model)

Sr.no	Predictors	Univariable logistic Regression		Multivariable logistic Regression	
		β(95% CI)	p-value	β(95%CI)	p-value
1	Site of delivery(outborn)	0.37(-0.13 ,0.87)	0.144	1.26(0.30, 2.32)	**0.014***
2	Gestational age	-0.03(-0.10, 0.05)	0.503	-0.15 (-0.31, -0.01)	**0.036***
3	Age at NEC Dx(<= 3days)	1.11(0.54, 1.71)	<0.001	2.38(1.30, 3.59)	**<0.001*****
4	Delayed 1st feeding beyond 48 hours	1.25(0.72, 1.81)	<0.001	2.07(1.02, 3.25)	**<0.001*****
5	Abdominal wall erythema(yes)	0.84 (0.26, 1.43)	0.005	1.35(0.34, 2.43)	**0.011***
6	Bell's stage(stage-III)	2.26 (1.37, 3.36)	<0.001	1.88(0.54, 3.44)	**0.009****
7	Severe thrombocytopenia (yes)	2.46(1.88, 3.08)	<0.001	2.02(1.07, 3.04)	**<0.001*****
8	Clinical deterioration within 48 hours	3.15(2.51, 3.84)	<0.001	2.42(1.42, 3.53)	**<0.001*****
9	Hospital Acquired infection(HAI)	2.72(2.11, 3.37)	<0.001	1.83(0.82, 2.89)	**<0.001*****

The AUC of the final model was 95.9% (95% CI: 94.2, 98.2), which still indicated excellent discriminative ability of the model in predicting mortality of neonates from NEC as shown in the ROC curve below (Fig.5). There is no significant drop in the performance from the original model. At the optimal cutoff point of 0.630, the model demonstrated a sensitivity of 87.5% (95% CI: 80.5, 92.7) and specificity of 91% (95% CI: 84.6, 95.5) in predicting NEC mortality. The positive predictive value (PPV) was 91% (95% CI: 84.5, 94.9), and the negative predictive value (NPV) was 87.5% (95% CI: 80.5, 93.5) with an overall accuracy of 89.3% (95% CI: 84.7, 92.8). The calibration test showed a p-value of 0.293, indicating no significant difference between the observed and predicted probabilities of mortality, thus demonstrating good calibration of the model. The table below displays the model's performance at different probability threshold cut points.

Table 5.6: model performance at different probability threshold cut points

Threshold of Predicted probability	Sensitivity	specificity	Predicted value positive	Predicted value negative	Accuracy
0.8	0.7500	0.9593	0.9505	0.7867	0.8526(0.8026,0.894)
0.7	0.8047	0.9350	0.9279	0.8214	0.8685(0.8203,0.9077)
0.630	**0.8750**	**0.9106**	**0.9106**	**0.8750**	**0.8928(0.8474, 0.9279)**
0.5	0.8906	0.8699	0.8769	0.8843	0.8805(0.8338,0.9179)
0.4	0.9219	0.8374	0.8551	0.9115	0.8805(0.8338, 0.9179)
0.3	0.9375	0.7967	0.8276	0.9245	0.8685(0.8203, 0.9077)
0.2	0.9688	0.7724	0.8158	0.9596	0.8725(0.8248, 0.9111)

The prediction density plot further evaluated the model's performance. It effectively identified positive cases (those who died) as the predicted probability approached 1 and negative cases as the probability approached 0. This illustrates the model's strong predictive capacity for mortality risk. The model's Brier score was 0.07 indicating that it is well calibrated and accurate.

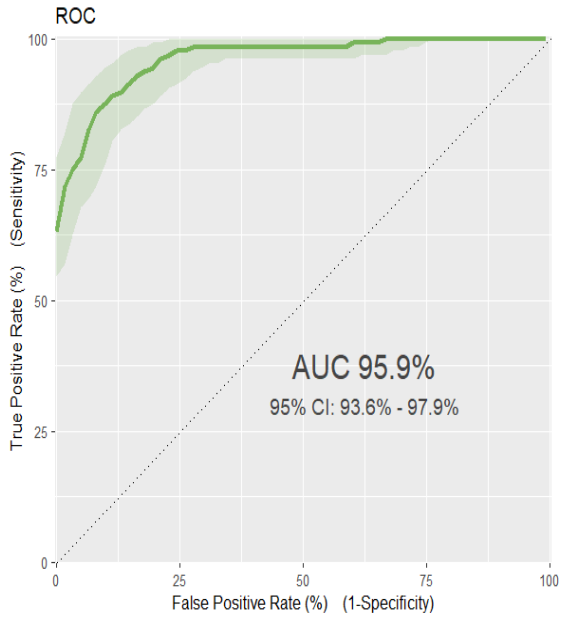


Fig.5: *AUC for mortality prediction nomogram*

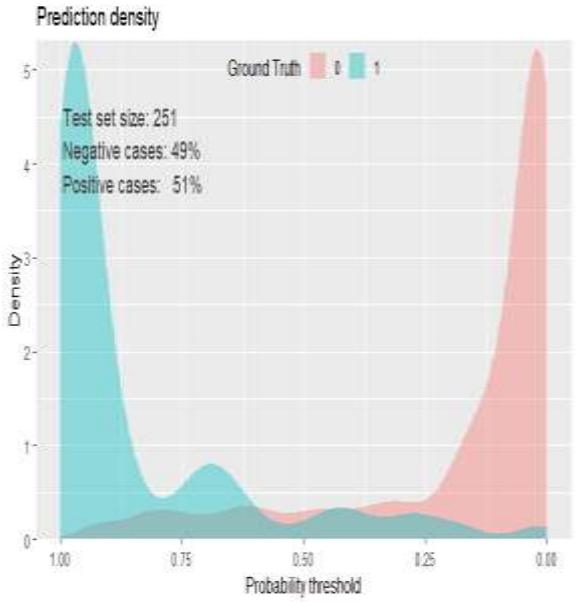


Fig.6: *density plot for mortality prediction nomogram*

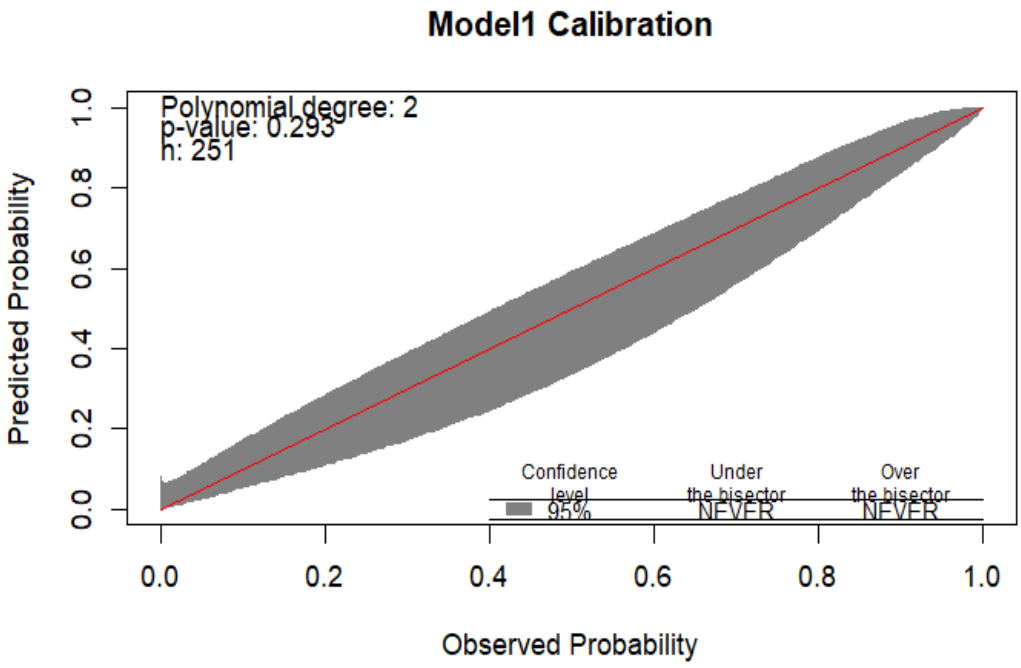


Fig.7: *The calibration plot evaluated the alignment between predicted probabilities and observed outcomes for the model. The model's predictions, represented by the gray confidence band (95% confidence interval), closely follow the red diagonal line, indicating good agreement between predictions and outcomes across the probability spectrum. The p-value of 0.293 (using a polynomial of degree 2) further suggests no statistically significant deviation from perfect calibration.*

The final model was internally validated with bootstrapping technique using 1000 bootstrap samples to determine model fitness, performance metrics and stability for generalization. The results from bootstrap analysis showed minimal deviation in performance metrics between the original data and training data. This indicates that the model's performance is consistent and stable across different resamples. Further evaluation using both the bootstrap calibration and the Hosmer-Lemenshow test provides strong evidence that the model was well calibrated and performs reliably. The corrected performance metrics, after accounting for optimism, showed an AUC of 95%, calculated as (corrected Dxy + 1) / 2 = (0.8990 + 1) / 2 = 0.9495 (≈ 95%), with an optimism coefficient of 0.0193. This indicates a slight over-optimism in the initial model, which was effectively adjusted through internal validation techniques. Despite the correction, the model retained a strong discriminative ability. Additionally, the p-value from the Hosmer-Lemenshow test was 0.164, which is greater than the significance threshold of 0.05, which indicated that there is no significant difference between the observed and expected outcomes, suggesting that the model is well-calibrated. These findings confirmed that the model accurately predicts the outcomes without significant bias or over fitting. Therefore; the model is stable, well-calibrated, and demonstrated strong generalizability making it suitable for Clinical application in predicting NEC mortality.

Table 5.7: performance metrics of the nomogram following bootstrapping with 1000 bootstrap samples

Index	Rig	Training	Test	Optimism Index	Corrected	n
Dxy	0.9183	0.9261	0.9068	0.0193	0.899	1000
R^2	0.7727	0.7898	0.7526	0.0372	0.7355	1000
Intercept	0	0	0.0069	-0.0069	0.0069	1000
Slope	1	1	0.8695	0.1305	0.8695	1000
Emax	0	0	0.0323	0.0323	0.0323	1000
D	0.8622	0.8942	0.8275	0.0668	0.7954	1000
U	-0.008	-0.008	0.0126	-0.0206	0.0126	1000
Q	0.8701	0.9022	0.8148	0.0874	0.7828	1000
B	0.08	0.073	0.0861	-0.0131	0.0931	1000
g	4.1238	4.6354	3.9262	0.7092	3.4146	1000
gp	0.4601	0.4624	0.454	0.0084	0.4517	1000

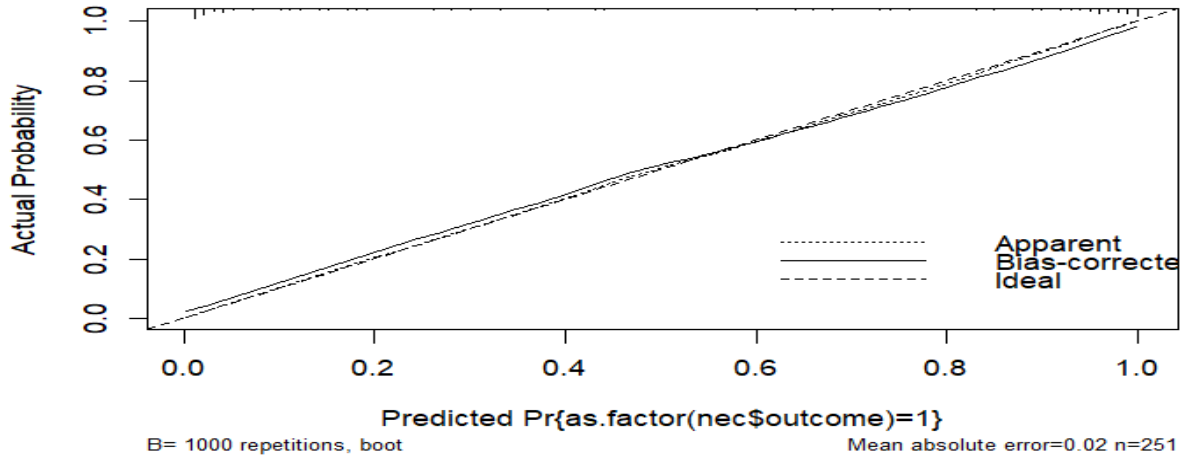


Fig.8: *calibration curve of the NEC mortality predictive model after bootstrapping with 1000 resamples*

As we see from the above curve (Fig.6), bias-corrected calibration curve (solid line) closely aligns with the ideal calibration curve (dashed line) suggests that the bootstrapped model is well-calibrated. Additionally, the minimal difference between the apparent calibration curve (dotted line) and the bias-corrected curve indicates that over fitting is not a significant concern, further supporting the model's reliability.

5.6. Nomogram Derivation

The nomogram was generated using rms package in R-software, where the glm function was used to fit a multivariable logistic regression model, incorporating variables included in the final model(site of delivery, Gestational age, Abdominal wall erythema, Bell's clinical staging, severe thrombocytopenia, clinical deterioration, HAI, age at NEC Dx, and delayed first feeding beyond 48hrs) with their corresponding β-coefficients. The model's performance was evaluated using goodness-of-fit tests and discrimination metrics. Additionally, calibration plots and decision curve analysis were performed to assess the clinical utility and predictive accuracy of the nomogram as already described above. The presence of clinical deterioration, early age NEC onset, and thrombocytopenia are the most important factors in predicting NEC mortality, with clinical deterioration having the largest impact. In contrast, site of delivery and abdominal wall erythema contributed less to the overall mortality risk. The nomogram assigns points to each predictor based on its coefficient, with the top line (1 to 100) representing points for each predictor. In the middle are the 9 predictors, with points assigned based on the presence (1) or absence (2) of a predictor, and specific gestational age values as it is a continuous variable. The bottom line (0 to 700) represents the total points, calculated by summing the points for each predictor. The total score is then mapped to the probability of NEC mortality, ranging from 0.001 to 0.999, where values closer to 1 indicate a higher mortality risk. For example, a neonate who was outborn (score = 55), born at 33 weeks of gestational age (score = 50), diagnosed with NEC on the 3rd day of life (score = 95), started on breast milk on the 2nd day of life (score = 0), has no abdominal wall erythema (score = 0), has Bell's stage III NEC (score = 77.5), has thrombocytopenia (score = 82), has clinical deterioration within 48 hours of diagnosis (score = 100), and has no healthcare-associated infection (score = 0) will have a total score of 459.5, which corresponds to a 99% probability of NEC mortality.

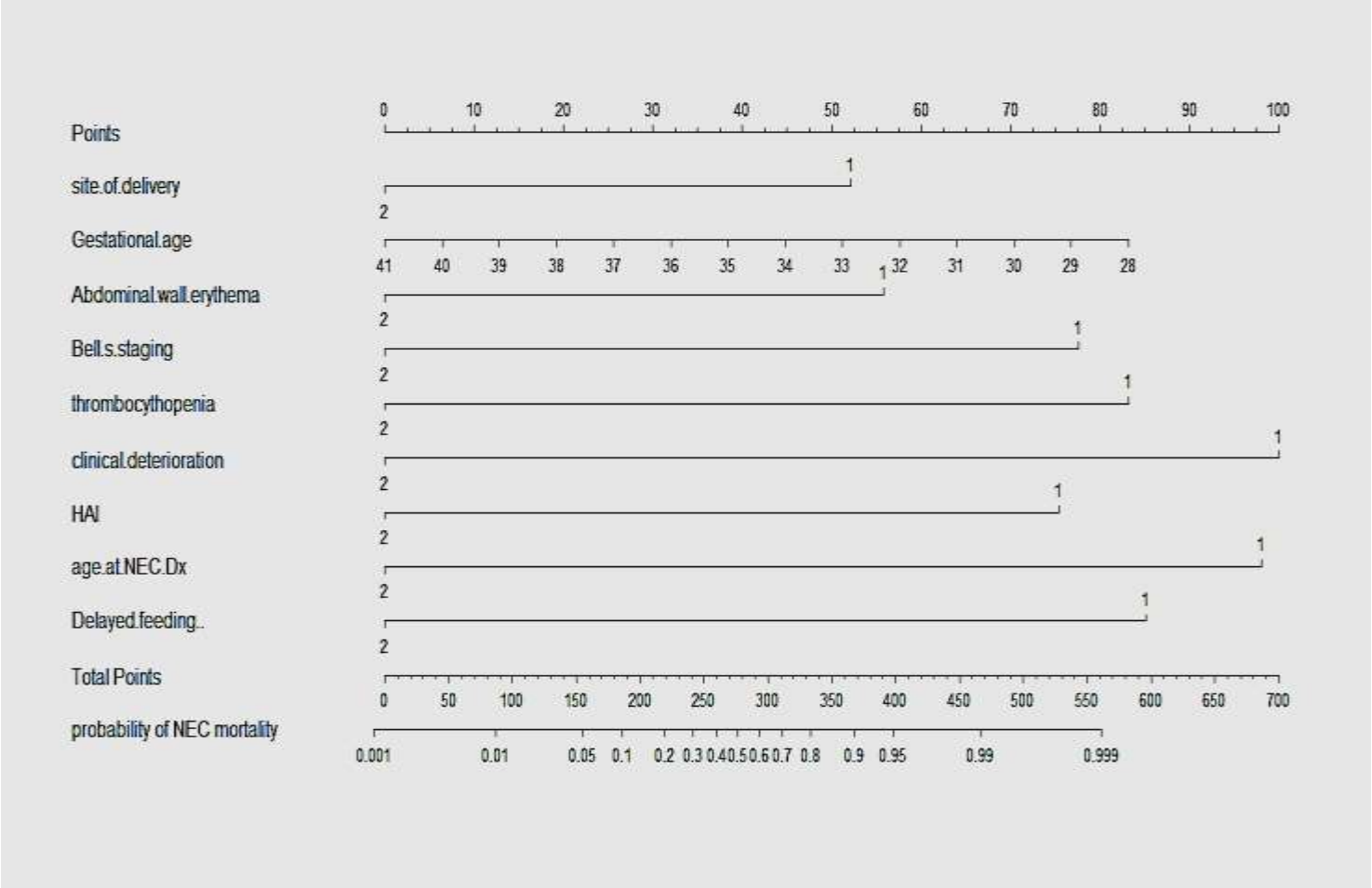


Fig.9: Nomogram developed for the prediction of mortality in neonates with NEC admitted at tertiary Hospitals in Bahir Dar city, 2024

5.7. Mortality Risk classification

At the optimal cut point of 0.630, the threshold of the predicted probability at which a prediction is classified as died or survived in the model, and maximum youden index "max J =0.79", risk of mortality due to NEC was classified as low risk (<0.630) and high risk (≥0.630). Accordingly out of total patients, 123(49%) were classified as high risk and 128(51 %) as low risk. The incidence of mortality was 12.5% and 91 % in low risk and high risk groups respectively as shown in the table below.

Table 5.8: Risk classification of neonatal mortality in neonates with NEC using nomogram (n =251)

Risk category	Number of patients	Incidence of mortality
Low risk(<0.630)	128(51%)	16(12.5%)
High risk (≥0.630)	123(49%)	112(91%)
Total	251(100%)	128(51%)

5.8. Decision curve analysis

The standardized net benefit of the model was assessed using decision curve analysis. The nomogram demonstrated the highest net benefit across all probability thresholds. Thus, treatment decisions based on the nomogram offer a higher net benefit compared to strategies of not treating at all or treating all patients, regardless of their risk threshold as shown in the curve below.

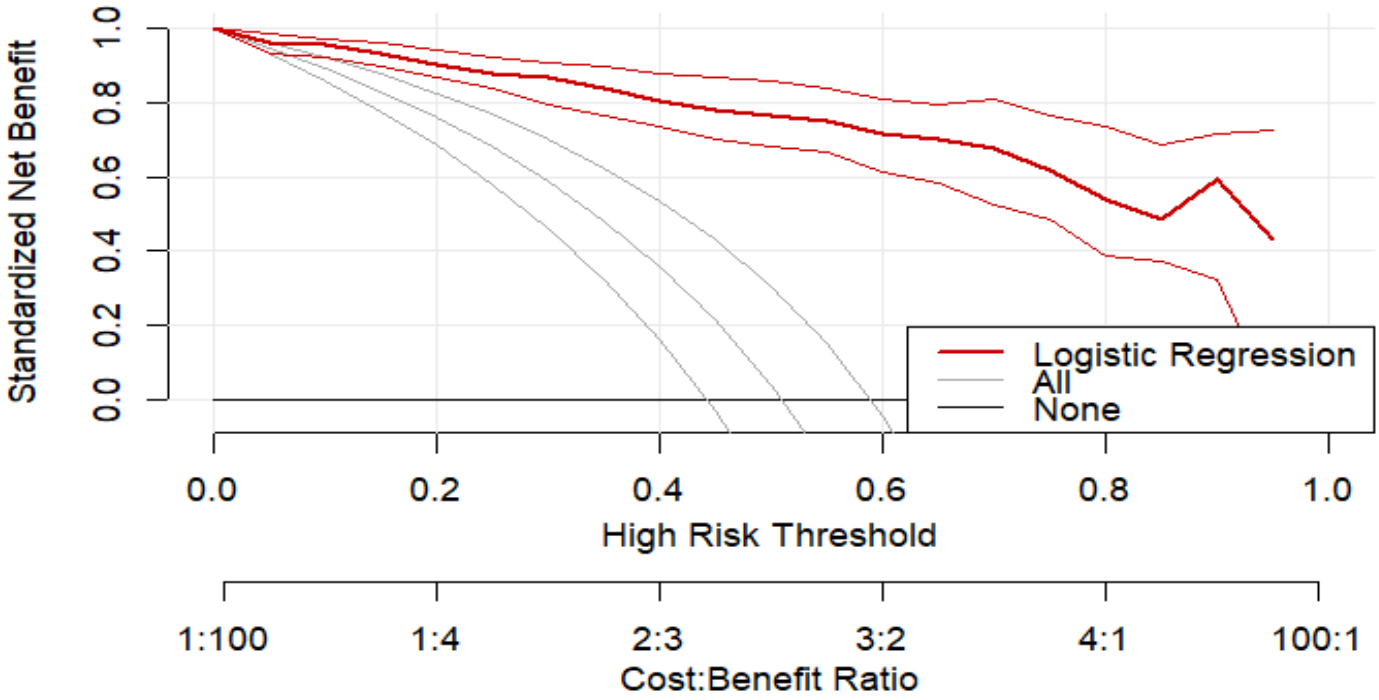


Fig.10: *A decision curve plot showing standardized net benefit (y-axis) against threshold probability with corresponding cost–benefit ratios (x-axis). The thick red line represents standardized net benefits of the nomogram across probability thresholds and the accompanying two thin red lines represent the 95% confidence interval; the grey line with its 95% confidence interval represents standardized net benefit of treating all neonates with NEC in the same way regardless of their mortality risk; the black line represents standardized net benefit of treating none of the neonates with NEC which is zero.*

6. Discussion

The mortality rate among neonates with NEC in this cohort was **51% (CI: 45.00-57.34)**. This observed NEC mortality rate was lower than reports from previous studies conducted at Felege Hiwot Comprehensive Specialized Hospital (82%), Northwestern Ethiopia Comprehensive Specialized Hospitals (including Gondar University Teaching Hospital, Felege Hiwot, Tibebe Ghion, Debre Tabor, and Debre Markos hospitals) (57%), a systematic review and meta-analysis of 12 studies from various Ethiopian hospitals (70%), and four governmental hospitals in Addis Ababa (Tikur Anbessa Specialized Hospital, Gandhi Memorial Hospital, Zewditu Hospital, and Yekatit 12 Hospital) (71%) (13, 16, 49-51) . The lower mortality rate observed in this cohort could be attributed to differences in study population as this study included both preterm and term neonates, whereas most other studies focused only on preterm neonates. Additionally, more recent studies may reflect improved medical treatment outcomes due to advancements in neonatal care practices and better institutional protocols. However, the mortality rate in this study was comparable to reports from Indonesia (56%), Charlotte Maxeke Johannesburg Academic Hospital, South Africa (49%), and Cape Town, South Africa (52%) (24, 36). In contrast, it was higher than mortality rates reported at Charlotte Maxeke Johannesburg Academic Hospital, South Africa (39.9%), a cohort study in UK (18%), Children's Hospital of Chongqing Medical University in China (14.2%), and Santiago in Chile (18.6%) (52-54). Generally, these findings align with global trends, where the burden of NEC remains disproportionately high in low-resource settings where preventive measures, such as promoting breast milk feeding, early diagnosis, and management of hospital-acquired infections remains a challenge. Even though NEC mortality rates tend to be lower in settings where advanced surgical interventions are available. However, in this study, as well as in most other studies conducted in Ethiopia and other low-income countries, neonates with NEC were managed medically, without any surgical intervention, which may partly explain the higher mortality rates observed in these settings.

In the multivariable logistic regression analysis site of delivery, Gestational age, Abdominal wall erythema, Bell's clinical staging, severe thrombocytopenia, clinical deterioration, HAI, age at NEC Dx, and delayed first feeding beyond 48hrs were found to be predictors of higher NEC mortality.

Neonates born outside the study facilities (at home or other facilities than the study hospitals) had a 1.26 unit increase in the log-odds of mortality from NEC compared to inborn neonates [(β = 1.26, 95% CI: 0.30 to 2.32), p = 0.014], indicating a significantly higher risk of mortality among outborn neonates. This finding is in line with studies conducted at California (40). Possible explanation for this association includes delayed

diagnosis and initiation of treatment, differences in quality of neonatal care, increased infection risk, transport-related physiological stress and delayed initiation of enteral feeding.

Neonates born at higher gestational ages had a lower risk of mortality from NEC. Each additional week of gestation was associated with a 0.15 unit decrease in the log-odds of mortality [(β = -0.15, 95% CI: -0.31 to -0.01), p = 0.036], indicating a protective effect. This finding aligns with studies conducted in developing countries, such as those at Ziauddin Medical University, Karachi, Pakistan, in 2016; Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia, in 2021; single center study in Tunisia in 2022 ((8, 9, 33). Similar associations have been observed in developed countries, as reported in the "Updates on Morbidity and Mortality outcomes" in 2020 (55), though the overall burden is generally lower due to better healthcare infrastructure and preventive measures. Low birth weight contributes to increased mortality risk by predisposing neonates to complications of NEC due to physiological immaturity, underdeveloped gastrointestinal systems, and a reduced ability to mount effective immune responses. These factors make low-birth-weight neonates particularly vulnerable to severe outcomes. Therefore, specialized neonatal care and early interventions are crucial to improving survival rates in this high-risk group. The finding emphasizes the importance of targeted management strategies for low-birth-weight infants with NEC to mitigate their heightened vulnerability and improve outcomes.

The timing of necrotizing enterocolitis (NEC) onset is a critical factor influencing its prognosis. In our study; multivariate regression analysis revealed that neonates diagnosed with NEC within the first three days of life had a 2.38 unit increase in log-odds of mortality [(β = 2.38, 95% CI: 1.30 to 3.59), p < 0.001], suggesting that early-onset NEC is highly fatal. This finding is supported with results from a study done in tertiary hospital in southwest china, Children's Hospital of Chongqing Medical University in china (56, 57) From the descriptive analysis, the mean age of NEC diagnosis was 4.8 days, which is earlier than the typical onset of NEC reported in most developed countries, where NEC in preterm infants without severe concomitant complications often occurs later, typically in the 2nd and 3rd weeks of life (58, 59). The earlier onset observed in our study suggests that neonates with early-onset NEC may be experiencing more severe forms of the disease, likely due to severe perinatal complications such as intrauterine hypoxia, sepsis, intrauterine growth restriction, metabolic complications and poor neonatal care. In developed countries, advanced prenatal care and timely perinatal interventions have reduced the incidence of severe perinatal complications, contributing to the later onset of NEC in preterm neonates (54, 56).

The presence of abdominal wall erythema was associated with a 1.35 unit increase in the log-odds of mortality [(β = 1.35, 95% CI: 0.34 to 2.43), p = 0.011], indicating a more severe disease progression. This

finding is consistent with studies conducted in both developing and developed countries, including Poland, United Kingdom, and Tunisia (42, 60, 61). The likely explanation is that abdominal wall erythema is a clinical marker of severe NEC or impending bowel perforation, both of which are strongly associated with high mortality.

A delay in initiating the first feeding was found to be significantly associated with higher mortality from necrotizing enterocolitis. Neonates whose first feeding was delayed beyond 48 hours after birth had a 2.07 unit increase in log-odds of mortality [(β = 2.07, 95% CI: 1.02 to 3.25), $p < 0.001$], highlighting the importance of early enteral feeding. This finding aligns with evidence from various studies, including a multicenter study conducted in different regions of China (2024), a systematic review of experimental and clinical studies (2021), research from a resource-restricted hospital in Cape Town, South Africa (2021), and a case-control study from the NICU of Nancy in France (2023) (24, 62-64). This is because delayed feeding hinders gut maturation, disrupts normal intestinal microbiota development, and prolongs exposure to parenteral nutrition, which increases infection risks. Timely initiation of first feeding and proper advancement, particularly with breast milk, is very important in supporting gut maturation, modulating immune responses, and reducing systemic inflammation, thereby lowering the risk of complications associated with NEC and its mortality. Breast milk is well-documented to promote intestinal growth and enhance the immune system, making it an essential intervention for improving outcomes in neonates at risk of NEC(65).

Neonates with Stage III NEC, representing severe disease with advanced complications, had significantly higher risk of mortality [(β = 1.88, 95% CI: 0.54 to 3.44), $p = 0.009$], with 1.88 unit increase in log-odds of death compared to those with Stage II. Similar findings have been reported in studies conducted at Dr. Sardjito Hospital, Yogyakarta, Indonesia (in 2021), and a retrospective cohort study in Tunisia (in 2022) (9, 33). The increased mortality in Stage III NEC is due to the critical nature of the disease, which involves severe complications such as intestinal perforation, peritonitis, systemic sepsis, multiorgan failure, and finally death (57, 66). The situation is even worse in this study setting, as well as in other similar settings, where surgical intervention; the primary option for managing such advanced stages of NEC is often unavailable.

Early clinical deterioration within 48 hours of diagnosis was significantly associated with a substantial increase in mortality risk among neonates with necrotizing enterocolitis (NEC). Neonates who experienced rapid clinical deterioration had 2.42 unit increase in log- odds of mortality compared to those who remained clinically stable during this critical period [(β = 2.42, 95% CI: 1.42 to 3.53), $p<0.001$)]. This result aligns

with findings from a retrospective study conducted at the Guangzhou Women and Children's Medical Center, China; Indonesia; USA (30, 48, 66, 67) This rapid decline is indicative of severe disease progression, overwhelming sepsis, or multi-organ failure. The high mortality risks associated with early deterioration indicates the need for close monitoring and prompts therapeutic interventions in the immediate period following NEC diagnosis. Addressing this window of vulnerability is crucial to improving survival rates.

Severe thrombocytopenia emerged as a significant predictor of mortality in this study, with neonates experiencing markedly low platelet counts had 2.02 unit increase in log-odds of death compared to those without severe thrombocytopenia [($\beta = 2.02$, 95% CI: 1.07 to 3.04), $p<0.001$). This finding aligns with prior research conducted at the University of Mississippi Medical Center (Mississippi), Chengdu Women's and Children's Central Hospital at the University of Electronic Science and Technology of China, a study in Tunisia, and a retrospective cross-sectional study in Pakistan (8, 9, 68, 69). Low platelet count is indicative of severe systemic inflammation, sepsis, or coagulopathy, all of which are common in advanced NEC. Thrombocytopenia exacerbates the risk of bleeding complications and compromises the neonate's ability to recover from severe illness.

Healthcare-Associated Infections (HAIs) in infants with NEC were found to be strongly associated with poor outcomes in this study, increasing the log-odds of mortality by 1.83 units compared to neonates without HAIs [($\beta = 1.83$, 95% CI: 0.82 to 2.89), $p<0.001$). Similar findings have been reported in studies conducted in Tunisia and Pakistan (8, 9). Neonates with NEC are particularly vulnerable to HAIs due to their immature immune systems, frequent exposure to invasive procedures (such as intravenous catheterizations, intubations, and surgical interventions), and prolonged hospital stays. HAIs further exacerbate systemic inflammation, leading to sepsis, multiorgan dysfunction, and worse clinical outcomes.

Limitations of the Study

This study had limitations that may have affected its findings. The limited follow-up period restricted the ability to assess long-term outcomes, potentially underestimating the full impact of NEC on neonatal health. Additionally, the constrained use of imaging techniques may have affected diagnostic accuracy, leading to potential misclassification of cases. Another significant limitation was the absence of surgical intervention in the studied cases, which could have influenced both patient management and overall prognosis. Future research should aim to address these limitations by incorporating extended follow-up periods, improving imaging utilization, and including surgical outcomes to enhance the comprehensiveness and applicability of findings. Although the bootstrap method demonstrated consistency with the model, the small sample size may affect the generalizability of the findings.

7. Conclusion

The NEC mortality rate in this study was 51%, which remains high compared to global reports. While it shows an improvement from previous local mortality reports, further efforts are needed to reduce it. The study identified key predictors for the mortality of neonates with NEC. Neonates who are outborn, born at a younger Gestational age, develop NEC early in the first 3 days of life, experience delayed first feeding, present with abdominal wall erythema, have Bell's clinical stage III NEC, severe thrombocytopenia, clinical deterioration within 48 hours, and hospital-acquired infections (HAI) are at high risk of mortality. The final logistic regression model used for nomogram development demonstrated strong performance in predicting NEC mortality, with an excellent calibration as evidenced by a high AUC of 95.9% and perfect calibration curve, supported by a high Hosmer-Lemenshow test p-value of 0.293. The model accounts for a significant proportion of variability in outcomes, demonstrating strong predictive accuracy, as evidenced by its R^2 value of 74%. Additionally, the model was internally validated with bootstrapping, and the Hosmer-Lemenshow test showed no significant difference between observed and expected outcomes (p-value = 0.164), confirming its robustness and reliability. bootstrapping demonstrated no significant difference between observed and expected outcomes (Hosmer-Lemenshow p-value = 0.164).

8. Recommendation

Clinicians should prioritize early identification and intervention for high-risk neonates, particularly those diagnosed within the first three days of life. Standardized feeding protocols should be strictly implemented to prevent delays in enteral nutrition, which has been associated with increased mortality. Additionally, early recognition of severe thrombocytopenia and abdominal wall erythema should prompt urgent platelet transfusion and surgical intervention, to mitigate the risk of disease progression.

Healthcare facilities, particularly neonatal intensive care units (NICUs), should ensure the practice of infection prevention strategies, Promote facility-based deliveries and strengthening neonatal transport and referral systems, integrate advanced monitoring systems to detect early clinical deterioration within 48 hours, allowing for timely escalation of care and potentially life-saving interventions including surgery.

Policymakers should prioritize the expansion of NICU capacity and the regionalization of neonatal care to enhance survival for outborn infants. Additionally, they should ensure the implementation of standardized feeding protocols to optimize the nutritional management of preterm infants.

Future researchers should focus on refining predictive models for NEC mortality by incorporating additional variables, such as molecular markers, to enhance accuracy, Validation of the current predictive model in different healthcare settings to ensure its applicability and reliability across diverse populations, Investigating the impact of surgical intervention on outcome of neonates with NEC is also crucial, with a focus on assessing its effectiveness in improving survival rates compared to medical management alone for advanced NEC.

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10. Annexes

10.1. Annex 1: Assent form (patient ID_____)

Bahir Dar University, College of Medicine and Health Sciences

Questionnaire for NEC mortality and its prognostic determinant factors among neonates admitted to TGSH and FHRH hospitals on 2024 G.C

My name is Dr Belaynew Zemed. I am conducting this research as part of the requirements for a Master's degree in Epidemiology at Bahir Dar University. I am collecting data from mothers of neonates diagnosed with NEC to assess mortality rates and its prognostic determinants. I am going to ask you some questions that are very important for my study. Your name will not be written in this form and the information you give is kept confidential and used only for this study. Your participation is completely voluntary. You may choose to skip any question or withdraw at any time without any consequences regarding your or your child's medical care. However, your willingness to answer all of the questions would be appreciated.

Do you agree to participate in this study?" ☐ Yes ☐ No

Name and Signature of Participant (Mother/Guardian): _____

Name and Signature of Data Collector: _____

Name and Signature of Supervisor: _____

Date: _____

<u>የ ስ ም ም ማ ት ቅ ፅ</u>

የ ታ ካ ሚ መ ላ ያ (ካ ር ድ) ቁ ጥ ር _____

ባ ህ ር ዳ ር ዩ ኒ ቨ ር ሲ ቲ፣ የ ሕ ክ ም ና የ ጠ ፍ ሳ ይ ን ስ ኮ ሌ ጅ

የ ጨ ቅ ላ ህ ፃ ና ት በ ከ ፍ ተ ኛ የ አ ን ጀ ት ቁ ስ ለ ት ም ክ ን ያ ት ስ ለ ሚ መ ጣ ሞ ት መ ጠ ን ና የ ት ን በ ያ ም ስ ክ ር ነ ቶ ች በ ጥ በ በ ግ ዮ ን እ ና ፈ ለ ገ ህ ይ ወ ት ሆ ስ ፒ ታ ሎ ች ወ ስ ጥ ተ ኝ ተ ው በ ሚ ታ ከ ሙ ጨ ቅ ላ ህ ፃ ና ት ላ ይ የ ሚ ከ ና ወ ን ጥ ና ት ላ ይ የ ሚ ያ ስ ፈ ል ጉ መ ረ ጃ ዎ ች ን ስ ለ መ ሳ ብ ሰ ብ፣

ስ ሜ ዶ/ር በ ላ ይ ነ ው ዘ መ ድ እ ባ ላ ለ ሁ ። ። በ ባ ህ ር ዳ ር ዩ ኒ ቨ ር ሲ ቲ፣ በ ሜ ህ በ ረ ሰ ብ ጠ ፍ ሳ ይ ን ስ፣ የ ኤ ፒ ዲ ሚ ዮ ሎ ጂ ማ ስ ተ ር ት ም ህ ር ት ም ሞ ያ የ ሚ ሆ ን የ ም ር ም ር ስ ራ እ የ ሰ ራ ሁ ነ ው ። ። የ ዚ ህ ጥ ና ት ዓ ላ ማ በ ከ ፍ ተ ኛ የ አ ን ጀ ት ቁ ስ ለ ት ም ክ ን ያ ት ስ ለ ሚ መ ጣ

የጨቅላ ህፃናት ሞት ማጠንና የትንበያ ምክክርነቶችን ማሳየት ነው። ለዚህ ጥናት በጨቅላ ህፃናት እናቶች እና በጨቅላ ህፃናት ዙሪያ አስፈላጊ የሆኑ ጥያቄዎችን እና ለጨቅላ ህፃናቶች በምርመራ የሚገኙ መረጃዎችን እሰብስባለሁ። እናንተ የምትሰጠኝ መረጃዎች ሚስጥራዊ ተደርገው ይያዛሉ። የህፃኑ ስም በዚህ ቅፅ ላይ አይፃፍም። መረጃዎቹ ለዚህ ጥናት ብቻ ይወላሉ። እርስዎ በዚህ ጥናት ለማሳተፍ ሙሉ በሙሉ የራስዎ ፈቃድ ነው። የትኛውንም ጥያቄ መልስ ሙሉረጥ ወይም በማንኛውም ጊዜ ከጥናቱ መውጣት ይችላሉ። ይህ በእርስዎ ወይም የልጆት ሕክምና ላይ ምንም ተጽዕኖ አያስከትልም። ነገር ግን፣ ሁሉንም ጥያቄዎች በመሳስ ቢተባበሩን ምክጋናችን ከፍ ያለ ነው።

በዚህ ጥናት ለማሳተፍ ፈቃደኛ ነወት?

☐ አዎ ☐ አይደለም

የተሳተፉ የእናት/አሳዳጊ ስምእና ፊርማ _____

የመረጃ ሰብሳቢ ስምእና ፊርማ _____

የመረጃ አስባስብ ተቆጣጣሪ ስምእና ፊርማ _____

ቀን: _____

10.2. Annex 2: Data collection tool (structured questionnaire and check list)

Part I: **Sociodemographic and perinatal factors**

1. Mother age in years ----------?

2. parity----------?

3. ANC follow up----------a. Yes b. no

4. Mode of Delivery---------- a. cesarean section b. SVD c. instrumental assisted

5. Place of delivery---------- a. Health center b. Hospital c. Home

6. Site of delivery----------a. Inborn b. outborn

7. Residence---------- a. urban b. rural

8. Maternal education-------a. Illiterate b. Primary c. Secondary d. Diploma e. Degree and above

9. Maternal occupation a. Housewife b. employee c. merchant

10. Household income ----------ETB

11. Age of neonate at admission to the hospital in hrs/days----------

12. Sex of neonate ---------- a. Male b. Female

13. Was there any medical /obstetric problem that the mother had been diagnosed during pregnancy / delivery? a. Yes b. No

14. If yes for question no 13, which medical/obstetric problem does the mother had?

a. Diabetes mellitus b. HIV/AIDS c. Cardiac diseases d. hypertensive disorder e. anemia f. APH g. Other --

15. Did the mother take antenatal steroid? a. Yes b. No

16. Access to NICU facility-----a. At place of delivery b. after 1 step referral c. after 2 step referral

Part II. **Clinical parameters**

17. Age of neonate at the time of diagnosis of NEC in days----------?

18. Gestational age in weeks----------?

19. Birth weight in grams----------?

20. APGAR score (1st minute…….. 5th minute……)

21. Was the newborn resuscitated at birth? a. Yes b. No

22. Was the neonate given oxygen treatment at NICU? a. Yes b. No

23. If yes for Q-22, how was mode of oxygen administration?

a. nasal cannula/catheter b. CPAP c. face mask d. mechanical ventilation

24. Number of newborns delivered? a. Singleton b. multiple

25. comorbidities----? a. Jaundice b. Perinatal Asphyxia c. Hypoglycemia d. Hypothermia e. Sepsis f. RDS g. congenital heart disease h. other specify ---------

26. Was the newborn started on enteral feeding before diagnosis of NEC? a. Yes b. No

27. If the answer is yes for Q-26, at what postnatal age was it started? ------- Days

28. What is the type of milk given? a. breast milk b. preterm formula c. Term formula

29. Which of the following symptoms and signs does the neonate have?

a. abdominal distension b. abdominal wall erythema c. GI bleeding c. apnea d. vomiting e. hypothermia e. respiratory distress

30. Bell's severity staging? a. stage-II b. stage-III (advanced stage)

31. is there any Hematologic abnormality of the neonate? a. Yes b. No

32. If the answer is yes for Q-31, which hematologic abnormalities are there?

a. thrombocytopenia b. neutropenia c. anemia d. pancytopenia

33. Degree of hematologic derangement----? a. mild b. moderate c. severe

34. Was the newborn Transfused with blood component? a. Yes b. No

35. If yes for Q-34, what blood component was transfused?

a. whole blood b. packed RBC d. platelet d. Fresh frozen plasma

36. Was the neonate diagnosed to have associated sepsis/HAI? a. Yes b. No

37. If yes for Q-36, was blood culture done? a. Yes b. No

38. If yes for Q-37, what is the result of blood culture?

a. gram positive bacteremia b. gram negative bacteremia c.no bacterial growth

39. Abdominal x-ray finding

a. pneumatosis intestinalis b. pneumoperitoneum c. air in the biliary tree d. normal e. not done

40. Abdominal u/s finding

a. intraperitoneal collection with debris b. free fluid collection without debris c. not done

Part III. Treatment related parameters

41. Was the baby on antibiotics before development of NEC?

a. Yes b. No

42. Type of management of NEC

a. medical only b. medical plus surgical with peritoneal drainage c. medical plus surgical with laparotomy

43. If the answer for Q-38 is c, was there bowel perforation? A. yes b. no

Part IV. Hospital course and outcome

44. Is there clinical deterioration from stage II to stage III NEC within 48 hrs? a. yes b.no

45. Was the neonate developed Complications? a. Yes b. No

46. If yes for Q-45, what complications were there?

a. AKI b. neonatal malnutrition c. sepsis/bacteremia d. short bowel syndrome e. stricture

f. DIC g. severe anemia g. severe thrombocytopenia h. others specify----------

47. After how many days feeding was initiated after diagnosis of NEC? ----------

48. How many days did it take to reach full feeding after feeding re-initiation? ----------

49. Final outcome of the neonate? a. died b. survived

50. Length of hospital stay before discharge or death? ----------days

Annex 3: Assurance of Investigator

...signed agree to accept responsibility for scientific, ethical and technical conduct of the research ...al for provision of required progress reports as per terms and condition of the research and ...e office of Bahir Dar University.

...he student:

...e Zerped (pediatrician and Epidemiology MSC student)

Signature

...f the advisors

...ame:-

Zelalem Anteneh (MPH & MSc in epidemiology, Assistant professor of Epidemiology)

...gnature Date 17/07/2017

Abebaw Gedif (Assistant prof. Of Biostatistics)

...ature Date 17/07/2017