2022-08-19

Time to Full Enteral Feeding and Predictors Among Very Low Birth Weight Neonates Admitted at Felege Hiwot Comprehensive Specialized Hospital, Bahir Dar City, Northwest Ethiopia.

Belay, Alemayehu

BAHIRDAR UNIVERSITY

COLLEGE OF MEDICINE AND HEALTH SCIENCES

SCHOOL OF HEALTH SCIENCES

DEPARTMENT OF PEDIATRICS AND CHILD HEALTH NURSING

TIME TO FULL ENTERAL FEEDING AND PREDICTORS AMONG VERY LOW BIRTH WEIGHT NEONATES ADMITTED AT FELEGE HIWOT COMPREHENSIVE SPECIALIZED HOSPITAL, BAHIR DAR CITY, NORTHWEST ETHIOPIA.

BY: BELAY ALEMAYEHU GETAHUN (BSC IN NEONATAL NURSE)

AUGEST, 2022

BAHIR DAR, ETHIOPIA

BAHIRDAR UNIVERSITY

COLLEGE OF MEDICINE AND HEALTH SCIENCES

SCHOOL OF HEALTH SCIENCES

DEPARTMENT OF PEDIATRICS AND CHILD HEALTH NURSING

TITLE: TIME TO FULL ENTERAL FEEDING AND PREDICTORS AMONG VERY LOW BIRTH WEIGHT NEONATES ADMITTED AT FELEGE HIWOT, BAHIR DAR CITY, NORTHWEST ETHIOPIA, 2022.

A THESIS RESULT SUBMITTED TO THE DEPARTMENT OF PEDIATRICS AND CHILD HEALTH NURSING, SCHOOL OF HEALTH SCIENCEs, COLLEGE OF MEDICINE AND HEALTH SCIENCES, IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR DEGREE OF MASTERS OF SCIENCE IN PEDIATRICS AND CHILD HEALTH NURSING

BY: BELAY ALEMAYEHU (BSc, MSc STUDENT IN PCHN)
Email: alembelay1980@gmail.com

PRINCIPAL ADVISOR: MR. HAILEMARIAM MEKONNEN (BSc, MSc, ASSIST.PROF. IN PCHN)
Email: hailemariam2129@gmail.com

CO-ADVISOR MR. SILESHI MULATU (BSc, MSc, ASSIST.PROF. IN PCHN)
Email: sileshimulatu@gmail.com

AUGEST, 2022

 BAHIR DAR, ETHIOPIA

Declaration

I’m Belay Alemayehu here by declare that to the best of my knowledge this thesis result is my own work; it has not been presented to any institution either partially or in total for any academic award or for publication. The works here in are original, where the works of others are quoted and appropriate reference has been given.

This thesis result is for partial fulfillment of degree of Master of Science in Pediatrics and Child Health Nursing of Bahir Dar University.

Investigator: Belay Alemayehu (BSc in neonatal nursing)

Signature _____ Date _____

This thesis result will be submitted with the approval of the following advisors and examiners:

APPROVAL SHEET

BAHIR DAR UNIVERSITY COLLEGE OF MEDICINE AND HEALTH SCIENCES SCHOOL OF HEALTH SCIENCES DEPARTMENT OF PEDIATRICS AND CHILD HEALTH NURSING

APPROVAL OF FINAL THESIS DOCUMENT

I hereby certify that I had advised, supervised, and evaluated this research paper which is entitled "time to full enteral feeding and predictors at Felege Hiwot Comprehensive Specialized Hospital, Bahir Dar City, Northwest Ethiopia, 2022". A retrospective follow-up study was investigated by Belay Alemayehu with my advice, guidance, and support. Hence, I approve as this thesis can be submitted as the final thesis draft for different purposes.

Advisors name:

1. Mr. Hailemariam Mekonnen (BSc, MSc, Assistant professor of pediatrics and child health nursing)

Signature ..... Date .....

2. Mr. Sileshi Mulatu (BSc, MSc, Assistant professor of pediatrics and child health nursing)

Signature ..... Date .....

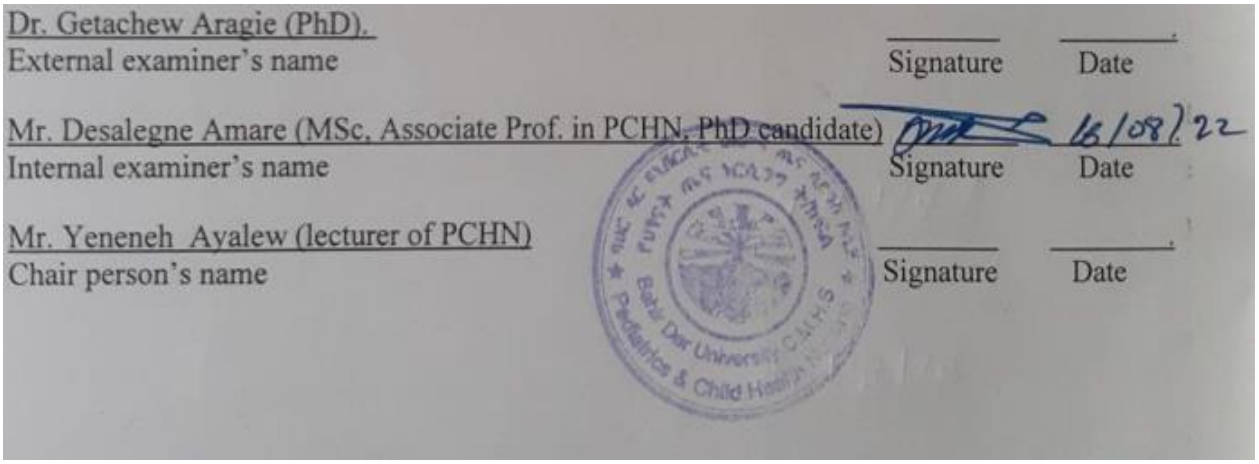
EXAMINER'S APPROVAL FORM

BAHIR DAR UNIVERSITY COLLEGE OF MEDICINE AND HEALTH SCIENCES SCHOOL OF HEALTH SCIENCES DEPARTMENT OF PEDIATRICS AND CHILD HEALTH NURSING

APPROVAL OF THESIS FOR DEFENSE RESULT

We hereby certify that we have examined this thesis entitled "time to full enteral feeding and predictors among VLBW neonates admitted at FHCSH, Bahir Dar City" by Belay Alemayehu. We recommend that thesis is approved for the degree of "Masters in Pediatrics and Child Health Nursing."

Board of examiners



Acknowledgements

First, I would like to thank Bahir Dar University College of Medicine and Health Sciences, School of Health Sciences, Department of Pediatrics and Child Health Nursing for giving me a chance to do this thesis work.

My special thanks and gratitude also go to my advisors Mr. Hailemariam Mekonnen (BSc, MSc, Assist.Prof. in PCHN) and Mr. Sileshi Mulatu (BSc, MSc, Assist. Prof. in PCHN) for their comments and guidance in the overall preparation of this paper.

I also advance my profound thanks to Felege Hiwot Comprehensive Specialized Hospital staff working at NICU, Card room and administrates for providing me access to the necessary data from their registers. And also, my special thanks go to data collectors and the supervisor for their willingness, commitment, and intensive works during data collection for the betterment of this research.

Finally, I would like to thank my wife Mrs. Eskedar Adane and my friends who supports me for the better accomplishment of this thesis work.

Table of Contents

Acronyms and Abbreviations

AGA	Appropriate for Gestational Age
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration
BSC	Bachelors Science
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
CS	Cesarian Section
FMOH	Federal Ministry of Health
HR	Hazard Ratio
ICU	Intensive Care Unit
IDR	Incidence Density Rate
INO_2	Intra Nasal Oxygen
IQR	Inter Quartile Range
KMC	Kangaroo Mother Care
MM	Mothers Milk
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
NIMV	Non-Invasive Mechanical Ventilator
PCHN	Pediatric and Child Health Nursing
PDA	Patent Ductus Arteriosus
PN	Parenteral Nutrition
PPROM	Premature Prolonged Rupture of Membrane
RDS	Respiratory Distress Syndrome
SGA	Small for Gestational Age
TFEF	Time to Full Enteral Feeding
VD	Vaginal Delivery
VLBW	Very Low Birth Weight
WHO	World Health Organization

List of Tables

List of Figures

Abstract

Introduction: Feeding is a major element of care for very low birth weight neonates. To grow and develop normally, they must have full enteral fed. Rapidly full enteral feeding conflicts with the physiologic immaturity of the gastrointestinal function with the occurrence of various comorbidities in the neonatal period. On contrast, delayed full enteral feeding also had resulted physical and neurological sequels. This requires determination of time to full enteral feeding and identification of predictors among very low birth weight neonates. However, there is limited research in the study area.

Objective: To determine time to full enteral feeding and predictors among very low birth weight neonates admitted at Felege Hiwot Comprehensive Specialized Hospital, Bahir Dar City, Northwest Ethiopia, 2022.

Methods: Institutional-retrospective follow-up-study design was conducted among 332 very low birth weight neonates admitted in Felege Hiwot Comprehensive Specialized Hospital from July 1, 2018 to June 30, 2021. Samples were selected through computer generating simple random sampling method and the data were entered into Epi data version 4.6 and then exported to STATA version 16 for analysis. Kaplan Meir with log-rank test were used to test for the presence of difference in survival among predictor variables. Model goodness-of-fit and assumptions were checked by Cox Snell residual and global test respectively. Variables with P-value < 0.25 in the bi-variable analysis were fitted to the multivariable Cox-proportional hazard model. Finally, the adjusted hazard ratio (AHR) with 95 % CI was computed and variables with a p-value less than 0.05 in the multivariable Cox-regression analysis were considered as significant predictors of time to full enteral feeding.

Result: A total of 332 neonates were followed for 2132 person-days of risk time and 167 (50.3%) of very low birth weight neonates were started full enteral feeding. The overall incidence rate of full enteral feeding was 7.8 per 100 person-day observations. The median survival time was 7 days. Very low birth weight neonates delivered from Pregnancy-induced-hypertension-free mothers (AHR: 2.1, 95% CI: 1.12, 3.94), gestational age of ≥33 weeks (AHR: 5, 95% CI: 2.29, 11.13), kangaroo mother care initiated (AHR: 1.4, 95% CI: 1.01, 2.00), avoid prefeed residual aspiration (AHR: 1.42, 95% CI: 1.002-2.03) and early enteral feeding (AHR: 1.5, 95% CI: 1.03, 2.35) were significant predictors.

Conclusion: According to this study, the time to full enteral feeding was relatively short. Neonates delivered from pregnancy-induced-hypertension-free mothers, gestational age ≥33 weeks, kangaroo mother care, prefeed residual aspiration and early enteral feeding were significant predictors.

Key words: Full enteral feeding, time to full enteral feeding, very low birth weight and neonate.

1. Introduction

1.1 Background

The World Health Organization (WHO) has defined very low birth weight neonates (VLBW) as 1000gm and less than 1500gm (1). They have few nutrient reserves at birth and are subject to physiological and metabolic stresses that increase their nutrient needs. Recommendations on nutrient requirements for VLBW neonates assume that the optimal rate of postnatal growth should be similar to that of uncompromised fetuses of an equivalent gestational age (2).

Feeding is a major element of care for VLBW neonates; nevertheless, great variability in enteral feeding practice has been reported. Adequate nutrition is essential for the optimal growth and health of very low birth weight (VLBW) neonates. Enteral nutrition is preferred to total parenteral nutrition (TPN) to avoid complications related to vascular catheterization, sepsis, adverse effects of TPN, and fasting. Reaching full enteral feeding in the shortest time is important to maintaining optimal growth and nutrition and avoiding the adverse consequences of rapid advancement of feeding. To grow and develop normally, neonates must have full enteral feed (3, 4).

Full enteral feeding (FEF) is defined as the newborn infants received 120ml to 150ml/kg/day of all their prescribed nutrition as milk feeds (either human milk or formula) and do not receive any other supplemental parenteral fluids or nutrition, and time to full enteral feeding (TFEF) is the time which neonates start to receive all of their prescribed nutrition as milk feeds (5). While starting enteral nutrition in VLBW babies, a mother's own breast milk is better tolerated than formula milk for its multiple short- and long-term health benefits (6, 7). Human milk has important anti-infective properties and there are benefits of early feeding in establishing appropriate gut flora, which help to protect the VLBW baby against necrotizing enterocolitis (NEC). The preterm formula is used only if breast milk is unavailable (4). Donor human milk also the best alternative whenever breastfeeding is impossible, or the mother's own milk is unavailable, as commonly occurs in neonatal intensive care units (NICUs) (8, 9).

Minimal enteral feeding should be started early and stopped only if there is clear evidence of feeding intolerance and gastrointestinal disease (4). Early enteral feeding strategies particularly the timing of introduction and the rate of advancement of milk feeds affect important outcomes in VLBW neonates, including nutrient intake, the risk of NEC, TFEF, growth, and development (10).

Furthermore, early enteral feeding is the best way, safer, and easier than parenteral which has biological effects with important implications for later health (on cognitive function and cardiovascular disease risk) (11, 12).

Approaches to early enteral feeding vary by the gestational age and clinical condition of the neonates(4). In most neonatal care facilities, particularly in high-income countries, the more common practice is to introduce enteral milk feeds for VLBW neonates at low volume (trophic feeds or minimal enteral nutrition) and then advance the feed volume slowly during the next one to two weeks. During this time, neonates receive most of their fluids and nutrition parenterally, usually in the form of commercially-available solutions containing amino acids, glucose, minerals, vitamins, and fats (4).

Conservative enteral feeding regimens delays gastrointestinal hormone secretion and motility which are stimulated by milk feeds, diminish the functional adaptation of the gastrointestinal tract and disrupt the patterns of microbial colonization(13). Intestinal dysmotility and dysbiosis might exacerbate feed intolerance and delay the establishment of enteral feeding independently of parenteral nutrition (13).

1.1 Statement of the Problem

To increase survival of VLBW neonates are challenging since often it needs intensive care in the neonatal period and are at increased risk of complications related to limited finances for providing parenteral nutritional (PN) support for a prolonged period. Therefore, the balance between adequate nutrition and its possible complications is critical for VLBW neonates. Early introduction and rapid achievement of full enteral feeding (FEF) is a priority in the nutritional management of VLBW neonates to reduce the need for central venous catheters, risk of infection, liver problems, persistent gut immaturity, and length of hospital stay(14, 15). And also, delay in the introduction of enteral feeding for VLBW neonate has potential disadvantages, related to the impairment of the functional adaptation of the gastrointestinal tract and disrupt the patterns of microbial colonization (13, 16).

On the other hand, intermittent feeding in VLBW is more physiological and increases protein synthesis in skeletal muscle, gastric emptying rate, and weight gain (17), and continuous feeding is more effective in transition to full enteral nutrition and in reducing the risk of hypoxic-ischemic intestinal injury (18) on the contrary, studies reporting that there is no difference between the intermittent feeding and the continuous feeding in terms of transition times to full enteral feeding (19).

Unlike the general recommendation to initiate early enteral feeding, a considerable number of the infants were kept nothing by mouth (NPO) in the first few days, receiving only maintenance fluid which increased the risk of death and the development of hypoglycemia. A study in Ethiopia showed that neonates were kept NPO 26.8% of the time they were in the hospital NICU. The percent of time the neonates were kept NPO increased with small for gestational age (SGA) and similarly, 24.9% of those who had a birth weight less than 1500 g were kept NPO for more than 3 days (20).

The need to FEF rapidly often conflicts with the physiologic immaturity of the gastrointestinal function of VLBW neonates and also with the occurrence of various comorbidities in the neonatal period (12, 21). Evidence exists that early enteral feeding strategies particularly the timing of introduction and the rate of advancement of milk feeds affect important outcomes in VLBW neonates, including nutrient intake, the risk of necrotizing enterocolitis (NEC), growth and development. Another, study showed that early introduction and progressive advancement of

enteral feeding are not associated with more NEC than slow feeding (22) but the evidence remains inconsistent (4, 23).

Even though there are potential disadvantages associated with delayed full enteral feeding in very low birth weight neonates, studies on time to full enteral feeding and predicators were limited. Early full enteral feeding faster results in earlier removal of vascular catheters, less sepsis and other catheter related complications in VLBW neonates (24). Furthermore, delayed full enteral feeding and on the contrast prolong the duration of parenteral nutrition also associated with infections and metabolic complications that increase short term and long-term morbidity and mortality, prolong hospital stay, increased the risk of early and late adverse outcomes, and adversely affect growth and development, including neurodevelopmental disabilities, respiratory, renal and cardiovascular problems, and features of the metabolic syndrome (10, 25). In order to tackle these complications and understand well, determine the time to full enteral feed and identify predictors among VLBW neonates were important. So, to prevent complications related to full enteral feeding it is better to determine the time to full enteral feeding and predictors among VLBW neonates in NICU. Therefore, the present study aims to determine the time to full enteral feeding and the role that some prenatal, neonatal, and enteral feeding predictors play in favoring the time to FEF among VLBW neonates at FHCSH of Bahir Dar City, Northwest Ethiopia.

1.2 Significance of Study

Assessing the time to full enteral feeding and predictors among Very low birth weight neonates will be relevant for different bodies especially for newborns with VLBWs, health care providers, future researchers, and policymakers.

Initially, this study is important for neonates with VLBW by providing enteral nutrition on the necessary time and decreases complications related to parenteral nutrition. Secondly, this study will use for health care professionals as a baseline information to determine when and what favors the VLBW neonates to start full enteral feeding, hence they plan appropriate interventions to reduce vascular catheterization related complications, sepsis, adverse effects of total parenteral fluids, fasting and maintaining optimal nutrition and growth.

It will be also gave direction for the hospital administrates to prepare training for the health care professionals and prepare feeding protocols for those VLBW neonates.

Lastly, it will provide evidence for the decision-makers in prioritizing the budgeting systems, training staff, and improving services, improve feeding outcome of very low birth weight neonates in public healthcare. In addition to this, it will use as a reference for other researchers in the field of study.

2. Literature Review

2.1 Time to full enteral feeding among VLBW neonates

Even though literature about the time to full enteral feeding and predictors among VLBW neonates are limited, few studies have been conducted in different parts of the world.

A retrospective follow-up study conducted at the Medical University of South Carolina in United States of America (USA) showed that 83% of VLBW neonates could achieved full enteral feeding with a median survival time of 7 days of age (26). A population-based retrospective cohort study done in North-Eastern Italy showed that 95.2% of the study participant could achieved FEF with a median survival time of 13 days of age. Among these 5.9% died during hospitalization and, of these, 18.4% died after having reached FEF (27). A combined retrospective and prospective cohort study in thirteen NICUs of five continents showed that VLBW neonates could achieve full enteral feeding with a median age of 9 days (28).

A multicenter randomized controlled trial done in the America Academy of Pediatrics showed that, full sustained, enteral feeding was achieved at an earlier age in the early group with a median age was 18 days (29).

A prospective cohort study done at China showed that the median time to full enteral feeding was 11 days (30). Among these, the median of birth weight (BW) and gestational age (GA) were 1210 and 31 weeks respectively (30). Another observational study done in the Tuscany Regional Health Service showed that the median survival time to full enteral feeding was 11 days (31).

2.2 Predictors of Time to Full Enteral Feeding

2.2.1 Prenatal Predictors

Prenatal predictors which affect the time to full enteral feedings are pregnancy-induced hypertension (PIH), chorioamnionitis, and antenatal steroids administration. Women with pre-eclampsia have a higher risk of having children born VLBW neonates with or not small for gestational age (SGA). Furthermore, infants born to pre-eclamptic mothers are at higher risk of feeding problems and increased hospital stay (32). Chorioamnionitis can also disturb fetal GI development and antenatal inflammation can impair GI function, leading to NEC (33, 34), antenatal steroids administration can influence gut permeability and the secretion of gut peptides

(35). A retrospective case-control study done at Switzerland showed that feeding problems occurred in 46% of the preeclamptic group, and 11% of the amniotic infection group. Therefore, pregnancy-induced hypertension delayed full enteral feeding by 7 to10 days (36). Another population-based retrospective follow-up study showed that maternal hypertension can delay time to FEF by 11.2%, whereas chorioamnionitis, preterm premature rupture of membrane (PPROM) and antenatal steroids administration didn't influence time to full enteral feeding (27, 30).

2.2.2 Neonatal Predictors

Mode of delivery, is defined as vaginal delivery (VD), which included spontaneous, induced and instrumental delivery, and delivery by cesarean section (CS). Infants born by CS have significantly different physiology at birth compared to those born by VD, including altered feeding and metabolism (37). Furthermore, gut flora in infants born by CS is different from that of infants born by SVD (38), and this can have implications in terms of feeding tolerance and GI function (37). A study showed that CS delivery delayed the time to full enteral feeding (TFEF) by 10.4% compared to VD (27).

A prospective cohort study done at India showed that sepsis, prematurity, respiratory distress syndrome, and APGAR score < 5 at 5 min, was a significant effects on time to full enteral feeding(30). Furthermore, sepsis took a median of 17 days to reach full enteral feeding longer than the neonates without sepsis (39). A study at Brazil showed that episodes of late-onset sepsis are more prevalent when the time to full enteral feeding exceeds 10 days (40)

A randomized clinical trial study showed that small for gestational age (SGA) is significantly prolonged the transition period from starting enteral feeding to full enteral feeding than AGA (41), on the contrary another prospective observational study conducted in Western Maharashtra showed that, SGA neonates reached full enteral feeding early (30).

A study showed that gestational age(GA) and PDA had a stronger effect on time to full enteral feeds; for each week of GA, time to full enteral feeding was reduced by 3 days and PDA increased time to FEF by 27.6% (4.2 days longer time needed to FEF than infants without PDA) (27, 42).

Another study showed that, early KMC facilitates early enteral feeding and reduced the time to full enteral feeding and other nutritional benefits in moderately ill VLBW neonates (43).

A retrospective study conducted in Bnai Zion Medical Center at Israel showed that a long time on Non-Invasive Mechanical Ventilation (NIMV) and continuous positive airway pressure (CPAP) also prolonged time to full enteral feeds (42, 44). Another study done at the Children's Hospital of Wisconsin at USA showed that a ventilation duration of >10 days led to a delay of 1.2 weeks in achieving FEF(45).

2.2.3 Enteral Feeding Practice Predictors

VLBW neonates with early introduction of enteral feeding achieved earlier full enteral feeding and reduce hospital stay (46). A Multicenter prospective cohort study done in Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network hospital study showed that, among the study participants those who started early enteral feeding (within 24 hours) could achieve full enteral feed at 4 days (47). Another hospital-based multicenter prospective study done in Ethiopia also showed that delay in enteral feeding was associated with an increased risk of death for 1 to 3 and 4 to 6 days of delay in enteral feeding, respectively. Furthermore, the length of delay in enteral feeding was associated with an increased risk of hypoglycemia (20). Another study done by multidisciplinary team showed that faster feeding advancement led to earlier full enteral feeds and decreases the time to full enteral feeding from 12.8 to 7.7 days and reduced central line utilization without significant change in NEC rate (46, 48). A meta-analysis study also showed that, slow feed advancement delayed the establishment of FEF by about 1 to 5 days (49). Furthermore, a retrospective cohort study done at the University of Alabama at Birmingham showed that a short duration of trophic feeding favors early initiation of full enteral feeding with no risk of necrotizing enterocolitis compared with a delayed duration of trophic feeding(50).

As another observational study showed that the type of feeding was a significant predictor of TFEF; among these 92% and 80% of the participants achieved FEF using any human milk and exclusive human milk respectively (31). Furthermore, enteral feeding was reached earlier in newborns who were fed human milk than fed formula, regardless of GA (31). On the contrary, a hospital-based multicenter prospective study done in Ethiopia showed that, the lowest mortality rate (15.6%) was seen in the hospital with the highest rate of preterm formula feeding (20). Evidence showed that routine prefeed gastric residue estimation leads to an increased risk of NEC (any stage) and delays the time to reach full feeds (42, 49).

2.3 Conceptual framework

The conceptual framework was developed from different comparable literature review which shows that the relationship of the outcome variable with each independent predictors through solid lines summarized as prenatal, neonatal, enteral feeding-related predictors (27, 28, 42, 43, 50, 51) (Figure: 1).

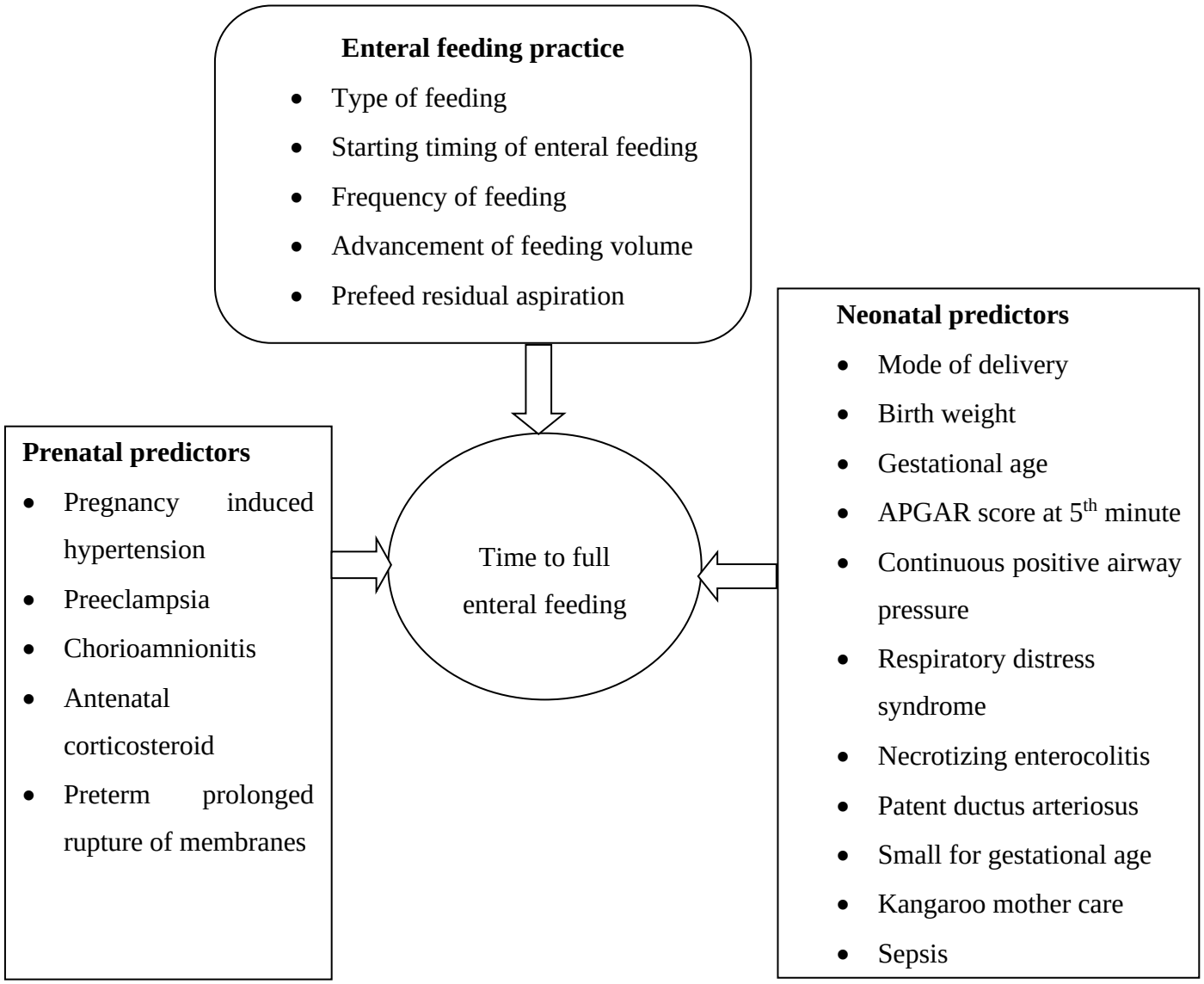


Figure 1: Schematic presentation of conceptual framework adapted after reviewing literature.

3. Objectives

3.1 General Objective

To assess time to full enteral feeding and predictors among very low birth weight neonates admitted at Felege Hiwot Comprehensive Specialized Hospital, Bahir Dar City, Northwest Ethiopia, 2022.

3.2 Specific Objectives

- To determine the time to full enteral feeding among VLBW neonates admitted at Felege Hiwot Comprehensive Specialized Hospital.
- To identify predictors associated with time to full enteral feeding among VLBW neonates admitted at Felege Hiwot Comprehensive Specialized Hospital.

4. Methods and Materials

4.1 Study area and period

The study was conducted from July 1, 2018 to June 30, 2021 and the data was extracted from May 13, 2022, to June 12, 2022, in Bahir Dar City, at Felege Hiwot Comprehensive Specialized Hospital. Bahir Dar is the capital city of Amhara regional state located in Northwest Ethiopia and 565 km away from Addis Ababa, the capital city of Ethiopia. Felege Hiwot Comprehensive Specialized Hospital is the former hospital, which was established in 1963 as a referral hospital. Now, it has 410 beds and serving for more than 5 million people. It is organized in different wards; medical ward, surgical ward, gynecology and obstetrics ward, orthopedics ward, oncology ward, pediatric ward, adult ICU, NICU, and different outpatient departments. According to the information from NICU coordinator, the ward has 71 neonatal beds with average annual admission of 2099 neonates and currently the total number of nurses, general practitioners and pediatric physicians working there are 35, 8 and 3 respectively.

4.2 Study Design

An institutional based retrospective cohort study was conducted.

4.3 Source Populations

All VLBW neonates admitted at FHCSH.

4.4 Study Population

All VLBW neonates admitted at FHCSH from July 1, 2018 to June 30, 2021.

4.5 Study Unit

Each VLBW neonate’s chart which was selected through a simple random sampling method.

4.6 Inclusion Criteria

Inclusion criteria were neonates with a body weight of 1000 to 1500 g and admitted to the NICU of FHCSH within 24 hours of birth from July 1, 2018 to June 30, 2021.

4.7 Exclusion Criteria

Exclusion criteria included gastroschisis, omphalocele, transfer to another hospital or died within 24 hours of birth and incomplete charts (if there were missing of variables; mode of delivery, starting time of enteral feeding, type of feeding, frequency of feeding, daily feeding volume advancement not included).

4.8 Study Variables

5.8.1 Dependent Variable

Time to full enteral feeding.

5.8.2 Independent Variables

Based on reviewing literature independent variables grouped into prenatal, neonatal and enteral feeding variables.

Prenatal Variables: Includes neonates delivered from mothers with pregnancy-induced hypertension (PIH), preeclampsia, chorioamnionitis, antenatal corticosteroid prophylaxis and preterm prolonged rupture of membranes (PPROM).

Neonatal Variables: Includes weight, gestational age (GA), SGA, sepsis, respiratory distress syndrome, necrotizing enterocolitis, PDA, APGAR score at the 5^{th} minutes, CPAP and KMC practice.

Enteral Feeding Variables: Includes starting time of enteral feeding or trophic feeding, type of enteral feeding (either breast milk or infant formula milk), frequency of enteral feeding, the advancing volume of feeding, and prefeed residual aspiration.

4.9 Operational Definitions and Measurement of Variables

Very low birth weight neonate: neonate birth weight is between 1000gm to 1500gm (52).

Full enteral feeding: An infant receiving a 120 to 150 mL/kg/d of either preterm formula or maternal breast milk sustained for 24 hours and does not receive any supplemental parenteral fluids or nutrition (5, 53).

Time to full enteral feeding: This is the time when neonates start to full enteral feeding up to 7 days of age after birth (5, 26).

Early enteral feeding: Introduction of enteral feeding birth up to three days of age (54).

Late enteral feeding: Introduction of enteral feeding after three days of birth (54, 55).

Slow advancement of enteral feeding: Increments of enteral feeding by 15-20ml/kg/day (26).

Faster advancement of enteral feeding: Increments of enteral feeding by 30-40ml/kg/day (26).

Survival status: Outcome of VLBW neonate either event or censored.

Event: All VLBW neonates with the outcome of FEF.

Censored: All VLBW neonates with predictors other than an event (lost follow-up, died after 24 hours of birth, not FEF over follow-up period, referred to another health facility before FEF and against medical treatment before FEF).

Survival time: It is the time from admission within 24hrs of birth to NICU up to the occurrence of an event/FEF.

Follow-up time: From the time of admission within 24hrs of birth until either an event or censorship occurs within seven days.

4.10 Sample Size Determination and Procedures

5.10.1 Sample Size Determination

The sample size was determined using the double population proportion difference formula by using predictor variable time to the initiation of enteral feeding from another study conducted in China. Time to the initiation of enteral feeding was considered a statistically significant independent predictor of time to full enteral feeding (56). By using STATA (version 16), regression slope, cox model comparing one slope to a reference value, considering these statistical assumptions; two-sided significant level (α) of 5%, power 80%, Za/2= Z value at 95 % confidence interval = 1.96, Hazard Ratio (HR) = 1.52, Survival probability of event = 0.59, the proportion of withdrawal = 10% incomplete charts with one-to-one allocation ratio of exposed to non-exposed was assumed. Finally, the total sample size was 338.

5.10.2 Sampling Technique and Procedures

Firstly, all VLBW neonates' card numbers were obtained from the NICU registration logbook. The total number of VLBW neonates who were admitted from July 1, 2018 to June 30, 2021 were 1350. All VLBW neonatal medical registration numbers were listed with a sample frame from 1 to 1350. Then study units from the sampling frame were selected by a simple random sampling technique through a computer-generating system by using statistical package for social sciences (SPSS) software (version 25). Finally, a total of 338 charts were selected.

4.11 Data Collection Tools and Procedures

Data were extracted from patient charts by using structured data collection tools adapted from previous studies as chart review checklist included by reviewing different related literature in terms of prenatal, neonatal, and enteral feeding variables (27, 28, 42, 43, 50, 51). Since the record was written in English and data collectors can read and write English, the tool was not translated into the Amharic language. The VLBW neonates' medical registration number were first obtained from the NICU ward federal ministry of health (FMOH) registration log book. After that, the required number of medical registration charts were selected by using a sampling procedure and then selected medical cards were obtained from the medical record office. The data was collected from admitted within 24 hours after birth to an event or censored occurred within the follow up period.

4.12 Data Quality Control

The data extraction checklist was adapted and structured from literature, and commented on by senior pediatricians for its consistency and completeness. Training was given to data collectors and a supervisor three days before data collection. A pretest was done on 17 VLBW neonates' cards in FHCSH two days before data collection. The data collectors were two BSc nurses and one MSc nurse working at FHCSH. Close supervisions were carried out by the supervisor during data collection time. Finally, all the collected data were checked by an investigator for their completeness, consistency and everyday data cleaning was done. Once the data was extracted from patient charts, it was coded to avoid duplication.

4.13 Data Processing and Analysis

The data were cleaned and coded by using Epi data version 4.6. Consistency of data were also checked before analysis and exported to STATA version 16 statistical software. Descriptive statistics (mean with standard deviation for normal distributions, median with the interquartile for skewed data, frequency with percentages) were computed depending on the nature of the variables, and results were presented as graphs and tables. The outcome of each participant was dichotomized into censored and event. Incidence Density Rate (IDR) was calculated for the entire study period. Kaplan Meir (KM) was used to estimating median survival time and cumulative probability of survival and a KM plot with a log-rank test were used to compare survival curves. Before performing the Cox-proportional hazard regression, model goodness-of-fit was checked by Cox Snell residuals and assumptions were checked by using Schoenfeld residual test. Those variables

with a p-value > 0.05 were entered into the model. Multicollinearity was also checked. For each independent predictor bivariable Cox proportional Hazard regression was performed. Then the variables with p-vale <0.25 were included in multivariable Cox proportional hazard regression. Adjusted hazard ratio with a 95% confidence interval and p-value <0.05 was used to measure the strength of association and considered as statistical significance predictors of time to full enteral feeding.

4.14 Ethical Consideration

Ethical approval was obtained from Bahir Dar University College of Medicine and Health Sciences Ethical Review Board with IRB number of CMHS/IRB 01-008 with protocol number of 396/2022. Then supporting officials at different levels in the hospital were communicated through legal letters taken from chief academic and research director. The collected data through papers were locked and the files of entered data in the software and final result of the study were protected with password. Confidentiality of the information was secured and the information was used only for the study purpose.

4.15 Dissemination of the Result

The result will be disseminated to Bahir Dar University, College of Medicine and Health science, school of Health Science, Department of Pediatrics and Child Health Nursing. And also, it will be submitted to Felege Hiwot Comprehensive Specialized Hospital and Amhara Health Bureau. Finally, the result will disseminate through presentations at specific conferences and through publication.

5. Results

5.1 Prenatal Information

Among VLBW neonates admitted to the NICU of FHCSH from July 1, 2018 to June 12, 2021 a total of 338 charts were reviewed. Of these, 332 medical records were included in the analysis which providing a completeness rate of 98%. From the reviewed charts, majority (93.3%) of VLBW neonates were delivered from chorioamnionitis free mothers. Among these, 51.6% could start full enteral feeding within seven days. Nearly one fourth (22%) of very low birth weight neonates were born from mothers treated with corticosteroid prophylaxis. Of them, nearly greater than half (53.4%) could start full enteral feeding within seven days of age. Among VLBW neonates delivered from PIH free mothers, 58.2% achieved full enteral feeding (Table 1).

Table 1: Prenatal predictors of time to full enteral feeding among very low birth weight neonates admitted at FHCSH, Bahir Dar City, Northwest Ethiopia, from 2018 to 2021.

Variables	Category	Outcome status				Total (332)	**%**	IDR/100 /PDO
		FEF	%	Censored	%			
ANC corticosteroid prophylaxis	No	128	49.4	131	50.57	259	78.0	7.7
	Yes	39	53.4	34	46.6	73	22.0	8.2
Preeclampsia	No	157	52.5	142	47.5	299	90.06	8.1
	Yes	10	30.3	23	69.7	33	9.94	4.7
Chorioamnionitis	No	160	51.6	150	48.4	310	93.3	7.9
	Yes	7	31.8	15	68.2	22	6.63	5.5
PIH	No	156	58.2	112	41.8	268	80.7	9.0
	Yes	11	17.2	53	82.8	64	19.3	2.7
PPROM	No	145	52.3	132	47.7	277	83.43	8.1
	Yes	22	40	33	60	55	16.57	6.1

Note: PPROM= preterm prolonged rupture of membrane, PIH= Pregnancy-induced hypertension, PDO=person day observation.

5.2 Neonatal Information

The majority (69.9%) of VLBW neonates were ≥33 weeks of gestational age. Among them, greater than two third (69.3%) could start full enteral feeding. The median weight and median GA of VLBW neonates were 1430 (IQR: 1350-1480gm) and 33 (IQR: 32-34 weeks) respectively. More than half (56.33%) of the total observations delivered through CS. Regarding KMC initiation, greater than one-third (40.36%) were initiated KMC (Table 2).

Table 2: Neonatal and clinical related information of time to FEF among VLBW neonates in NICU of FHCSH. Bahir Dar City, Northwest Ethiopia, from 2018 to 2021 (N=332).

Variables		Outcome status				Total		IDR/100 /PDO
		FEF	%	Censored	%	N=332	%	
Mode of delivery	CS	89	47.6	98	52.4	187	56.33	7.5
	SVD	78	53.8	67	46.2	145	43.67	8.1
Gestational age (weeks)	28-32	7	6.9	94	93.1	101	30.4	11.4
	33-37	160	69.3	71	30.7	231	69.6	10.5
Sepsis	No	74	53.6	64	43.4	138	41.57	8.3
	Yes	93	47.9	101	52.1	194	58.43	7.4
Respiratory distress syndrome	No	132	52.8	118	47.2	250	75.3	8.1
	Yes	35	42.7	47	57.3	82	24.7	6.7
Necrotizing enterocolitis	No	143	53.6	124	46.4	267	80.42	8.2
	Yes	24	36.9	41	63.1	65	19.58	5.8
Patent ductus arteriosus	No	160	51.1	153	49.9	313	94.28	7.9
	Yes	7	36.8	12	63.2	19	5.72	5.9
SGA	No	156	53.1	138	46.9	294	88.55	8.2
	Yes	11	28.9	27	71.1	38	11.45	4.4

Table 2 continued

APGAR score at the 5th minutes	≤5	64	43.2	84	56.8	148	44.58	6.9
	>5	103	56.0	81	44.0	184	55.42	8.5
Continuous positive airway pressure	No	105	61.8	65	38.2	170	51.2	9.5
	Yes	62	38.3	100	61.7	162	48.8	5.9
Kangaroo mother care	No	59	29.8	139	70.2	198	59.64	4.6
	Yes	108	80.6	26	19.4	134	40.36	12.3

5.3 Enteral Feeding Information

More than half (62.05%) of the participants started enteral feeding before three days of age and nearly greater than half (61.75%) were breast milk. Almost greater than one-third (43.98%) of neonates were checked prefeed residual aspiration, and more than one-third (42.47%) were fed every six hours per day (Table 3).

Table 3: Baseline Enteral Feeding Practice Information of time to FEF among VLBW neonates at FHCSH. Bahir Dar City, Northwest Ethiopia, from 2018 to 2021.

Variables		**Outcome status**				Total N=332		IDR/100/ PDO
		FEF	%	Censored	%	Frequency	%	
Feeding type	FM	59	46.5	68	53.5	127	38.25	7.3
	BM	108	52.7	97	47.3	205	61.75	8.1
Starting time of EF	>3 days	30	23.8	96	76.2	126	37.95	3.8
	≤3 days	137	66.5	69	33.5	206	62.05	10.1
Daily VA of feeding (kg/day)	10-25ml	93	46	109	54	202	60.84	7.2
	30-40ml	74	56.9	56	43.1	130	39.16	8.7

Table 3 continued

Feeding frequency	Q6hrs	78	55.3	78	46.7	141	42.47	8.8
	Q2hrs	38	40.9	55	59.1	93	28.01	6.3
	Q3hrs	51	52.0	47	48	98	29.52	7.9
Prefeed residual aspiration	No	123	66.1	63	33.9	186	56.02	10
	Yes	44	30.1	102	69.9	146	43.98	4.7

Note: EF=Enteral Feeding, Q=Every, ml=milliliter, FM= Formula Milk, BM=Breast Milk, FEF= Full Enteral Feeding, VA=Volume Advancement, IDR=Incidence Density Rate.

5.4 Survival Status of Neonates on Time to FEF

Three hundred thirty-three study participants were followed for a total of 2132 person days risk time, with a minimum of two days and a maximum of seven days observation. The mean follow-up time was 6.4 days and median follow up time was 7 IQR (6-7) days. During the follow up time 167 (50.3%) neonates were started full enteral fed. From the total study participants, 107 (32.2%) were on follow up at the end of the study period, 32(9.6%) were left against medical advice, and 26 (7.8%) were died (Figure 2). The cumulative incidence probability of starting full enteral feeding was 50.3%, among this by the end of 3, 4, 5, 6 and 7 days was 0.3, 1.2, 3.6, 8 and 38.4 respectively. The overall incidence density rate (IDR) of full enteral feeding was 7.8 per 100 (95% CI: 7) person-days. The incidence rate that VLBW neonates start FEF was 0.3, 3.8, 9.9, 53.2 per 100 person-days in the first 4, 5, 6 and 7 days after birth, respectively. The median survival time to full enteral feeding was 7 (95% CI: 7) days.

Overall outcome status of the studied VLBW neonates throughout the follow-up period

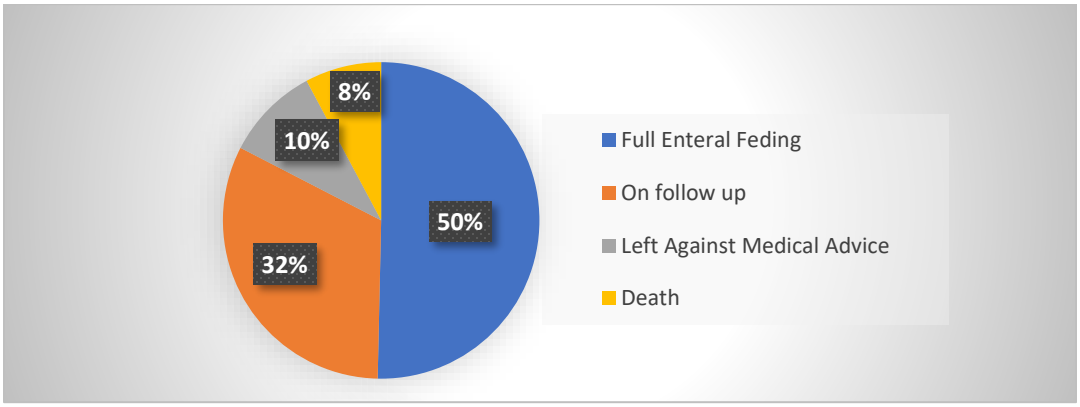


Figure 2: Outcome Status of time to FEF among VLBW neonates admitted at FHCSH, Bahir Dar City, Northwest Ethiopia, from 2018 to 2021.

The estimated cumulative survival probability of not full enteral feeding was 99.69% (95% CI: 0.9785 – 0.9996) for the first three days, 98.44% (95% CI: 0.963 – 0.9935) at the end of fourth day, 94.47% (95% CI: 0.9126 – 0.9653) at the end of fifth day, 84.87% a (95% CI: 0.8019 – 0.8852) at the end of sixth day, and 25.89% (95% CI: 0.2021 – 0.3192) at the end of seventh day of follow up period correspondingly. The finding illustrates that the overall full enteral feeding probability of very low birth weight neonates admitted in NICU of FHCSH was increasing as follow-up time increases where the highest incidence rate of time to full enteral feeding happened during the seventh day (Table 4).

Table 4: Survival probabilities FEF among VLBW neonates admitted at FHCSH, Bahir Dar City, Northwest Ethiopia, from 2018 to 2021.

Time interval	Beginning total	FEF	Censored	Cumulative survival probability	95% CI
2 - 3	332	0	2	1	..
3 - 4	330	1	5	0.9969	0.9785 - 0.9996
4 - 5	324	4	10	0.9844	0.9630 - 0.9935
5 - 6	310	12	25	0.9447	0.9126 - 0.9653
6 - 7	273	27	15	0.8487	0.8019 - 0.8852
7 - 8	231	123	108	0.2589	0.2021 - 0.3192

Note; FEF= Full Enteral Feeding.

Survival estimates of full enteral feeding among VLBW neonates admitted at FHCSH.

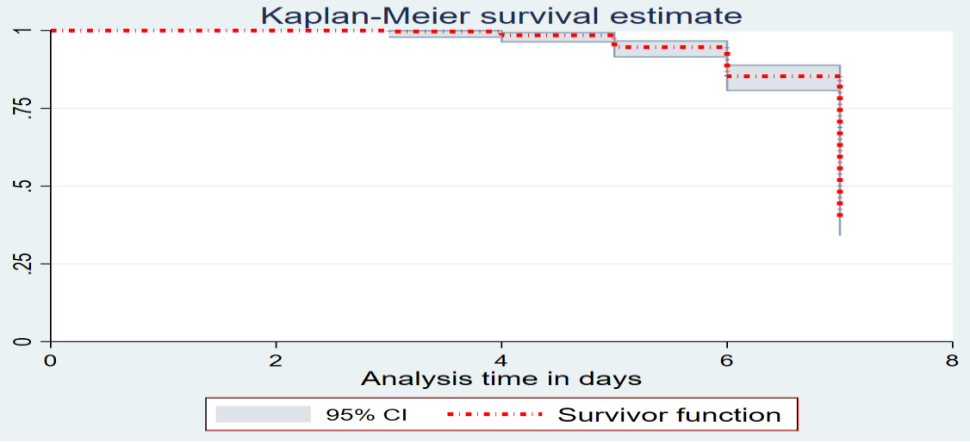


Figure 3: The Kaplan-Meier survival estimates of time to FEF among VLBW neonates admitted at FHCSH, Bahir Dar City, Northwest Ethiopia from 2018 to 2021 (N=332).

5.5 Log rank test result comparison on different categorical variables

In addition to the overall survival estimate, the survival experience of neonates with different categorical variables was executed to compare the status of FEF between groups. The statistical significance of the difference in the survival experience of FEF was checked with a log-rank test ($p < 0.05$). Even though this process is executed for all categorical variables, some of them are displayed for ease of presentation (Figure 4).

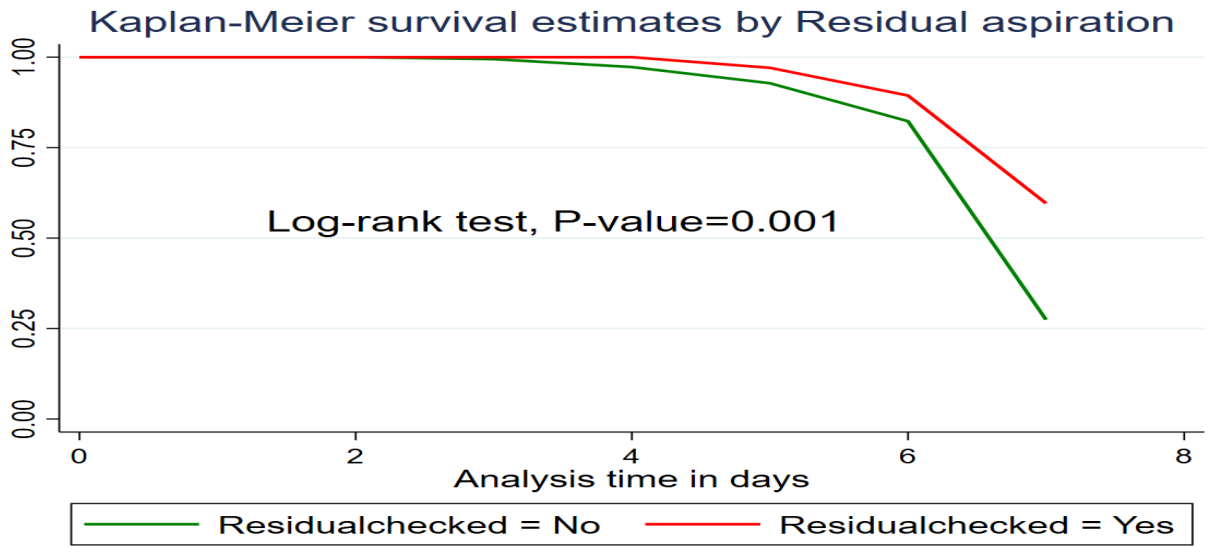


Figure 4: Kaplan-Meier survival estimate of time to full enteral feeding based on the prefeed residual aspiration of VLBW neonates admitted at FHCSH, Bahir Dar City, Northwest Ethiopia from 2018 to 2021 (N=332).

5.6 Cox-Proportional Hazard Assumption

The scaled Schoenfeld residuals proportional hazard assumption test for each variable and the overall global test were done. The p-value was > 0.05 for each individual variable as well as the overall global test (p-value = 0.6875). This indicates we fail to reject the null hypothesis; it assures that the assumption is satisfied (Table 5).

Table 5: Scaled Schoenfeld residuals proportional hazard assumption test for each variable and overall global test among Very low birth weight neonates at FHCSH, Bahir Dar City, Northwest Ethiopia from 2018 to 2021.

Predicators	rho	Chi^2	df	P-Value
Preeclampsia	0.03890	0.26	1	0.6101
Pregnancy induced hypertension	0.04911	0.42	1	0.5162
Small for gestational age	0.02716	0.13	1	0.7177
Continuous positive air way pressure	0.07933	1.13	1	0.2881
Kangaroo mother care	-0.00903	0.01	1	0.9051
Residual aspiration	0.04611	0.37	1	0.5435
Gestational age	0.11216	2.28	1	0.1313
Starting time of EF	0.09311	1.61	1	0.2043
Global test		5.64	8	0.6875

5.7 Testing the model goodness of fitness

The goodness of fit test for cox- proportional hazard regression model was done by cox -Snell residual test. The overall adequacy of the fitted model was checked by the Cox-Snell residuals were estimated based on the Kaplan–Meier estimated survivor function. This graphical plot of the cumulative hazard versus cox-Snell residuals curve follows the 45-degree line closely as we can confirm from the graph below indicates that the model fits the data (Figure 5).

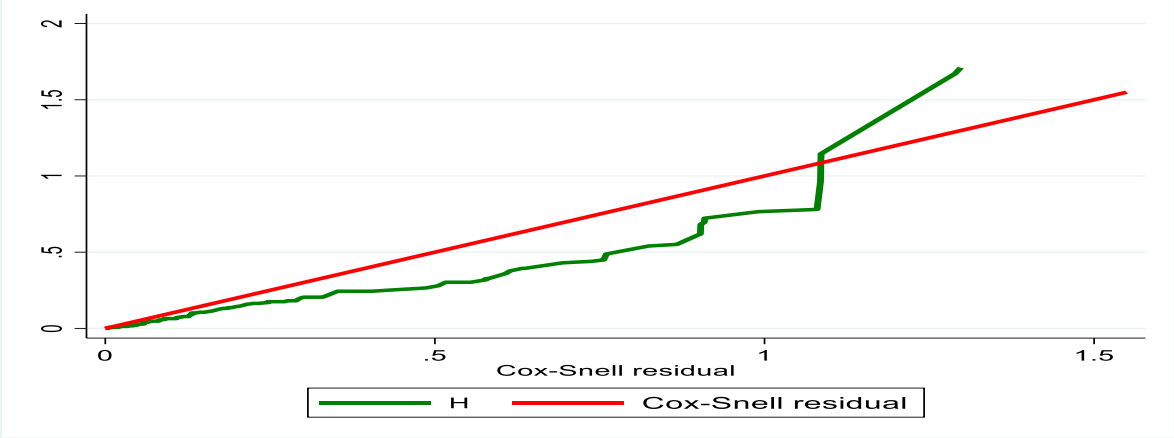


Figure 5: Cox Snell residual test to the goodness of fit of Cox proportional hazard model among Very low birth weight neonates admitted at FHCSH, Bahir Dar City, Northwest Ethiopia from 2018 to 2021 (N=332).

5.8 Predictors of Time to FEF

During bi-variable cox proportional regression analysis, the following five variables such as gestational age, pregnancy induced hypertension, initiation of KMC, avoid prefeed residual aspiration and early enteral feeding or early trophic feeding initiation were found to be significant predictors of time to full enteral feeding at 5% of the level of significance ($p<0.05$). Furthermore, other variables which have p-value of < 0.25 in the bi-variable analysis including SGA, CPAP and preeclampsia were fitted into multivariable Cox –proportional hazard model. Then, the final multivariable Cox proportional regression model had identified the following variables as statistical predictors of time to full enteral feeding. Those variables include pregnancy-induced hypertension, GA, starting time of enteral feeding, KMC practice and prefeed residual aspiration were statistically significant variable at 5% of the level of significance.

Very low birth weight neonates who were not prefeed residual aspirated were 1.4 times more likely to full enteral feeding as compared with neonates who were prefeed residual aspirated (AHR: 1.42,

95% CI: 1-2.03). Neonates with gestational age of greater than or equal 33weeks were 5 times more likely to full enteral feeding as compared with gestational age of 28-32week. (AHR: 5, 95% CI: 2.29, 11.13). Furthermore, VLBW neonates who initiated KMC were 1.4 times more likely to be full enteral fed than those who didn't initiated KMC (AHR: 1.4, 95% CI: 1.01, 2.00). With this regard, the hazard of FEF among neonates who have early enteral feeding was 1.56 time more likely as compared with neonates with late enteral feeding (AHR: 1.5, 95% CI: 1.03, 2.35). VLBW neonates delivered from PIH free mothers were 2.1 times more likely FEF as compared with VLBW neonates delivered from mothers with PIH (AHR: 2.1, 95% CI: 1.12, 3.94) (Table 6).

Table 6: Multivariable Cox regression analysis predictors of time to FEF among VLBW neonates who were admitted at FHCSH, Bahir Dar City, Northwest Ethiopia from 2018 to 2021 (N = 332).

Variables	Category	Event	censored	CHR (95% CI)	AHR (95% CI)
Preeclampsia	No	157	142	1.7(0.90-3.23)	1.19(0.65-2.28)
	Yes	10	23	1	1
Pregnancy-induced hypertension	No	156	112	3.1(1.68-5.71)	2.1(1.12-3.94) *
	Yes	11	53	1	1
Gestational age	28-32	7	94	1	1
	33-37	160	71	7.8 (3.67-16.67)	5(2.29-11.13) **
Starting time of trophic feeding	>3 days of age	30	96	1	1
	≤3 days of age	137	69	2.3 (1.58-3.48)	1.56(1.03-2.35) *
SGA	No	156	138	1.8 (1.02-3.47)	1.78(0.95- 3.33)
	Yes	11	27	1	1
CPAP	No	105	65	1.6 (1.17- 2.19)	1.20(0.87-1.65)
	Yes	62	100	1	1
KMC Practice	No	59	139	1	1
	Yes	108	26	2.6 (1.91-3.61)	1.42(1.01-2.00) *
Prefeed residual aspiration	No	123	63	1.9(1.36-2.72)	1.42(1.002-2.03) *
	Yes	44	102		

Note: * indicates p-value<0.05, ** indicates p-value≤0.001, both * and ** statistically significant variables in the multi-variable analysis, SGA=small for gestational age, CPAP=continuous positive air way pressure.

6. Discussion

This study aimed to assess the time to FEF and its predictors among VLBW neonates admitted in the study hospital. In this study, the incidence of FEF was 7.8 per 100 person days of risk time. At the end of follow-up, 50.3% (95% CI: 44.9%, 55.7%) of very low birth weight neonates were full enteral fed. Among those who started FEF, only one (0.3%) of VLBW neonates started within the first 3 days of birth. In this study, 0.3%, 1.2%, 3.6%, 8% and 37% of very low birth weight neonates started FEF at the first 4, 5, 6 and 7 days of birth, respectively. This indicates that only a small proportion of VLBW neonates started FEF within the first 7 days of birth. This finding is lower as compared to institution-based retrospective cohort study conducted in Ethiopia (63.4%) (57), Italy (95.2%) (27) and South Carolina, United States of America (83%)(26). The median survival time of full enteral feeding among VLBW neonates in this study was 7 days. The median survival time to FEF in this study was shorter when compared with a study conducted in public hospitals in Hawassa city with a median survival time of 8 days (IQR: 7-10) (57). This finding in lines with a study conducted at Kenya and Nigeria with a median of 8 (IQR 6–12) days (58), and Italy with a median time to FEF was 13 days (IQR 7-24 days) (27). On the other hand, it indicates reaching full enteral feeding earlier as compared with a cohort study done at South China median of (8-11) days (28), a retrospective cohort study in University of Alabama at Birmingham Hospital median of 11 days (IQR: 8–13)(50), in Indonesia 11 days (IQR8-21) (51), and study India median of 11 (IQR: 8–15) day(30). The difference might be due to the study population differences, study setup, study design (retrospective versus prospective), study period, follow up time, sample size difference, and socio-demographic variations, and differences in regional variation in neonatal management protocols (27, 57).

According to this study, gestational age >32weeks, pregnancy induced hypertension, early starting of enteral feeding or trophic feeding, prefeed residual aspiration, initiation of KMC were statistically significant predicators of time to full enteral feeding among very low birth weight neonates.

The hazard of full enteral feeding among very low birth weight neonates born greater than 32 weeks of gestation was 5 times more likely as compared to those born ≤32 weeks of gestation. This might be due to differences in physiological maturity among these groups of neonates on whom necrotizing enterocolitis and feeding intolerance are less common while gestational age

increases. The finding is supported by a study done on tertiary hospital NICUs in different countries that revealed the higher gestational age was the reason for full enteral feeding(4). Furthermore, a study done in Israel showed that as gestational age increased the time taken to full enteral feeding was decreased (42).

Early enteral feeding was another statistically significant predictor. The hazard of starting full enteral feeding among very low birth weight neonates with early enteral feeding was 1.5 times more likely as compared to neonates with late enteral feeding. This finding might be because of accelerate gastrointestinal physiological, endocrine and metabolic maturity and so allow infants to transition to full enteral feeding independent of parenteral nutrition more quickly(59). This finding also in line with a study that revealed early enteral or trophic feeding stimulates gastrointestinal hormone secretion and motility, decrease time to full enteral feeding. On the contrast late enteral feeding may diminish the functional adaptation of the gastrointestinal tract and disrupt the patterns of microbial colonization(59).

Likewise, in this study, VLBW neonates who initiated KMC were increased the hazard of full enteral feeding by 1.4 times as compared to with their counterparts. This finding is supported with an observational study in India, reported that kangaroo position during KMC reduces gastric residual volume, thereby improving feeding tolerance and could explain the shorten time to full enteral feeding(43). Another study conducted in Bangladesh revealed that kangaroo mother care reduced time to full enteral feeding due to early initiation of breastfeeding and increases mother to newborn bonding(60). Additionally, a guideline on very low birth weight neonates recommended that kangaroo mother care reduces time to full enteral feeding (61).

Very low birth weight neonates who were delivered from pregnancy-induced hypertension free mothers were 2.1 times more likely to full enteral feeding as compared with those very low birth weight neonates who were delivered from pregnancy induced hypertension mothers. This finding was supported with a study conducted in North-Eastern Italy revealed that maternal hypertension delayed time to FEF by 11.2%, probably because of decreased utero-placental blood perfusion, leads to small for gestational age and also provision of timely and effective care to the new born might be difficult (27). On the other hand, very low birth weight neonates borne from mothers diagnosed with maternal hypertension most likely developed NEC as a result of this time to full

enteral feeding was prolonged. And this is supported by a study conducted in Israel showed that maternal hypertension was an independent risk factor for the development of NEC in neonates of very-low-birth weight (62).

Likewise, the hazard of time to full enteral feeding among very low birth weight neonates who were not frequent prefeed residual aspirated was 1.42 times more likely as compared with their counterparts. This finding was supported with a study in Israel avoiding routine gastric residual volume evaluations contributed to earlier attainment of full enteral feeding(42), In addition a study conducted in Italy showed that avoidance of routine prefeed evaluation of gastric residuals was associated with earlier starting of full enteral feeding, shorten duration of hospitalization, and also lower incidence of late-onset sepsis(63). These results were explained by the inappropriate discontinuation of enteral feeding with subsequent delays in advancement of enteral nutrition associated with routine prefeed assessment of gastric residuals(64). Furthermore, a random control trial study in University of Florida, USA revealed that very low birth weight (VLBW) infants found that undergoing routine aspiration and evaluation of gastric residual aspiration delayed time to full feedings (150 mL/kg/d) by 6 days (65).

7. Limitation of the Study

Since the data were collected from a secondary source of medical records, other important predictors of time to full enteral feeding like availability of feeding milks, maternal and paternal sociodemographic status were not assessed.

Study design and follow up time also might affect the strengthen of this study and we recommended for the next investigators shall to study with prospective cohort.

8. Conclusions and Recommendations

8.1 Conclusions

The overall median survival time to full enteral feeding was relatively short in the study hospital. Among the studied VLBW neonates most of them were full enteral fed at the seventh day of age. Gestational age greater than or equal to 33 weeks, early trophic or early enteral feeding, kangaroo mother care practice, avoidance of prefeed residual aspiration, neonates delivered from maternal pregnancy induced hypertension free mothers were predictors found to hinder the time to full enteral feeding.

8.2 Recommendations

Based on the finding of this study, the following recommendations were forwarded to respective stakeholders.

For Health care providers

It is better to avoid check feeding intolerance via gastric tube aspiration unless it is obligatory since it is not reliable due to tube placement, shall document all thing what they did. Health care providers shall give special emphasis and close follow up regarding early initiation of feeding. They shall give special considerations for those neonates delivered from mothers who diagnosed as pregnancy induced hypertension. The last but not the least they should also strengthen and promote KMC practices for those VLBW neonates.

For Felege Hiwot Comprehensive Specialized Hospital

It is better to prepare feeding protocol for very low birth weight neonates as a unit level and close monitoring shall be facilitated on the adherence of early initiation of enteral feeding and KMC practices. Mentoring shall be promoted and facilitated regarding to time to FEF among VLBW neonates.

For Amhara Regional Health Bureau

Shall provide continuous mentorship regarding feeding practices among these VLBW neonates since they are high risk groups.

For the researchers

We recommended for the future researchers shall consider prospective studies by including different variables like availability of breast milk, maternal and paternal sociodemographic status, professional feeding practice variants among different hospitals.

References

1. Cutland CL, Lackritz EM, Mallett-Moore T, Bardají A, Chandrasekaran R, Lahariya C, et al. Low birth weight: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017;35(48Part A):6492.
2. Horbar JD, Ehrenkranz RA, Badger GJ, Edwards EM, Morrow KA, Soll RF, et al. Weight growth velocity and postnatal growth failure in infants 501 to 1500 grams: 2000–2013. Pediatrics. 2015;136(1):e84-e92.
3. Draper ES, Agostino R, Cuttini M, Zeitlin J. Approaches to supporting lactation and breastfeeding for very preterm infants in the NICU: a qualitative study in three European regions.
4. Klingenberg C, Embleton ND, Jacobs SE, O'Connell LA, Kuschel CA. Enteral feeding practices in very preterm infants: an international survey. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2012;97(1):F56-F61.
5. Nangia S, Bishnoi A, Goel A, Mandal P, Tiwari S, Saili A. Early total enteral feeding in stable very low birth weight infants: a before and after study. Journal of tropical pediatrics. 2018;64(1):24-30.
6. Underwood MA. Human milk for the premature infant. Pediatric Clinics. 2013;60(1):189-207.
7. Bernardo H, Cesar V, Organization WH. Long-term effects of breastfeeding: a systematic review. 2013.
8. Moro GE, Arslanoglu S, Bertino E, Corvaglia L, Montirosso R, Picaud J-C, et al. XII. Human milk in feeding premature infants: consensus statement. Journal of pediatric gastroenterology and nutrition. 2015;61(1):S16-S9.
9. Perrine CG, Scanlon KS. Prevalence of use of human milk in US advanced care neonatal units. Pediatrics. 2013;131(6):1066-71.
10. Embleton ND. Early nutrition and later outcomes in preterm infants. Nutrition and Growth. 2013;106:26-32.
11. Tsang R, Uauy R, Koletzko B, Zlotkin S. Nutrition of the preterm infant: scientific basis and practical guidelines. Digital Educational Publishing, Inc.; 2005.
12. Rennie JM. Rennie & Roberton's Textbook of Neonatology E-Book: Elsevier Health Sciences; 2012.

13. Embleton ND, Berrington JE, Dorling J, Ewer AK, Juszczak E, Kirby JA, et al. Mechanisms affecting the gut of preterm infants in enteral feeding trials. Frontiers in Nutrition. 2017;4:14.

14. Kandasamy Y. Infection control during administration of parenteral nutrition in preterm babies. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2009;94(1):F78-F.

15. Berseth C. Neonatal small intestinal motility: motor responses to feeding in term and preterm infants. The Journal of pediatrics. 1990;117(5):777-82.

16. Burrin DG, Stoll B. Key nutrients and growth factors for the neonatal gastrointestinal tract. Clinics in perinatology. 2002;29(1):65-96.

17. El-Kadi SW, Boutry C, Suryawan A, Gazzaneo MC, Orellana RA, Srivastava N, et al. Intermittent bolus feeding promotes greater lean growth than continuous feeding in a neonatal piglet model. The American journal of clinical nutrition. 2018;108(4):830-41.

18. Dani C, Pratesi S, Barp J. Continuous milk feeding versus intermittent bolus feeding in preterm infants. Early human development. 2013;89:S11-S2.

19. Selalmaz M, Uysal G, Zubarioglu U, Bulbul A. The Effect of Intermittent and Continuous Feeding on Growth and Discharge Time in Very Low Birth Weight Preterm Infants. The Medical Bulletin of Sisli Etfal Hospital. 2021;55(1):115.

20. Gidi NW, Mekasha A, Nigussie AK, Goldenberg RL, McClure EM, Worku B, et al. Preterm nutrition and clinical outcomes. Global Pediatric Health. 2020;7:2333794X20937851.

21. Wijaya IMS, Sukmawati M, Putra PJ, Kardana IM, Artana IWD. Nutritional status of preterm neonates at discharge in sanglah hospital. International Journal of Health Sciences. 2020;4(3):10-9.

22. Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database of Systematic Reviews. 2021(8).

23. Viswanathan S, McNelis K, Super D, Einstadter D, Groh-Wargo S, Collin M. Standardized slow enteral feeding protocol and the incidence of necrotizing enterocolitis in extremely low birth weight infants. Journal of Parenteral and enteral nutrition. 2015;39(6):644-54.

24. Salas AA, Li P, Parks K, Lal CV, Martin CR, Carlo WA. Early progressive feeding in extremely preterm infants: a randomized trial. The American journal of clinical nutrition. 2018;107(3):365-70.

25. Abitbol CL, Rodriguez MM. The long-term renal and cardiovascular consequences of prematurity. Nature Reviews Nephrology. 2012;8(5):265-74.
26. Fenin A, Newman JC, Taylor SN. Very low birth weight infants receive full enteral nutrition within 2 postnatal weeks. Journal of Perinatology. 2020;40(12):1849-56.
27. Corvaglia L, Fantini MP, Aceti A, Gibertoni D, Rucci P, Baronciani D, et al. Predictors of full enteral feeding achievement in very low birth weight infants. PloS one. 2014;9(3):e92235.
28. de Waard M, Li Y, Zhu Y, Ayede AI, Berrington J, Bloomfield FH, et al. Time to full enteral feeding for very low-birth-weight infants varies markedly among hospitals worldwide but may not be associated with incidence of necrotizing enterocolitis: The NEOMUNE-NeoNutriNet cohort study. Journal of Parenteral and enteral nutrition. 2019;43(5):658-67.
29. Leaf A, Dorling J, Kempley S, McCormick K, Mannix P, Linsell L, et al. Early or delayed enteral feeding for preterm growth-restricted infants: a randomized trial. Pediatrics. 2012;129(5):e1260-e8.
30. Patwardhan G, Soni A, Rachwani N, Kadam S, Patole S, Pandit A. Factors associated with time to full feeds in preterm very low birth weight infants. Journal of tropical pediatrics. 2018;64(6):495-500.
31. Berti E, Puglia M, Perugi S, Gagliardi L, Bosi C, Ingargiola A, et al. Feeding practices in very preterm and very low birth weight infants in an area where a network of human milk banks is in place. Frontiers in pediatrics. 2018;6:387.
32. Bertino E, Di Nicola P, Varalda A, Occhi L, Giuliani F, Coscia A. Neonatal growth charts. The Journal of Maternal-Fetal & Neonatal Medicine. 2012;25(sup1):67-9.
33. Wolfs TG, Buurman WA, Zoer B, Moonen RM, Derikx JP, Thuijls G, et al. Endotoxin induced chorioamnionitis prevents intestinal development during gestation in fetal sheep. PloS one. 2009;4(6):e5837.
34. Been JV, Lievense S, Zimmermann LJ, Kramer BW, Wolfs TG. Chorioamnionitis as a risk factor for necrotizing enterocolitis: a systematic review and meta-analysis. The Journal of pediatrics. 2013;162(2):236-42. e2.
35. Costalos C, Gounaris A, Sevastiadou S, Hatzistamatiou Z, Theodoraki M, Alexiou E, et al. The effect of antenatal corticosteroids on gut peptides of preterm infants—a matched group comparison: corticosteroids and gut development. Early human development. 2003;74(2):83-8.

36. Ersch J, Baenziger O, Bernet V, Bucher HU. Feeding problems in preterm infants of preeclamptic mothers. Journal of paediatrics and child health. 2008;44(11):651-5.
37. Hyde MJ, Mostyn A, Modi N, Kemp PR. The health implications of birth by Caesarean section. Biological Reviews. 2012;87(1):229-43.
38. Berrington JE, Stewart CJ, Embleton ND, Cummings SP. Gut microbiota in preterm infants: assessment and relevance to health and disease. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2013;98(4):F286-F90.
39. de Sousa JCS, de Carvalho AVD, Monte de Prada LdC, Marinho AP, de Lima KF, Macedo SKdO, et al. Nutritional Factors Associated with Late-Onset Sepsis in Very Low Birth Weight. Nutrients. 2022;14(1):196.
40. de Sousa JCS, de Carvalho AVD, Monte de Prada LdC, Marinho AP, de Lima KF, Macedo SKdO, et al. Nutritional Factors Associated with Late-Onset Sepsis in Very Low Birth Weight Newborns. Nutrients. 2021;14(1):196.
41. Bache M, Pizon E, Jacobs J, Vaillant M, Lecomte A. Effects of pre-feeding oral stimulation on oral feeding in preterm infants: a randomized clinical trial. Early human development. 2014;90(3):125-9.
42. Riskin A, Cohen K, Kugelman A, Toropine A, Said W, Bader D. The impact of routine evaluation of gastric residual volumes on the time to achieve full enteral feeding in preterm infants. The Journal of pediatrics. 2017;189:128-34.
43. Pandya D, Kartikeswar GAP, Patwardhan G, Kadam S, Pandit A, Patole S. Effect of early kangaroo mother care on time to full feeds in preterm infants-A prospective cohort study. Early human development. 2021;154:105312.
44. Tyagi P, Gupta N, Jain A, Upadhyay P, Puliyel J. Intra-gastric pressures in neonates receiving bubble CPAP. The Indian Journal of Pediatrics. 2015;82(2):131-5.
45. Jadcherla SR, Wang M, Vijayapal AS, Leuthner SR. Impact of prematurity and co-morbidities on feeding milestones in neonates: a retrospective study. Journal of Perinatology. 2010;30(3):201-8.
46. Arnon S, Sulam D, Konikoff F, Regev RH, Litmanovitz I, Naftali T. Very early feeding in stable small for gestational age preterm infants: a randomized clinical trial. Jornal de Pediatria (Versão em Português). 2013;89(4):388-93.

47. Brumbaugh JE, Colaizy TT, Saha S, Van Meurs KP, Das A, Walsh MC, et al. Oral feeding practices and discharge timing for moderately preterm infants. Early human development. 2018;120:46-52.
48. Chu S, Procaskey A, Tripp S, Naples M, White H, Rhein L. Quality improvement initiative to decrease time to full feeds and central line utilization among infants born less than or equal to 32 0/7 weeks through compliance with standardized feeding guidelines. Journal of Perinatology. 2019;39(8):1140-8.
49. Banait N, Basu S, Desai P, Dutta S, Kumar A, Kumar J, et al. Feeding of Low Birth Weight Neonates. Journal of Neonatology. 2020;34(1-2):28-51.
50. Salas AA, Kabani N, Travers CP, Phillips V, Ambalavanan N, Carlo WA. Short versus extended duration of trophic feeding to reduce time to achieve full enteral feeding in extremely preterm infants: an observational study. Neonatology. 2017;112(3):211-6.
51. Hendrayanti T, Ramadanti A, Indrayady I, Indra RM. Achievement of full enteral feeding using volume advancement in infants with birth weight 1,000 to< 2,000 grams. Paediatrica Indonesiana. 2020;60(4):173-7.
52. Saini N, Rahman J. Care of extremely low birth weight babies. IJAR. 2017;3(4):303-7.
53. Thoene MK, Lyden E, Anderson-Berry A. Improving Nutrition Outcomes for Infants< 1500 Grams With a Progressive, Evidenced-Based Enteral Feeding Protocol. Nutrition in Clinical Practice. 2018;33(5):647-55.
54. Abbott J, Berrington J, Boyle E, Dorling J, Embleton N, Juszczak E, et al. Early enteral feeding strategies for very preterm infants: current evidence from Cochrane reviews. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2013;98(6):F470-F2.
55. Nakubulwa C, Musiime V, Namiiro FB, Tumwine JK, Hongella C, Nyonyintono J, et al. Delayed initiation of enteral feeds is associated with postnatal growth failure among preterm infants managed at a rural hospital in Uganda. BMC pediatrics. 2020;20(1):1-9.
56. Wu T, Jiang PP, Luo P, Chen Y, Liu X, Jiang YN, et al. Availability of donor milk improves enteral feeding but has limited effect on body growth of infants with very-low birthweight: Data from a historic cohort study. Maternal & Child Nutrition. 2022:e13319.
57. Tewoldie MT, Girma M, Seid H. Determinants of time to full enteral feeding achievement among infants with birth weight 1000-2000g admitted to the neonatal intensive care unit of public

hospitals in Hawassa city, Sidama region Ethiopian, 2019: A retrospective cohort study. PloS one. 2022;17(7):e0271963.

58. Tongo OO, Olwala MA, Talbert AW, Nabwera HM, Akindolire AE, Otieno W, et al. Enteral Feeding Practices for Very Preterm and Very Low Birth Weight Infants in Nigeria and Kenya. Frontiers in pediatrics. 2022;10.

59. Stewart CJ, Nelson A, Scribbins D, Marrs ECL, Lanyon C, Perry JD, et al. Bacterial and fungal viability in the preterm gut: NEC and sepsis. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2013;98(4):F298-F303.

60. Hoque MM, Jahan N, Rahman MM, Saha LC, Akhter RJ, Chowdhury M. Effectiveness of kmc on success of breast feeding in preterm low birth weight neonate. Birth. 2017;12(30):348ns.

61. Ethiopian Neonatal Intensive care Unit Manual guideline2021.

62. Bashiri A, Zmora E, Sheiner E, Hershkovitz R, Shoham-Vardi I, Mazor M. Maternal hypertensive disorders are an independent risk factor for the development of necrotizing enterocolitis in very low birth weight infants. Fetal diagnosis and therapy. 2003;18(6):404-7.

63. Singh B, Rochow N, Chessell L, Wilson J, Cunningham K, Fusch C, et al. Gastric residual volume in feeding advancement in preterm infants (grip study): a randomized trial. The Journal of pediatrics. 2018;200:79-83. e1.

64. Khatony A, Abdi A, Karimi B, Aghaei A, Brojeni HS. The effects of position on gastric residual volume of premature infants in NICU. Italian journal of pediatrics. 2019;45(1):1-6.

65. Parker L, Torrazza RM, Li Y, Talaga E, Shuster J, Neu J. Aspiration and evaluation of gastric residuals in the NICU: state of the science. The Journal of perinatal & neonatal nursing. 2015;29(1):51.

Annex

Annex I: Information sheet for concerned Hospital administrative bodies

Good morning/afternoon

My name is Belay Alemayehu Getahun. Currently I am a Master's graduate student at Bahir Dar University, College of Medicine and Health Sciences, School of Health Sciences, Department of pediatrics and child health nursing. Now I am interesting to conduct a study on the title: -

Title of the research: Time to full enteral feeding and predicators among VLBW neonates admitted at NICU.

Name of investigator: Belay Alemayehu

Name of organization: Bahir Dar University College of Medicine and Health Sciences, School of Health Sciences, Department of Pediatrics and Child Health Nursing.

Purpose of the study: To assess time to full enteral feeding and its predictors among very low birth weight neonates admitted at FHCSH from July 1, 2018 to June 30, 2021.

Data extraction time: From May 13, to June 12, 2022 (for 1-month duration).

Study unit: Very low birth weight neonates' chart.

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

Benefits: No direct benefits for those subjects whose documents reviewed. However, results will provide knowledge for health care professionals, used to policy and decision makers for designing appropriate measures to improve their feeding protocol. So, this study will benefit indirectly for neonates admitted at FHCSH.

Annex II: Consent Form for the head of the hospital

As I mentioned above, I am working a thesis proposal submitted to Bahir Dar University, college of medicine and health sciences, school of health sciences, department of pediatrics and child health nursing, in partial fulfillment of the requirement for degree of master of science in pediatrics and chilled health nursing. I believe that the findings of this study will be used as evidence for decision making and reviewing management protocol in the NICU. So that, information necessary for the study will be taken from review of very low birth weight neonatal medical registration card. It will not harm the participant as well as confidentiality will be kept. No name and other identification will be written.

Belay Alemayehu (MSc student in pediatrics and child health nursing at Bahir Dar University College of Medicine and Health Sciences: Principal investigator
Email: alembelay1980@gmail.com

Mr. Hailemariam Mekonnen (BSc, MSc, Asist. Prof. in PCHN) at Bahir Dar university college of medicine and health sciences: Principal advisor
Email: - hailemariam2129@gmail.com

Mr. Sileshi Mulat (BSc, MSc, Asist. Prof. in PCHN) at Bahir Dar university college of medicine and health sciences: Co-advisor
Email: - silshimulatu@gmail.com

Annex III: Data Extraction Questioner

Data extraction questioner was prepared only for those variables found at neonatal chart. It incorporates prenatal, neonatal, enteral feeding predictors and outcome related information. Data collectors were BSc nurses working at FHCSH, Bahir Dar City.

Part I: Data extraction tool on Prenatal Predicator Related

No	Questions	Response	Skip
101	Did the mother receive corticosteroid therapy antenatally?	1. Yes 2. No	
102	Did the mother diagnose with preeclampsia?	1. Yes 2. No	
103	Did the mother diagnose with pregnancy induced hypertension?	1. Yes 2. No	
104	Did the mother diagnose with Chorioamnionitis?	1. Yes 2. No	
105	Did the mother diagnose with preterm prolonged rupture of membrane?	1. Yes 2. No	

Part II: Neonatal Predicator Related

No	Questions	Response	Skip
201	Birth weight	____in weeks	
202	Gestational age	____in weeks	
203	What was the current mode of delivery?	1. Vaginal 2. Cesarian Section	
204	Did the neonate diagnose with neonatal sepsis?	1. Yes 2. No	
205	Did the neonate diagnose with neonatal RDS?	1. Yes 2. No	
206	Did the neonate diagnose with neonatal PDA?	1. Yes 2. No	

207	Did the neonate diagnose with neonatal NEC?	1. Yes 2. No	
208	Did the neonate diagnose with SGA?	1. Yes 2. No	
209	what was the APGAR at 5th minutes?	_____	
210	Was the neonate on respiratory support?	1. Yes 2. No	
211	Was the neonate on CPAP?	1. Yes 2. No	
212	Was the neonate initiated KMC?	1. Yes 2. No	

Part III: Enteral Feeding Practices Related

No	Questions	Response	
301	Date of birth DD/MM/YY	_____	
302	Time of admission after birth	_____	
303	Age of neonate when start enteral feeding (trophic feeding)?	_____in days	
304	For how long the neonate stay on trophic feeding?	_____in days	
305	Type of feeding	1. Breast milk 2. Formula milk	
306	Frequency of feeding	_____	
307	What was the daily volume advancement of feeding?	_____in ml/kg/day	
308	Was the feeding residual checked before every feeding?	1. Yes 2. No	
Part IV Outcome related			
401	The outcome of the patient	1. FEF 2. On follow up 3. Death	

		4. Transfer 5. Other (specify....)	
402	Time of development of the outcome	_____DD/MM/YY	
403	Total duration of follow-up in days	_____DD/MM/YY	