
**PHARMA COLLEGE**

**SCHOOL OF PUBLIC HEALTH**

# TIME TO INITIATE TROPHIC FEEDING AND ITS PREDICTORS AMONG PRETERM NEONATES ADMITTED TO NEONATAL INTENSIVE CARE UNIT OF ADARE GENERAL HOSPITAL

**BY: SOSINA ASRAT (MD)**

**JANUARY 2025**

**HAWASSA, ETHIOPIA**

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**HAWASSA, ETHIOPIA**

**ADVISOR APPROVAL SHEET**

## PHARMA COLLEGE SCHOOL OF PUBLIC HEALTH

I, the undersigned student, declare that I have submitted my original thesis work titled **"**Time to initiate trophic feeding and its predictors among preterm neonates admitted to Neonatal Intensive Care Unit of Adare General Hospital Hawassa, Ethiopia.**"** in partial fulfillment of the requirement for the Masters of Public Health in General MPH.

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Place of submission: School of Public Health, Pharma College.

Date of Submission: _____

This thesis report work has been submitted with my approval as a college advisor.

| **Anteneh Fikrie (PhD Cand, Ass't Prof)** | _____ | _____ |
|---|---|---|
| Name of Major Advisor | Signature | Date |

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# ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| AGA | Appropriate for Gestational Age |
| AGH | Adare General Hospital |
| AHR | Adjusted Hazard Ratio |
| ANC | Ante Natal Care |
| CPAP | Continuous Positive Airway Pressure |
| GA | Gestational Age |
| HIV | Human Immuno-deficiency Virus |
| KMC | Kangaroo Mother Care |

| | |
|---|---|
| MAS | Meconium Aspiration Syndrome |
| NEC | Necrotising Enterocolitis |
| NICU | Neonatal Intensive Care Unit |
| NPO | Nill Per Os |
| PDA | Patent Ductus Arteriosus |
| PNA | Perinatal Asphyxia |
| PROM | Premature Rupture of Membrane |
| RDS | Respiratory Distress Syndrome |
| SDGs | Sustainable Development Goals |
| SGA | Small for Gestational Age |
| TF | Trophic Feeding |
| WHO | World Health Organization |

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# Abstract

**Background:** Optimal nutrition is critical for premature newborns' growth and survival, and delays in starting enteral feeding are linked to complications and death. Despite a high rate of preterm birth and mortality, little has been searched and limited data is available concerning the time to initiation of trophic feeding in preterms in Ethiopia. Therefore, this study will determine the time to initiation of trophic feeding and the predictors in the NICU of Adare General Hospital.

**Method:** A facility-based retrospective follow-up study was done among 291 preterm neonates selected using systematic random sampling from the preterms admitted to AGH from January 2021-December 2023. Data was extracted using data extraction checklist using Kobo Toolbox and then exported to Stata (version 16) for analysis. The incidence density was measured in person-hour observations. Kaplan-Meier survival curve and the log-rank test were used to estimate the survival time and compare survival curves respectively. Bi-variable Cox-regression was computed for each variable and a P-value of <0.2 was used as cut-off point to enter variables to multi-variable Cox-regression. Result of the final model is expressed in terms of AHR with 95% Confidence intervals.

**Result:** From the total of 291 preterm neonates followed 232 (79.7%) started trophic feeding. The overall incidence rate was 2.2 per 100 person hour observations and the median time to initiate trophic feeding was 34.8 (IQR: 2.5-67.6) hours. Having a birth weight of less <1500 grams (AHR: 0.48, 95% CI: 0.34, 0.69), a first minute APGAR of ≥ 7 (AHR: 2.66, 95% CI: 1.83, 3.87), having no hemodynamic instability (AHR: 2.08, 95% CI: 1.43, 3.03), no CPAP therapy (AHR: 3.82, 95% CI: 2.44, 5.99), and being born to a non PROM mother (AHR: 1.59, 95% CI: 1.08, 2.36) were found to be significant predictors of the time to initiate trophic feeding.

**Conclusion**: There was a significant delay in the initiation of trophic feeding in the study hospital. Birth weight, first minute APGAR, hemodynamic instability, CPAP and PROM were significant predictors. Therefore, it is recommended to implement a uniform standardized premature neonate feeding guideline and work on the improvement of the identified predictors.

**Keywords:** Trophic feeding, Preterm neonate, Time to initiate, Predictors

# 1. INTRODUCTION

### 1.1.Background

The World Health Organization (WHO) defines preterm birth as births before 37 completed weeks of gestation or fewer than 259 days from the first date of a woman's last menstrual period (LMP) (1). Preterm birth is categorized in to extremely preterm (less than 28 weeks), very preterm (28 to less than 32 weeks) and moderate to late preterm (32 to 37 weeks) based on gestational age (2). In 2020, 13.4 million neonates were born prematurely, with the majority (more than 60%) occurring in southern Asia and sub-Saharan Africa (3). Moreover, preterm births are the leading cause of newborn deaths, resulting in over one million deaths annually (4). In 2021, Ethiopia's preterm birth prevalence was 11.4% (5), with as high as 20.1% of mothers delivering preterm in HUCSH (6). The incidence of preterm mortality is 30% in Ethiopia (7).

Trophic feeding is the practice of supplying small volumes of enteral milk feeds (10-24 ml/kg/day) to the preterm neonate to promote the development of the immature gastrointestinal tract of the premature neonate and is not considered to contribute to nutrition (8). Alternative names include gut priming, minimal enteral nutrition (MEN) and early hypocaloric feeding (9). Optimal nutritional quantity and quality are fundamental for normal growth and development of preterm infants (10).

Preterm birth disrupts normal fetal gastrointestinal tract function, leading to intestinal villous atrophy which is even worsened by delay in enteral feeding initiation, which can be reversed with proper provision (11). Benefits of trophic feeding include improved feeding tolerance, greater postnatal growth, reduced systemic sepsis and a shorter hospital stay (12). Failure to timely provide the necessary amounts of all of the essential nutrients produces not only growth failure, but also increased morbidity and less than optimal neurodevelopment (10). Early enteral feeding should begin with trophic amounts and advanced as rapidly as tolerated, decreasing IV nutrition accordingly, while maintaining nutrient intakes at recommended rates (10). Parenteral feeding in preterm neonates can lead to risks such as starvation, growth restriction, infection, cardiac tamponade, osteopenia, metabolic disturbance, and additional expenses, compromising the overall health of the child. (13, 14).

The WHO and Ethiopian NICU management protocols recommend early mother's milk for newborns including preterm. If not available, donor human milk or formula can be used (9, 15, 16). However, optimal feeding timing is debated due to potential health complications (8, 17). Studies in African countries (18-21) and Ethiopia have documented delays in trophic feeding for preterm neonates (22-24). The WHO and national guidelines suggest early trophic feeding initiation within 24 hours of birth (8, 9, 15, 25, 26), while the American Society for Parenteral and Enteral Nutrition (ASPEN) suggests 48-72 hours (4) and as late as 4 to 5 days of birth (27). In this study, I will adhere to the latest WHO definition and recommendation, limiting trophic feeding to 24 hours as an early initiation.

Different studies have identified factors associated with a delay in the initiation of trophic feeding in preterms which include, a gestational age (GA) of less than 34 weeks, being small for

gestational age (SGA), low APGAR score at the first and fifth minutes, Cesarian delivery, presence of Perinatal asphyxia (PNA), Respiratory distress syndrome (RDS), and hemodynamic instability (22, 23, 28, 29).

Although many researches are done in the developed countries of the world, there is a significant lack of data on trophic feeding observed in lower and middle income countries including Ethiopia (30, 31). Despite the high incidence of preterm birth in Ethiopia, the time to start trophic feeding in preterm neonates is unknown in most parts of the country including Sidama region. Therefore, this study aims to determine the time to initiate trophic feeding and its predictors among preterm neonates admitted to the NICU of Adare General Hospital in Hawassa city, Sidama region, Ethiopia.

### 1.2. Statement of the problem

Premature birth poses a significant challenge in neonatal healthcare, necessitating specialized care and timely enteral feeding, which can lead to complications and increased mortality rates. Different studies in developing nations including sub-Saharan Africa reveal that there is a delay in the initiation of enteral feeding in preterm neonates in the NICUs (13, 17, 20-24, 32). With as high as 76 % of the neonates not starting feeding in the first 24 hours of birth and 22% of them in the 72 hours after birth and the infants were kept NPO 26.8% of the time they were in the hospital NICU (33). And another study found that as high as 80-90% of neonates did not start trophic feeding until 48 hours of birth (13).

Preterm infants experience a nutritional emergency due to the sudden transition from in-utero to extra-uterine life, leading to short and long-term complicatons (19). Delayed enteral feeding initiation increases the risk of feeding intolerance, hypoglycemia, infections, hospitalization, and additional healthcare expenses (18, 19, 32-36). Malnutrition and neurodevelopmental delay are common, with a 20% prevalence (19, 37). They have an increased risk of mortality ranging from 2 to 5 fold (33). Preterms also face chronic disorders (4, 38).

The field of preterm neonatal feeding is a contentious area with varying practices among neonatologists and pediatricians (8, 17, 39). There is no consensus on the duration or method of

trophic feeding, and many studies challenge the assumption that early initiation can cause feeding intolerance, spontaneous intestinal perforation, and necrotizing enterocolitis (NEC) (18, 27, 32, 34, 40, 41). At the international level, a group of neonatologists, pediatricians, and nutrition experts had many times convened to discuss and framed evidence-based recommendations and interventions for optimizing nutrition in preterm low birth weight (LBW) infants (4). The Sustainable Development Goals (SDGs) also aims to reduce global neonatal mortality rates to 12 per 1,000 live births by 2030 and the WHO has set standards to enhance the quality of maternal and neonatal care (42).

Eventhough some efforts are being exerted to minimize neonatal morbidity and mortality earlier through the adoption of the Millenium Development Goals (MDGs) and currently the SDG and the HSTP (Health Service Transformation Plan) aligning with the SDG , the neonatal mortality in Ethiopia did not show improvement as expected (42-45). With the high rate of preterm birth and the associated high neonatal mortality (33/1000 live births) and complications of preterm birth in Ethiopia, focus on interventions for optimizing the nutrition of the preterm neonate is not yet well emphasized (44).

In Ethiopia, there are gaps in the availability of guidelines and protocols, specifically targeting preterm and low birth weight newborn care. Evidences concerning optimal nutrition of the preterm neonate, the time of initiation of trophic feeding and specifically the risk factors are lacking. Identifying those factors associated with the delay in initiation will immensely help in tackling the problem at hand and for setting evidence based, universally accepted, agreed up on and utilized national guideline (31, 32).

Despite the critical role of trophic feeding, limited data exists on the factors influencing the timing of its initiation in Ethiopia. Moreover, the majority of the international recommendations do not stem from developing country data, which emphasizes the need for more and in depth researches and studies in this field of interest (30, 31). Therefore, this study aims at filling this gap by determining the time to initiate trophic feeding and its predictors among preterms admitted to the NICU of AGH in Hawassa city. The findings from this research hold the

potential to significantly improve feeding practices in Hawassa's NICUs, ultimately leading to better clinical outcomes and potentially saving countless premature lives.

### 1.3. Significance of the study

The evidence base informing feeding of preterm neonates in resource-limited settings in sub-Saharan Africa including Ethiopia is extremely limited (31, 34, 37) and pragmatic studies are needed to generate evidence to guide management and improve outcomes for these highly vulnerable infants (30).

The study findings will be helpful for the study hospital to know and assess their practices towards preterm neonatal nutrition, compare and conform their practice in accordance with the mostly accepted recommendations.

More importantly, the findings of this study will lead to evidence based practices among health care workers and health institutions which in turn, help in reducing the high rate of complications and mortality among the preterm neonates by developing a relevant and evidence based national feeding guideline for preterm neonates in collaboration with regional health bureau (RHB), the Federal Ministry of Health (FMOH), different non-governmental organizations (NGOs) and international organizations.

This study will also contribute for administrators and policy makers to prioritize and target these problems while health service planning by developing interventions to tackle the issue from the roots by bringing the problem in to the light.

The finding of this study can be used as a source of data and standing point for other researchers to understand the feeding practices of preterm neonates regarding the time to initiate trophic feeding and the predictors and more researches to be studied in here and other parts of the country as well.

# 2. LITERATURE REVIEW

## 2.1. Time to initiate trophic feeding among preterm neonates

There is a worldwide variability in the time of initiation of minimal enteral feeding. An observational study done in Italy found that, 74.1% of the neonates were started trophic feeding within the first postnatal day (46). In another observational study done in 15 hospitals in the East of England, only 5 neonatal units started enteral feeds within 24 hours after birth, two of the neonatal units delayed enteral feeding until day 7, and the remainder introduced enteral feeding between 48 hours and up to 5 days after birth (47). And another study found that as high as 80-90% of neonates did not start trophic feeding until 48 hours of birth (13).

The median time to the first enteral feeding was found to be 1 day in a study done in New Zealand (48). A Portuguese retrospective cohort study found that 97% of preterm neonates were initiated on enteral feeding within 72 hours, with a median time of 3 days for minimal EF (49). In another multicenter web based study done in hospitals in Spain, enteral feeding was initiated within 24 hours of birth in 65% of the units (50).

In a cohort study done in Iran, only 27% of the neonates were started on enteral feeding within the first post natal day and 73% were initiated on enteral feeds within 48 hours after birth. And 15% of them were not initiated on enteral feeding until fifth post natal day (35). A multicenter prospective study done in China, the median time of initiating enteral nutrition in preterm neonates was 23 hours (34). In another prospective follow up study done in Jordan, the mean age of starting trophic feeding was 72 hours after birth (51).

In a multicenter observational study done in Africa, the median time to first feed was 46 hours of life (21). In another cross-sectional survey conducted among pediatricians and neonatologists in Nigeria and Kenya, only 48% of the neonates were initiated on breast milk feeding within 24 hours postnatally (20). A retrospective cohort study done in Uganda found out that enteral feeding was initiated within the first 48 h in 80.1% of these preterm infants (19). Another observational study done in South Africa only 30.8% of the preterm neonates were initiated on enteral feeding in the first day postnatally (52).

In a multicenter prospective study done in Ethiopia, 76 % of preterm neonates were kept NPO for the first 24 hours after birth and 22% didn't commence enteral feeds for 72 hours after birth. And the neonates were kept NPO 26.8% of the time they were admitted in the NICUs (22). In another prospective study done in Ethiopia, 85% of the neonates were initiated on enteral feeding and only 24.3% of the neonates were initiated in the first 24 hours after birth and 77.8% were initiated by the end of 72 hours. The median time of initiation was found to be 41 hours (23).

A multicenter study done in Northwestern Ethiopia found out that 90.95% of the neonates were started on TF. The median time for initiation was found to be 42 hours after birth. Trophic feeding was initiated in 22%, 53.8%, and 72.74% of the neonates by the end of 24, 48, and 72 hours respectively and the overall incidence of starting trophic feeding was 2 per 100 person-hours observations (22). Another retrospective cohort study done in the Sidama region of Ethiopia, the mean age when an enteral feed (trophic feeding) was first commenced was 2.13 days (24).

## 2.2. Predictors of time to initiate trophic feeding in preterm neonates

### 2.2.1. Neonatal related factors

Different studies are done worldwide to determine the predictor factors for the tme to initiate enteral feeding. Many researchers found that a GA below 34 weeks was found to be a significant predictor of longer time to initiation of enteral feeding (21-24, 28, 29, 48, 53-57). The percent of time the infants were kept NPO increased with lower GA (33). In a cohort study done in Ethiopia, GA reduced the time to enteral feeding by 18.8% for each additional week of gestation (24). And in a cross-sectional web-based survey done South Africa, the proportions of commencing feeds within the first day were found to be 24% in neonates with <25 weeks' gestational age, 36% in neonates with 25-27 weeks, and 65% in neonates with 28-31 weeks of GA (54).

Many studies proved that there is an inverse relation between birth weight or weight for gestatioal age and postnatal age at which enteral feeding was initiated (24, 29, 33, 48, 55-61). Another study done in Ethiopia found that 24.9% of preterm neonate with a birth weight of less than 1500 g were kept NPO for more than 72 hours compared to 13.2% of preterms who weighed greater than 1500 g (33). In a retrospective cohort study done in Sidama region, time to achieve enteral feeding was found to be shorter by 70.4% in neonates were SGA, as compared with that appropriate for gestational age (AGA) (24)

Different researchers found that low APGAR score (< seven) at the first and fifth minute, being diagnosed with PNA, presence of RDS and hemodynamic instabiliy were found to be significant predictors of delay in initiation enteral feeding (21-23, 57, 62). Diagnosis with late onset neonatal sepsis (LOS) is also proved to be a significant predictor of the time to initiate trophic feeding in different studies (49, 57, 63). Moreover, diagnosis of hospital acquired infection and being on antibiotics were also found to be associated with the time for enteral feeding initiation in a prospective cohort study done in Ethiopia (58).

Many researches undergone on the attainment of feeding milestones including commencment of enteral feeding showed significant delay in infants with medical complications, including NEC (21, 28, 59) and bronchopulmonary dysplasia (BPD) (28, 56, 59, 61). And an inverse correlation

was found between a diagnosis of patent ductus arteriosus (PDA) and the time to start enteral feeding in preterm neonates in different studies (28, 29, 49, 55, 57, 59). A population-based retrospective cohort study done in Italy showed that newborns with PDA took a median time which is 4.2 days longer compared to those without PDA to achieve full enteral feeds (29).

In a retrospective study done in Portugal, requirement of ventilatory support was associated with a longer time to achieve enteral feeding initiation (49). A delay in initiation of TF was found in preterm neonates on CPAP in a retrospective study done in the USA (64). A positive correlation was also found between the days of oxygen requirement and the length of time needed to initiate feeding in an observational retrospective study done in Spain (55). In one study, duration of respiratory support and age at which respiratory support was stopped were found to be positively related with the time to initiate feeding (60). A requirement of non-invasive ventilation ≤3 days was associated with early commencement of enteral feeding in preterm neonates in a retrospective study done in Turkiye (56). Researchers showed that preterm neonates who received red blood cells transfusion were also found to have a late initiation of trophic feeding (49, 55). A diagnosis of apnea of prematurity (49), retinopathy of prematurity (55) and altered umbilical flow (62) were associated with a delay in initiation of enteral feeding. Preterm neonates who needed gastrointestinal surgical procedures were also found to have a higher postmenstrual age at achievement initiating enteral feedings (61).

### 2.2.2. Maternal related factors

Maternal related predictors for the time to initiate trophic feeding are usually broadly classified in to socio-demographic (age, place of residence, level of education) and obstetric and medical (parity, place of delivery, mode of delivery, pre-pregnancy body mass index (BMI), premature rupture of membranes, Chorioamnionitis, preeclampsia, anemia and HIV/AIDS). (18, 20, 22, 23, 29, 65).

Different studies show that Cesarean section delivery and out born deliveries (delivery out of the study hospitals) to be significant predictors of the time to initiate trophic feeding among preterm neonates (22, 23, 58). In the prospective study done in Ethiopia, a preterm neonate born with a

cesarean section was found to be 53% less likely to initiate trophic feeding as compared to those delivered vaginally (23). In the similar study done in the northern Ethiopia, preterms born with cesarean section were 31% less likely to start trophic feeding than that of spontaneous vaginal delivery and neonates who were not born within the study hospitals, were 47% less likely to start trophic feeding than those who were born within the study hospitals (22).

In a retrospective cohort study done in Italy, maternal hypertention was found to be a significant predictor of the time to initiate minimal enteral feeding in preterm neonates (29). And another study found that maternal educational level was also a predictor factor for the initiation of enteral feeds in preterm neonates (58).

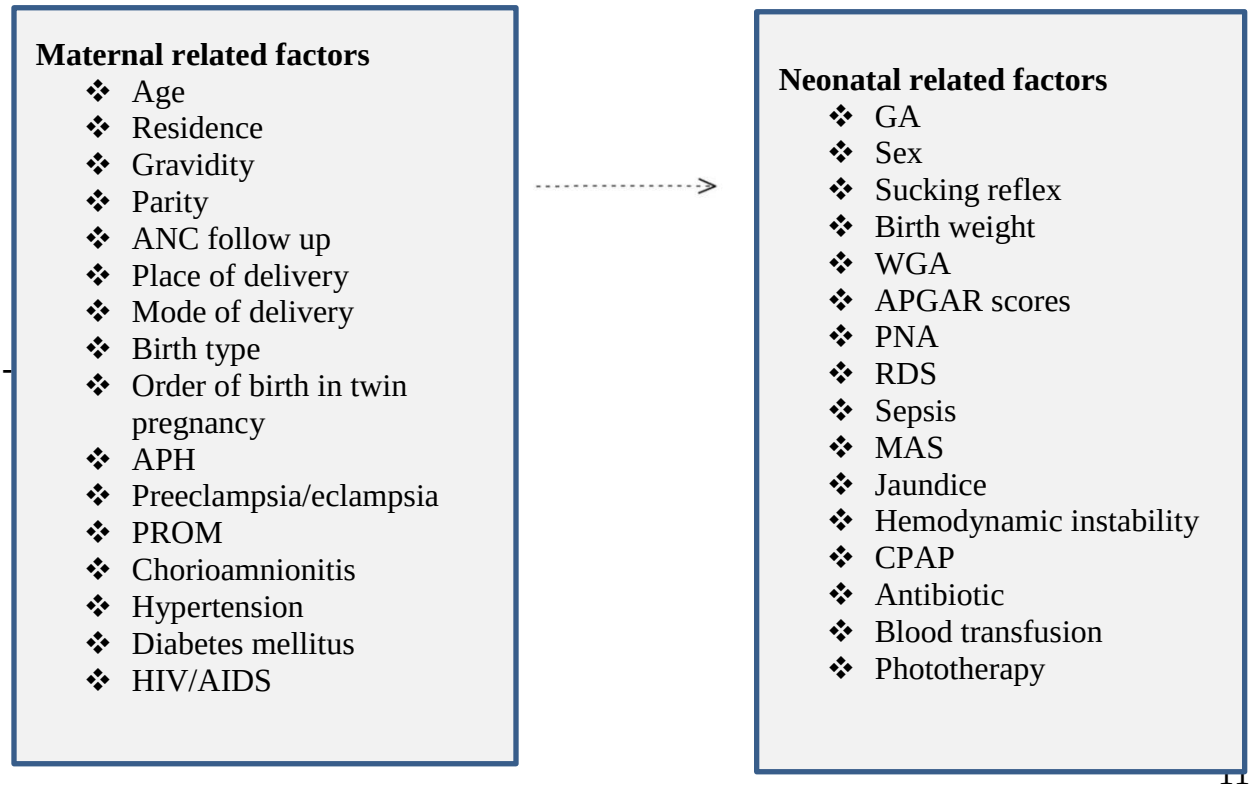
### 2.2.3. Service related factors

Health service related factors to the time of initiation of trophic feeding include, Kangaroo mother care (KMC) provision, level of hospitals, type of milk provided and frequency of order revision (9, 16, 28, 58, 63). Many researches showed that preterm neonates who received KMC had a significantly shorter time to the initiation of enteral feeding (56, 61, 63, 66, 67). In an experimental randomized trial done in Turkiye, the time to start enteral feeding was significantly shorter, and feeding intolerance was experienced significantly less in the preterm neonates on a KMC (67).

Different studies found that well equipped level III hospitals with specialized NICUs, routine gastric residual evaluation and convenient NICU (hospital) location were significant predictors of a shorter time to initiate trophic feeding (16, 48, 58).

In a longitudinal randomized study done in North Carolina, the type of milk provided for the preterm neonates was found to be a significant covariate, suggesting that infants fed with breast milk achieved earlier enteral feed initiation than formula-fed infants (28). Another retrospective cohort study done in Italy also found that exclusive formula feeding was associated with delayed initiation of enteral feeding (29).

### 2.3. Conceptual framework



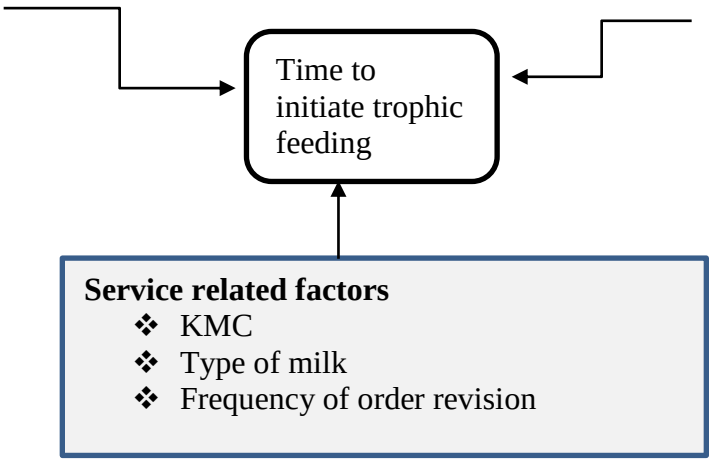



**Figure 1:** A conceptual framework for the study of time to initiate trophic feeding and its predictors among preterm neonates admitted to the NICU of AGH, January 2021- December 2023.

**Source**: Adapted from different literature reviews (16, 20-24, 28, 29, 49, 57, 58, 63).

# 3. OBJECTIVES

### 3.1.General objective

- To determine the time to initiate trophic feeding and its predictors among preterm neonates admitted to the NICU of Adare General Hospital from January 2021- December 2023.

### 3.2.Specific objectives

- To determine the time to initiate trophic feeding among preterm neonates admitted to the NICU of Adare General Hospital from January 2021- December 2023.
- To determine the incidence of trophic feeding initiation among preterm neonates admitted to NICU of Adare General Hospital from January 2021- December 2023.

- To identify predictors of time to initiate trophic feeding among preterm neonates admitted to the NICU of Adare General Hospital from January 2021- December 2023.

# 4. METHODS AND MATERIALS

## 4.1 Study area and period

The study was conducted in Hawassa city, Sidama regional state, Ethiopia. Hawassa is a city in the Great Rift valley of Central Ethiopia with a total area of 157 sq.km and 273 km south of the capital, Addis Ababa with a latitude and longitude of 7°3'N, 38°28'E. The city has four public hospitals (One comprehensive specialized hospital, one general hospital and two primary hospitals), six private hospitals, seven health centers, forty seven private clinics and fifteen health posts.

Adare General Hospital (AGH) was established in 1982 as a health center and has been serving as a general hospital since 2016. It receives referral patients from Hawassa town and nearby zones. The hospital provides services such as outpatient, emergency, inpatient, laboratory, radiology and dental services. Has a total of 444 health care workers and 125 supporting staff. The NICU of the hospital has 18 beds which give service under the pediatrics department. The NICU has three pediatrician specialists. The hospital has 65 and 780 monthly and annual

admissions to the NICU as of the 2015 EFY report, respectively. And of these admissions, 18 and 210 are monthly and annual admissions of preterm neonates respectively.

The study was conducted from September 15-30, 2024.

### 4.2. Study design

A facility based retrospective followup study was conducted among preterm neonates admitted to the NICU of Adare General Hospital from January 2021- December 2023.

### 4.3. Population

#### 4.3.1. Source population

All preterm neonates admitted to the NICU of AGH.

#### 4.3.2. Study population

All preterm neonates that were admitted to NICU of AGH from January 2021 - December 2023.

### 4.4. Eligibility criteria

#### 4.4.1. Inclusion criteria

All preterm neonates that were registered and admitted within 24 hours of birth at the NICU of AGH from January 2021 - December 2023 were included.

#### 4.4.2. Exclusion criteria

Preterm neonates' charts which were incomplete, neonates who were started on enteral feeding (direct breast milk or other form) at home or referring facilities before the admission, pre-diagnosed stage II/III necrotizing enterocolitis, those with congenital anomalies interfering with feeding, unknown gestational age, unknown APGAR score and unknown birth weight were excluded from this study.

### 4.5. Sample size determination

The sample size was determined by Stata version 16 using the log rank test by using weight for gestational age as an exposure variable with AHR = 0.7 from a previous study (24) and considering these statistical assumptions; two-sided significance level (α) of 5%, power 80%, a 1:1 ratio of exposed (SGA) to non-exposed (AGA) and the proportion of withdrawal = 0.2. A sample size of 316 was attained and utilized for the study (Table 1).

### 4.6. Sampling technique and procedure

The total number of preterm neonate admission to the hospital from January 2021 - December 2023 was 783. Out of these 51 were excluded from registry book revision. And there were 94 pairs of twins and only one of the sets of twins was selected using simple random sampling (lottery method) which made the sample size to be 638. Systematic random sampling was utilized to select the study population. The sampling interval was calculated by dividing 638 by the sample size (n) calculated (316). A sampling interval (k) of 2 was utilized. The sampling frame was the hospital's registry for NICU admissions (Figure 2).

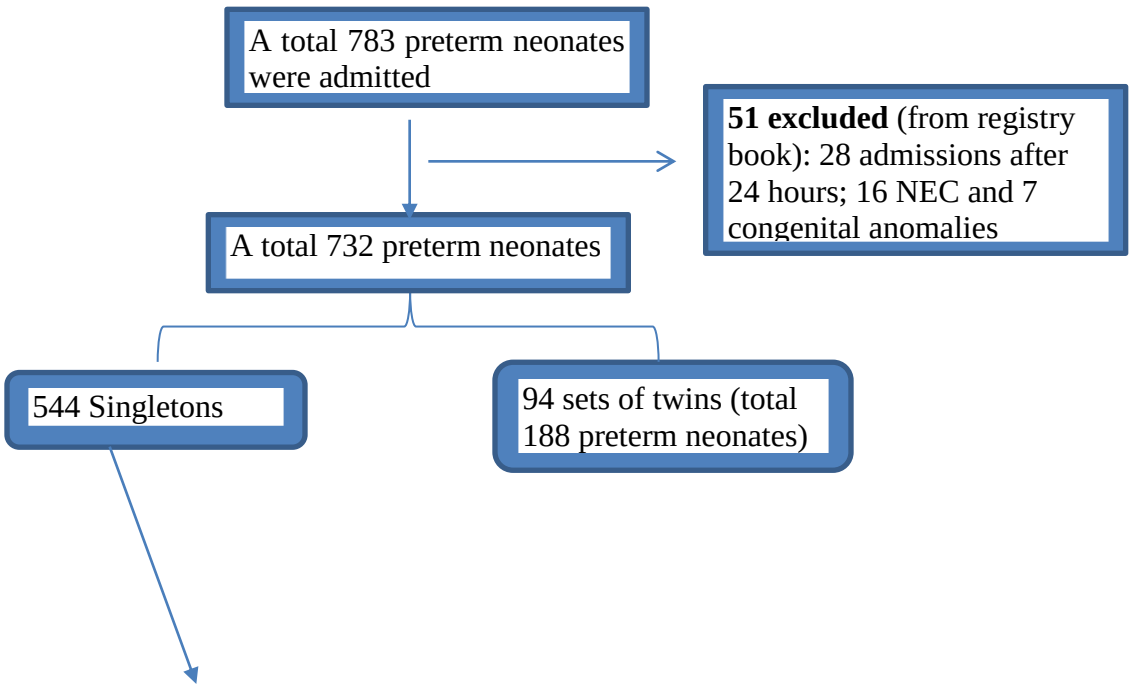
**Table 1:** Sample size determination for the time to initiate trophic feeding and its predictors among preterm neonates admitted to NICU of AGH from January 2021-December 2023.

| **Variables** | **Event** | **AHR** | **Sample size after 20% adjustment for incomplete charts** | **Reference** |
|---|---|---|---|---|
| Gestational age | 58 | 0.54 | 72 | (23) |
| Weight for gestational age | 253 | 0.296 | **316** | (24) |
| First minute APGAR | 126 | 0.4 | 158 | (23) |
| Hemodynamic instability | 153 | 0.37 | 192 | (22) |
| RDS | 71 | 0.5 | 90 | (22) |
| CS delivery | 84 | 0.47 | 104 | (23) |

### 4.7. Data extraction tool and procedure

A data extraction checklist was adapted from different literatures (18, 20, 22, 23, 29, 65). Data was extracted using Kobo Toolbox by recruiting six data extractors who had atleast one data extraction experience and good communication skills. Out of the six recruited 2 (1 at each site) of them were supervisors (BSc degree in health science related field) and 4 (2 at each site) of them were data extractors (diploma graduates in health related field). Time to initiate trophic feeding was the outcome variable of this study and was determined by subtracting the date and time of birth from the date and time of first trophic feeding.

The data extraction checklist included maternal related factors (age of the mother, place of residence, ANC followup, number of ANC visits, gravidity, parity, mode of delivery, birth type, order of twin pregnancy, place of delivery, PROM, Chorioamnionitis, preeclampsia/eclampsia, APH, HIV, anemia and diabetes mellitus), neonatal (date and time of birth, date and time of first trophic feeding, GA, birth weight, first and fifth minutes APGAR score, suckling reflex, PNA, being on CPAP, being on antibiotics, hemodynamic instabilities, RDS, PDA, MAS, blood transfusion, phototherapy) and health service- related factors (KMC, milk type and frequency of order revision).



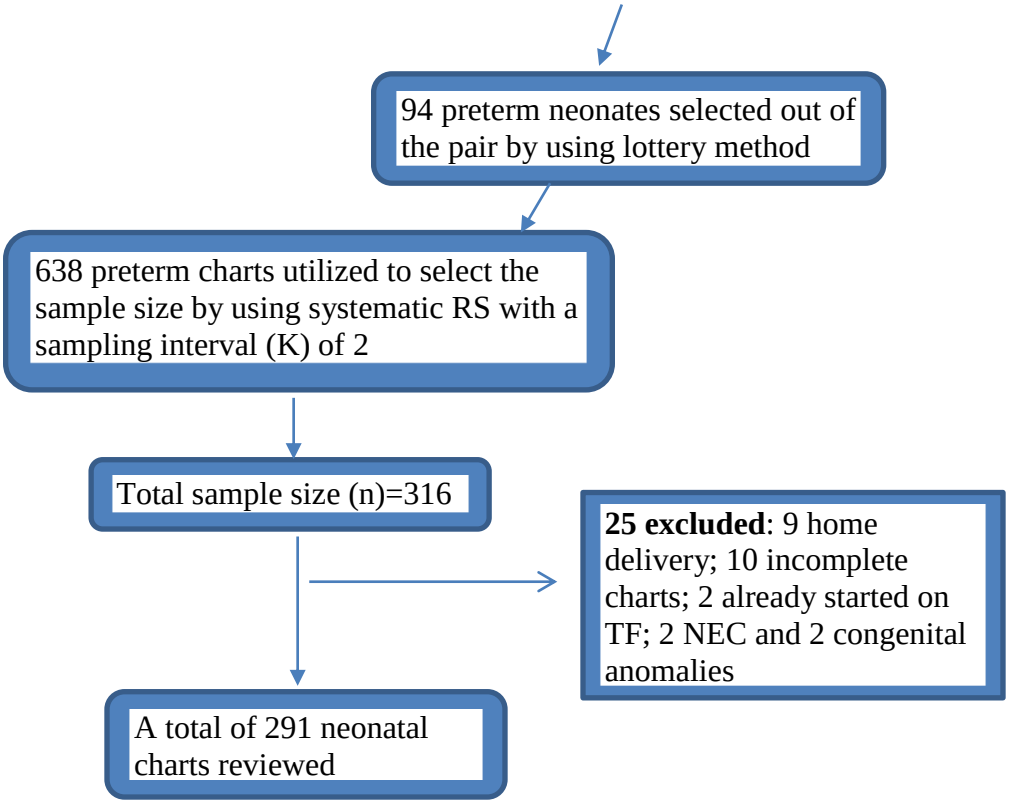



**Figure 2:** Sampling procedure and techniques utilized to determine the time to initiate trophic feeding and its predictors among preterm neonates admitted to the NICU of AGH from January 2021- December 2023.

### 4.8. Study variables

#### 4.8.1. Dependent variable

Time to initiate trophic feeding was our dependent variable.

#### 4.8.2. Independent variables

**Neonatal related factors:** Sex, gestational age, birth weight, First minute APGAR score, Fifth minute APGAR score, sucking reflex, weight for gestational age, PNA, RDS, being on CPAP, being on antibiotics, being on phototherapy, MAS, hypothermia, hemodynamic instability, jaundice, blood transfusion and sepsis.

**Maternal related factors:** Age, place of residence, parity, gravidity, ANC follow up, number of ANC visits, mode of delivery, place of delivery, birth type, order of birth in twin pregnancy, preeclampsia/eclampsia, chorioamnionitis, PROM, APH, hypertension, sero status for HIV, anemia and diabetes mellitus.

**Service related factors:** Kangaroo mother care, milk type and frequency of order revision.

### 4.9. Operational definitions

**Enteral feeding:** Feeding that includes direct breastfeeding and feeding by cups, naso- or orogastric tubes (9).

**Trophic feeding:** Trophic feeding is the practice of supplying small volumes of enteral milk feeds to the infant to promote the development of the immature gastrointestinal tract (8).

**Early feeding:** is when neonates are started on trophic feeding within 24 hours of birth (8, 9, 15).

**Delayed feeding:** is when preterm neonates start trophic feeding after 24 hours of birth (8, 9, 15).

**Censored:** neonates who died, transferred or referred before starting trophic feeding or not started on trophic feeding at the end of follow-up.

**Follow up time:** the length of time in hours the preterm neonates are followed starting from birth to the first trophic feeding or censorship.

**Survival time:** time from birth up to the study subjects start trophic feeding.

**Event:** initiation of first trophic feeding for preterm neonates.

**Hemodynamic instability**: occurs when the body can't get enough energy and blood flow due to abnormal or unstable blood pressure secondary to Blood group and RH incompatibility, Anemia, Polycythemia, Bleeding disorders or blood glucose disturbances (68).

### 4.10. Data quality assurance

A two days training was given for data extractors and supervisors on the study objectives, data extraction tool, techniques, and procedures prior to data extraction. A pretest was done on 5% of the neonates' charts and necessary amendments were done based on the pre-test findings. The consistency and completeness of data was checked by the principal investigator and supervisors on a daily basis. The quality of data was checked on the spot of data extraction by the supervisor to evaluate the data completeness, consistency, and accuracy and up on data entry in to the software by the investigator.

### 4.11. Data processing and analysis

The data was cleaned coded and exported to Stata version 16 for analysis. Descriptive statistics was reported with a median (interquartile range) for continuous data and with frequency and proportion for categorical data. The outcomes of study participants were dichotomized into code '1' as a failure (starting trophic feeding) and code '0' as a censor. The variance inflation factor (VIF) was used to assess multi-collinearity.

The Kaplan Meier survival curve was used to estimate the survival time, and a log-rank test was used to compare the survival curves of categorical variables. The necessary assumption for the Cox-proportional hazard regression model was checked using the Schoenfeld residual test and the graphical methods.

A bi-variable Cox-regression was computed for each predictor variable and a P-value of <0.2 was used as a cut-off point to enter variables to multi-variable Cox-regression. The confounding effect was minimized using proper inclusion and exclusion criteria and a multi-variable analysis.

The result of the final model is expressed in terms of Adjusted Hazard Ratio (AHR) with a 95% Confidence interval. A significant association is declared with a p-value less than 0.05 in a multivariable Cox regression model. Finally, the result of this study is presented with text narrations, tables and graphs.

### 4.12. Ethical consideration

Approval letter was obtained from Pharma College Institutional Research Ethics Review Board Committee (IRERCB) and then from Sidama public health institute (SiPHI). Then approval was asked from the medical director of AGH. The NICU head of AGH was fully informed about the research objective and benefits. Confidentiality was maintained through anonymity and privacy measures were taken to preserve the right of the study subjects throughout the research work. Names and unique numbers of the study subjects were not included in the data extraction instrument and the data was not disclosed to any other person than the principal investigator.

### 4.13. Result dissemination plan

The result of this study will be presented to the department of Public health of Pharma college as a partial fulfillment of a master's degree in public health. Summary report will be disseminated to the hospital and the regional health bureau. The finding will also be presented on different related workshops and conferences. The final manuscript will be sent for peer reviewing and publication on a reputable journal for it to be available to the medical and public health community at large.

# 5. RESULTS

### 5.1. Socio-demographic characteristics of the preterm neonates and their mothers

A total of 291 preterm neonates' charts were included in the final analysis with a retrieval rate of 92.08%, of which, 232 (79.72%) were started on TF and 59 (20.28%) were censored (25 referred, 18 died, and 16 left against medical advice). The median age of the mothers was 27 years with an interquartile range of 23-31 and 59.79% of the mothers are from urban areas (Table 2).

Out of the total preterm neonates 53.26% were females. The median birth weight of the neonates was 1900 grams with an interquartile range of 1400-2200 grams. Concerning gestational age, the minimum and maximum gestational ages at birth were 28 and 36 weeks respectively. The two groups of preterm neonates (Started on TF and Censored) shown a statistically significant difference in terms of residence, birth weight and gestational age (Table 2).

**Table 2:** Socio demographic characteristics of the preterm neonates and their mothers admitted to the NICU of AGH from January 2021 - December 2023 (n=291).

| **Variables** | | **Initiation of TF** | | **$\chi^2$ p-value** |
|---|---|---|---|---|
| | | **Initiated (%)** | **Censored (%)** | |
| Maternal age | 15-24 | 78 (26.80) | 16 (5.49) | 0.442 |
| | 25-34 | 120 (41.24) | 36 (12.37) | |
| | ≥ 35 | 34 (11.68) | 7 (2.41) | |
| Residence | Rural | 84 (28.87) | 33 (11.34) | 0.006 |
| | Urban | 148 (50.86) | 26 (8.93) | |
| Sex of the neonate | Male | 111 (38.14) | 25 (8.59) | 0.452 |
| | Female | 121 (41.58) | 34 (11.68) | |
| Gestational age (GA) in weeks | <34 | 87 (29.89) | 46 (15.81) | < 0.001 |
| | ≥ 34 | 145 (49.83) | 13 (4.47) | |
| Birth weight (BW) in grams | <1500 | 50 (17.18) | 30 (10.31) | < 0.001 |
| | ≥ 1500 | 182 (62.54) | 29 (9.97) | |

### 5.2. Maternal, obstetric and medical related characteristics of the mothers of the preterm neonates

Among all the mothers included in the study, 87.97% had ANC follow up during their last pregnancy out of which, 58.20% had four or more visits. And 56.70% of the mothers were multiparous. Regarding the mode of delivery, the majority (65.52%) delivered via SVD. All of the studied preterm neonates were born at a health facility, out of which, 80.41% were delivered at the study hospital. Of all the studied preterm neonates, 18.21 % were twins, out of which, 52.83% were first born in the order of birth. There were no triplets (Table 3).

Regarding the maternal obstetric and medical characteristics, APH (7.56%), Preeclampsia/ eclampsia (17.18%), PROM (16.84%), chorioamnionitis (4.12%), DM (2.75%), hypertension (1.37%) and HIV (1.37%) were identified. The two groups of preterm neonates (Started on TF and Censored) shown a statistically significant difference in terms of ANC visit, type of current pregnancy, chorioamnionitis and PROM (Table 3).

### 5.3. Other neonatal and service related characteristics of the preterm neonates

Of all the preterm neonates included, 42.07% were SGA. Concerning APGAR scores, 24.74% and 16.49% had an APGAR score of less than 7 in the first and fifth minute respectively. Majority (74.91%) of the preterm neonates had no intact sucking reflex (Table 4).

Among the 182 neonates who are less than 2000 grams, KMC was initiated in 36.26%. The frequency of order revision was less than 24 hours for all neonates. Most (90.72%) of the neonates were started on antibiotics and majority (60.82%) were put on CPAP. Regarding other management related factors, 20.27% were given blood transfusion and 11.00% of them were put on phototherapy. Among the preterm neonates initiated on trophic feeding, most (91.38%) were fed on breast milk and the remaining were given formula feeding. The two groups of preterm neonates had shown a statistically significant difference in terms of weight for gestational age, first minute APGAR score, CPAP and phototherapy (Table 4).

**Table 3:** Maternal, obstetric and medical related characteristics of the mothers of the preterm neonates admitted to the NICU of AGH from January 2021 - December 2023 (n=291).

| **Variables** | | **Initiation of TF** | | **$\chi^2$ p-value** |
|---|---|---|---|---|
| | | **Started (%)** | **Censored (%)** | |
| Antenatal care visits | Yes | 210 (72.16) | 46 (15.81) | 0.008 |
| | No | 22 (7.56) | 13 (4.47) | |
| Number of Antenatal care visits (n=256) | 1-3 | 86 (33.59) | 21 (8.20) | 0.558 |
| | ≥4 | 124 (48.44) | 25 (9.77) | |
| Gravidity | Nulligravida | 87 (29.89) | 21 (7.22) | 0.963 |
| | Low multigravida | 92 (31.62) | 24 (8.25) | |

| | | | | |
|---|---|---|---|---|
| | Grand multigravida | 53 (18.21) | 14 (4.81) | |
| Parity | Nullipara | 102 (36.05) | 24 (8.25) | 0.872 |
| | Low multipara | 92 (31.62) | 24 (8.25) | |
| | Grand multipara | 38 (13.06) | 11 (3.78) | |
| Type of current pregnancy | Singleton | 198 (68.04) | 41 (14.09) | 0.006 |
| | Twin | 35 (12.03) | 18 (6.19) | |
| Order of twin delivery (n=53) | First twin | 17 (32.08) | 11 (20.75) | 0.386 |
| | Second twin | 18 (33.96) | 7 (13.21) | |
| Mode of delivery (n=290) | Spontaneous vaginal | 153 (52.76) | 37 (12.76) | 0.611 |
| | Cesarean section | 78 (26.89) | 22 (7.59) | |
| Institutional delivery | The study hospital | 191 (65.64) | 43 (14.78) | 0.103 |
| | Out born | 41 (14.09) | 16 (5.49) | |
| Antepartum hemorrhage | Yes | 15 (5.15) | 7 (2.41) | 0.161 |
| | No | 217 (74.57) | 52 (17.87) | |
| Chorioamnionitis | Yes | 6 (2.06) | 6 (2.06) | 0.009 |
| | No | 226 (77.66) | 53 (18.21) | |
| Preeclampsia/eclampsia | Yes | 39 (13.40) | 11 (3.78) | 0.739 |
| | No | 193 (66.32) | 48 (16.49) | |
| PROM | Yes | 34 (11.68) | 15 (5.15) | 0.048 |
| | No | 198 (68.04) | 44 (15.12) | |

**Table 4:** Other neonatal and service related characteristics of the preterm neonates admitted to the NICU of AGH from January 2021- December 2023 (n=291).

| **Variable** | | **Outcome** | | **$\chi^2$ p-value** |
|---|---|---|---|---|
| | | **Started TF (%)** | **Censored (%)** | |
| Weight for gestational age (n=290) | SGA | 90 (31.03) | 32 (11.03) | 0.034 |
| | AGA | 141 (48.62) | 27 (9.31) | |
| 1$^{st}$minute APGAR score | <7 | 49 (16.84) | 23 (7.90) | 0.005 |
| | ≥7 | 183 (62.89) | 36 (12.37) | |

| | | | | |
|---|---|---|---|---|
| 5th minute APGAR score | <7 | 34 (11.68) | 14 (4.81) | 0.094 |
| | ≥ 7 | 198 (68.04) | 45 (15.46) | |
| Intact sucking reflex | Yes | 64 (21.99) | 9 (3.09) | 0.051 |
| | No | 168 (57.73) | 50 (17.18) | |
| KMC (n=182) | Yes | 51 (28.02) | 15 (8.24) | 0.122 |
| | No | 77 (42.31) | 39 (32.43) | |
| CPAP | Yes | 125 (42.96) | 52 (17.87) | < 0.001 |
| | No | 107 (36.77) | 7 (2.41) | |
| Antibiotic | Yes | 211 (72.51) | 53 (18.21) | 0.792 |
| | No | 21 (7.22) | 6 (2.06) | |
| Phototherapy | Yes | 19 (6.53) | 13 (4.47) | 0.002 |
| | No | 213 (73.19) | 46 (15.81) | |
| Blood transfusion | Yes | 45 (15.46) | 14 (4.81) | 0.460 |
| | No | 187 (64.26) | 45 (15.46) | |

### 5.4. Neonatal medical diagnoses among the preterm neonates

Concerning the medical diagnosis of the preterm neonates, respiratory distress syndrome (53.61%), perinatal asphyxia (24.74%), sepsis (57.73%), hypothermia (23.02%) jaundice (2.06%), meconium aspiration syndrome (4.47%) and hemodynamic instability (47.42%) were identified. The two groups of the neonates showed statistically significant difference in terms of having RDS, PNA, MAS and hemodynamic instability (Table 5).

**Table 5:** Neonatal medical diagnoses of the preterm neonates admitted to the NICU of AGH from January 2021-December 2023 (n=291).

| **Variable** | | **Outcome** | | **$\chi^2$ p-value** |
|---|---|---|---|---|
| | | **Started TF (%)** | **Censored (%)** | |
| RDS | Yes | 109 (37.46) | 47 (16.15) | < 0.001 |
| | No | 123 (42.27) | 12 (4.12) | |
| PNA | Yes | 47 (16.15) | 25 (8.59) | < 0.001 |

| | | | | |
|---|---|---|---|---|
| | No | 185 (63.57) | 34 (11.68) | |
| Sepsis | Yes | 136 (46.74) | 32 (10.99) | 0.543 |
| | No | 96 (32.99) | 27 (9.28) | |
| Hypothermia | Yes | 48 (16.49) | 19 (6.53) | 0.061 |
| | No | 184 (63.23) | 40 (13.75) | |
| MAS | Yes | 6 (2.06) | 7 (2.41) | 0.002 |
| | No | 226 (77.66) | 52 (17.87) | |
| Hemodynamic instability | Yes | 97 (33.33) | 41 (14.09) | < 0.001 |
| | No | 135 (46.39) | 18 (6.19) | |

### 5.5. Time to initiate trophic feeding and overall survival function to start trophic feeding among preterm neonates

A total of 291 preterm neonates were followed for 10554.9 person-hours of observation. The minimum and maximum follow up time were 0.25 and 182.9 hours respectively. The overall incidence rate of starting TF was 2.2 per 100 person-hour observations. The median time for premature neonates to start TF was found to be 34.8 (IQR: 2.5-67.6) hours. Among the total preterm neonates, 41.92%, 56.35%, and 71.47% started TF by the end of 24, 48, and 72 hours respectively.

The overall Kaplan-Meier survival estimate curve shows that the probability of survival to initiate trophic feeding among the preterm neonates decreases as time increases (See figure 3). And the overall Kaplan-Meier failure estimate curve shows that an increasing failure probability as time increases (See figure 4).

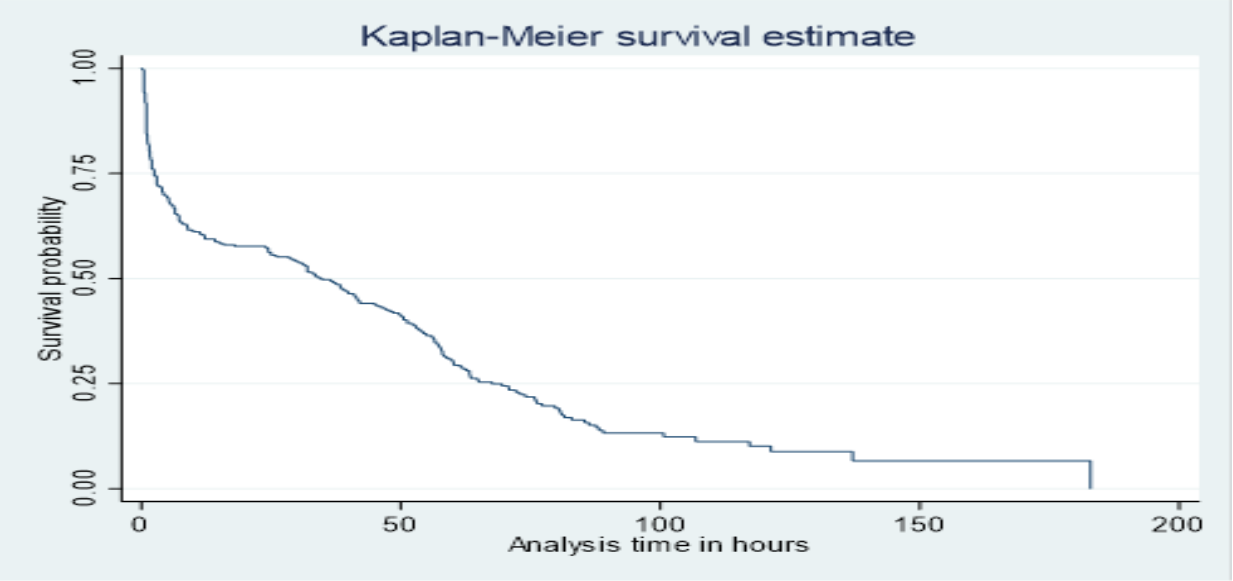



**Figure 3:** Kaplan Meier Survival estimate of time to initiate TF among preterm neonates admitted to the NICU of AGH from January 2021-December 2023 (n=291).

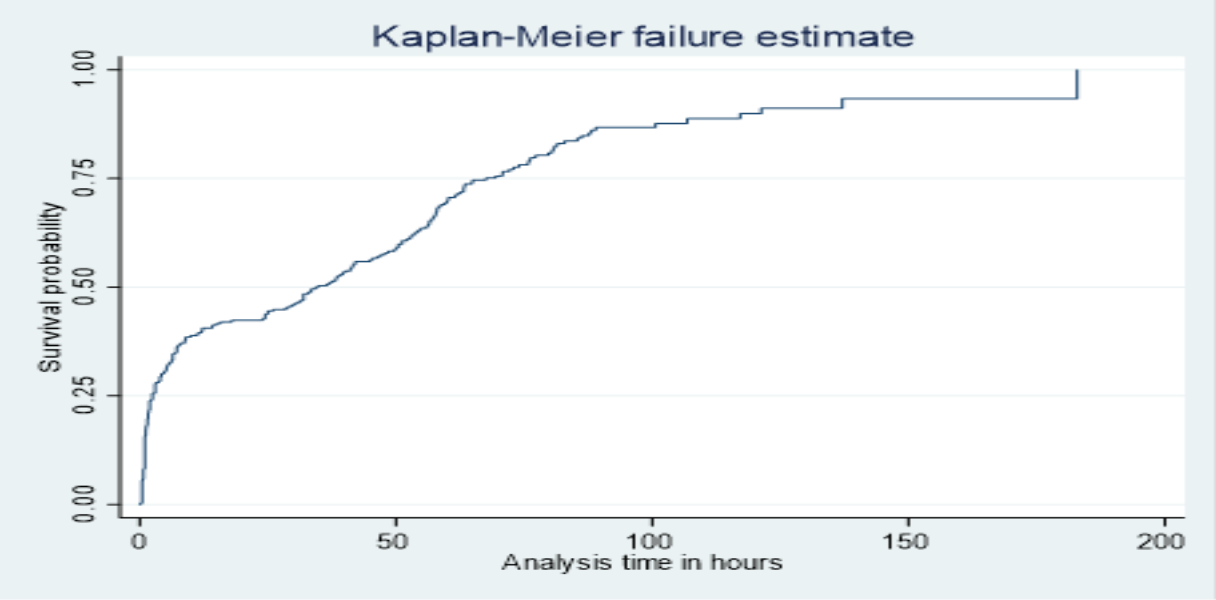



**Figure 4:** Kaplan Meier Failure estimate of time to initiate TF among preterm neonates admitted to the NICU of AGH from January 2021-December 2023 (n=291).

Moreover, the life table analysis constructed with a 24 hours interval indicated that there was highest number of events (number of preterm neonates started on TF) and highest decrease in

survival probability to start TF during the 0 - 24 hour interval. An increase in the cumulative failure and decrease in survival probability over time in indicates the higher likelihood of initiating TF as time progresses (Table 6).

**Table 6:** The life table analysis of preterm neonates to start TF among preterm neonates admitted to the NICU of AGH from January 2021 - December 2023 (n=291).

| Interval | Total entering interval | Started TF | Censored | Cumulative failure | Survival probability | 95% CI for survival probability |
|---|---|---|---|---|---|---|
| 0-24 | 291 | 122 | 7 | 0.4243 | 0.5757 | (0.5163, 0.6304) |
| 24-48 | 162 | 42 | 12 | 0.5793 | 0.4207 | (0.3624, 0.4777) |
| 48-72 | 108 | 44 | 19 | 0.7672 | 0.2328 | (0.1826, 0.2866) |
| 72-96 | 45 | 18 | 10 | 0.8720 | 0.1280 | (0.0865, 0.1780) |
| 96-120 | 17 | 3 | 6 | 0.8994 | 0.1006 | (0.0611, 0.1515) |
| 120-144 | 8 | 2 | 3 | 0.9304 | 0.0696 | (0.0320, 0.1272) |
| 144-168 | 3 | 0 | 1 | 0.9304 | 0.0696 | (0.0320, 0.1272) |
| 168-192 | 2 | 1 | 1 | 0.9768 | 0.0232 | (0.0009, 0.1343) |

### 5.6. Comparison of survivorship functions among different categorical variables

Kaplan-Meier survival curve graphs were done for every categorical variable (See Figure 5, 6, and 7) and the log rank test analysis was done.

The log rank test analysis indicated that there were substantial differences in the median time to initiate TF among preterm neonates across categories of several variables. Accordingly, there was a significant difference in median time to initiate TF between birth weight < 1500 grams neonates, 65 (95% CI, 52.57-77.43) hours, and those ≥ 1500 grams, 7.33 (95% CI: 3.09, 11.57) hours. There is a statistically significant difference in the median time to start TF between preterm neonates with a gestational age of < 34 weeks, 63.33 (95% CI: 54.18, 72.49) hours, and those with a gestational age ≥ 34 weeks, 3 (95% CI: 1.62, 4.38) hours. Similarly, there is a statistically significant difference in the median time to initiate TF between preterm neonates

with first minute APGAR score of <7 76.27 (95% CI: 55.36, 97.17) hours and those with a score of ≥ 7 18.06 (95% CI: 4.55, 31.45) hours (Table 7).

Regarding neonatal medical diagnosis related characteristics, there is a statistically significant difference in the median time to start TF between neonates with a diagnosis of RDS 58 (95% CI: 53.01, 62.99) hours, and those without RDS 3 (95% CI: 1.39, 4.61) hours. There is a statistically significant difference in the median time to initiate TF between neonates with a diagnosis of PNA 80.5 (95% CI: 70.12, 88.89) hours and those without PNA 8.83 (95% CI: 3.87, 13.79) hours. There is also a statistically significant difference in the median time to initiate TF between neonates with a hemodynamic instability 61.5 (95 % CI: 56.65, 66.35) hours and those without hemodynamic instability 4.75 (95% CI: 2.61, 6.89) hours (Table 7).

In relation to service related characteristics, there is a statistically significant difference in the median time to initiate TF between preterm neonates put on CPAP 58 (95% CI: 54.24, 61.76) hours and those who were not on CPAP 2 (95% CI: 1.37, 2.63) hours (Table 7).

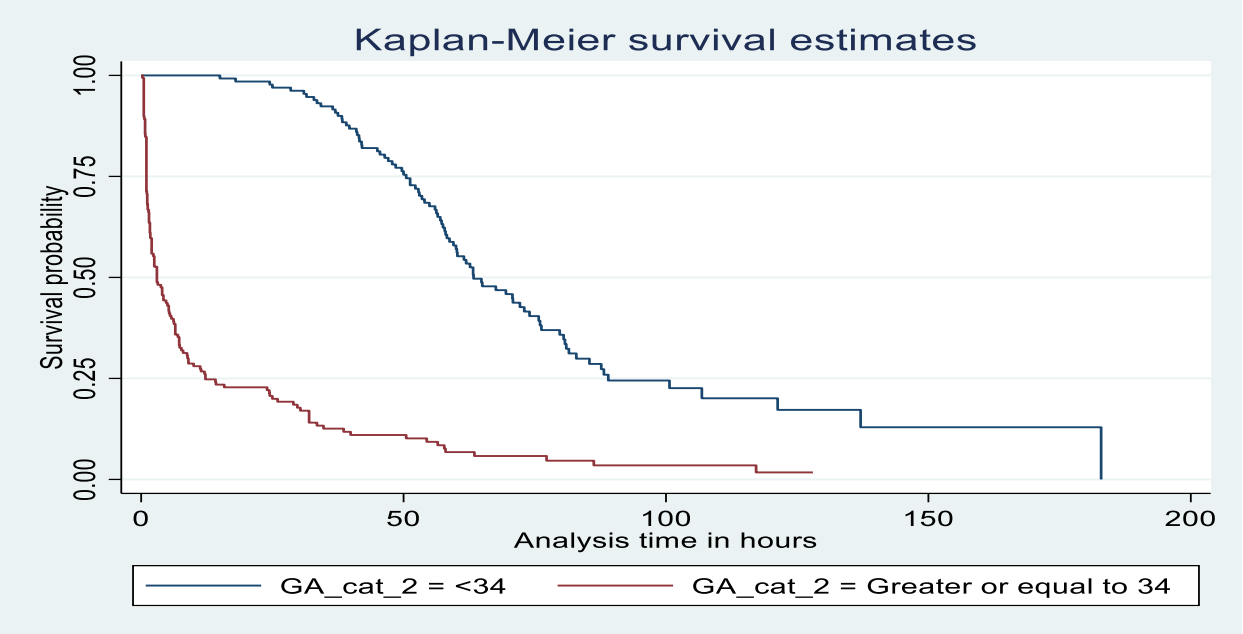



**Figure 5:** Kaplan-Meier survival estimate of starting TF based on gestational age among neonates admitted in NICU of AGH from January 2021 - December 2023 (n=291).

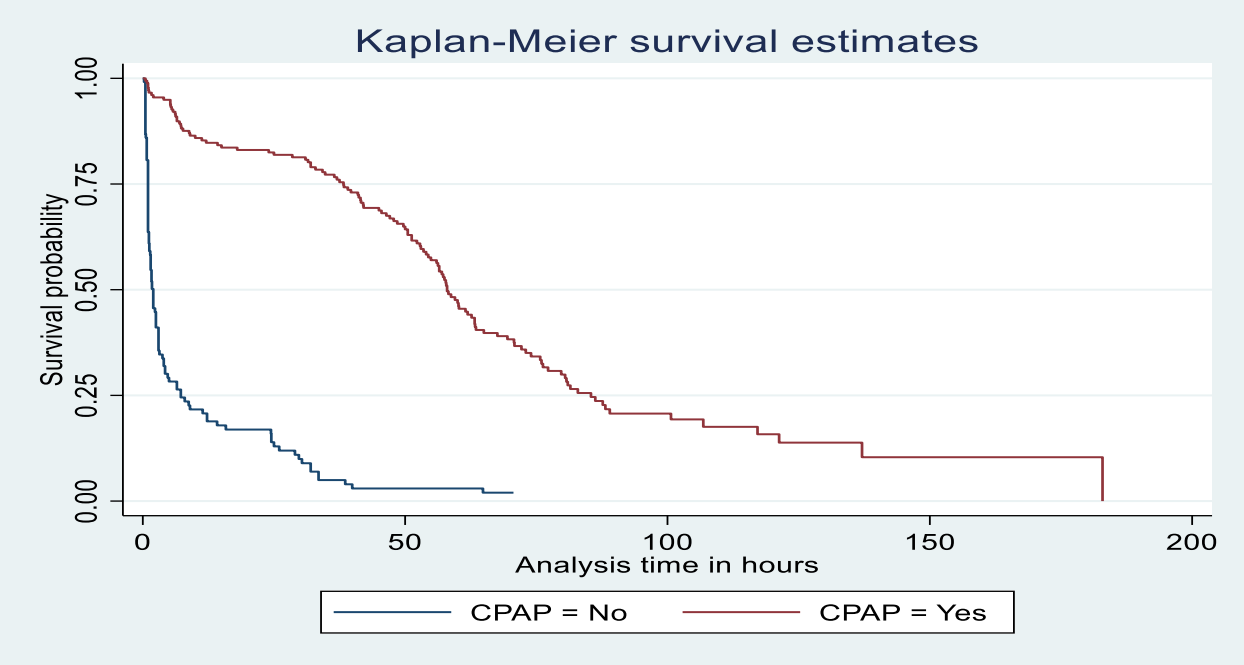



**Figure 6:** Kaplan-Meier survival estimate of starting TF based on CPAP among neonates admitted in NICU of AGH from January 2021 - December 2023 (n=291).

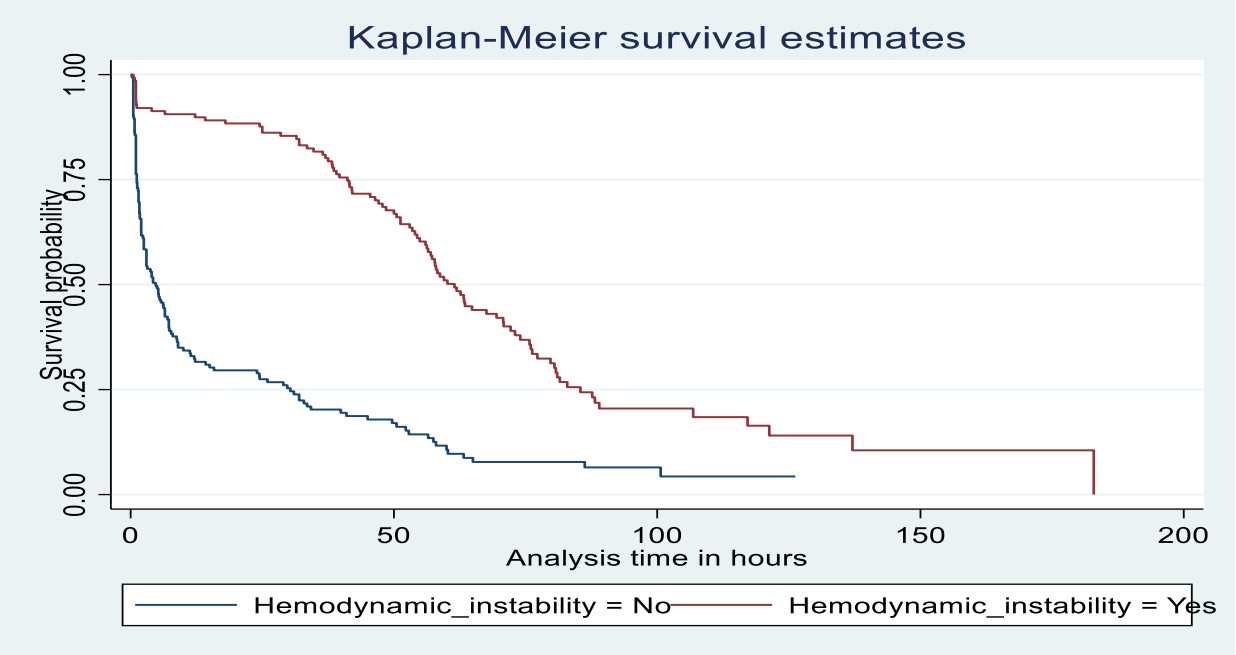



**Figure 7:** Kaplan-Meier survival estimate of starting TF based on hemodynamic instability among neonates admitted in NICU of AGH from January 2021 - December 2023 (n=291).

**Table 7:** Median survival time and log rank test analysis for the study population according to different characteristics of preterm neonates admitted to the NICU of AGH from January 2021 - December 2023 (n=291).

| **Variables** | | **Median survival time in hours (95% CI)** | **Log rank test $\chi^2$** | **P value** |
|---|---|---|---|---|
| Birth weight | <1500 | 65.00 (52.57, 77.43) | 55.31 | <0.001 |
| | ≥1500 | 7.33 (3.09, 11.57) | | |
| Gestational age | <34 | 63.33 (54.18, 72.49) | 165.13 | <0.001 |
| | ≥ 34 | 3.00 (1.62, 4.38) | | |
| ANC | Yes | 32.00 (22.65, 41,36) | 5.47 | 0.019 |
| | No | 54.92 (42.32, 67.51) | | |
| Place of delivery | Study hospital | 30.33 (15.81, 44.85) | 5.21 | 0.022 |
| | Out born | 56.25 (49.43, 63.07) | | |
| PROM | Yes | 57.75 (45.96, 69.54) | 5.61 | 0.018 |
| | No | 31.00 (16.24, 45.76) | | |
| First minute APGAR score | <7 | 76.27 (55.36, 97.17) | 47.76 | <0.001 |
| | ≥ 7 | 18.06 (4.55, 31.45) | | |
| Fifth minute APGAR score | <7 | 65.00 (42.24, 87.76) | 22.65 | <0.001 |
| | ≥ 7 | 28.50 (16.69, 40.31) | | |
| Sucking reflex | Yes | 6.17 (3.32, 9.02) | 29.96 | <0.001 |
| | No | 48.50 (40.37, 56.63) | | |
| CPAP | Yes | 58.00 (54.24, 61.76) | 207.65 | <0.001 |
| | No | 2.00 (1.37, 2.63) | | |
| Antibiotics | Yes | 39.08 (30.76, 47.41) | 12.09 | 0.001 |
| | No | 1.67 (1.05, 2.28) | | |
| Phototherapy | Yes | 76.00 (51.61, 100.39) | 16.89 | <0.001 |
| | No | 29.75 (16.01, 43.49) | | |
| Blood transfusion | Yes | 60.17 (47.31, 73.02) | 17.89 | <0.001 |
| | No | 14.17 (0.494, 27.84) | | |
| RDS | Yes | 58.00 (53.01, 62.99) | 79.11 | <0.001 |
| | No | 3.00 (1.39, 4.61) | | |
| PNA | Yes | 80.50 (70.12, 88.89) | 78.32 | <0.001 |
| | No | 8.83 (3.87, 13.79) | | |
| Hypothermia | Yes | 61.92 (54.95, 68.88) | 16.21 | <0.001 |
| | No | 14.25 (0.37, 28.13) | | |
| Hemodynamic instability | Yes | 61.50 (56.65, 66.35) | 85.78 | <0.001 |
| | No | 4.75 (2.61, 6.89) | | |

### 5.7. Predictors of the time to initiate trophic feeding among preterm neonates

The assumptions for the proportionality of hazard ratio were checked for all covariates statistically using Schoenfeld residual test and graphically using log-log plots and Kaplan- Meier curves. Bivariate cox regression was done and birth weight, first minute APGAR score, RDS, hypothermia, ANC visit, place of delivery, PROM, sucking reflex, hemodynamic instability, and

Table 8: The final model containing predictors of time to initiate TF among preterm neonates admitted to the NICU of AGH from January 2021- December 2023 (n=291).

| **Predictor variables** | | **TF** | | **CHR (95% CI)** | **AHR (95% CI)** |
|---|---|---|---|---|---|
| | | **Initiated** | **Censored** | | |
| ANC visit | Yes | 210 | 46 | 1.68 (1.08, 2.60) | 1.55 (0.99, 2.42) |
| | No | 22 | 13 | 1 | 1 |
| Place of delivery | Study hospital | 191 | 43 | 1.48 (1.05, 2.09) | 1.17 (0.81, 1.57) |
| | Out born | 41 | 16 | 1 | 1 |
| PROM | Yes | 34 | 15 | 1 | 1 |
| | No | 198 | 44 | 1.54 (1.07, 2.22) | 1.59 (1.08, 2.36) * |
| Birth weight | < 1500 | 50 | 30 | 0.31 (0.23, 0.43) | 0.48 (0.34, 0.69) *** |
| | ≥ 1500 | 182 | 29 | 1 | 1 |
| RDS | Yes | 109 | 47 | 1 | 1 |
| | No | 123 | 12 | 3.14 (2.40, 4.09) | 1.11 (0.73, 1.69) |
| Hypothermia | Yes | 48 | 19 | 1 | 1 |
| | No | 184 | 40 | 1.91 (1.38, 2.64) | 0.98 (0.65, 1.25) |
| First minute APGAR | < 7 | 49 | 23 | 1 | 1 |
| | ≥ 7 | 183 | 36 | 3.14 (2.24, 4.42) | 2.66 (1.83, 3.87) *** |
| Sucking reflex | Yes | 64 | 9 | 2.24 (1.66, 3.02) | 0.91 (0.65, 1.25) |
| | No | 168 | 50 | 1 | 1 |
| Hemodynamic instability | Yes | 97 | 41 | 1 | 1 |
| | No | 135 | 18 | 3.42 (2.59, 4.49) | 2.08 (1.43, 3.03) *** |
| CPAP | Yes | 125 | 52 | 1 | 1 |
| | No | 107 | 7 | 7.71 (5.64, 10.53) | 3.82 (2.44, 5.99) *** |

**Note**: *statistically significant p-value <0.05, **statistically significant p-value<0.01, ***statistically significant p-value<0.001.

CPAP were entered in to the final multivariable cox regression model with a p value of less than 0.2. By the end of the analysis, five covariates were found to be statistically significant independent predictors of the time to initiate TF with a P value of < 0.05 (Table 8).

The multivariable analysis showed that the hazard of initiating TF was 52% less likely among preterm neonates with a birth weight of less than 1500 grams compared to those with a birth weight of ≥ 1500 (AHR: 0.48, 95% CI: 0.34, 0.69). The hazard of initiating TF was 2.66 times more likely among preterm neonates with a first minute APGAR score of ≥ 7 compared to those with a first minute APGAR score of < 7 (AHR: 2.66, 95% CI: 1.83, 3.87). Also, the hazard of initiating TF was 2.08 times more likely among preterm neonates without a hemodynamic instability than those with hemodynamic instability (AHR: 2.08, 95% CI: 1.43, 3.03) (Table 8).

Moreover, the hazard of initiating TF was 3.82 times more likely among preterm neonates who were not put on CPAP than those who were put on CPAP (AHR: 3.82, 95% CI: 2.44, 5.99). And lastly, the hazard of initiating TF was 1.59 times more likely among preterm neonates born to mothers without a diagnosis of PROM compared to those who were born to mothers with a diagnosis of PROM (AHR: 1.59, 95% CI: 1.08, 2.36) (Table 8).

# 6. DISCUSSION

This study aimed to determine the time to initiate TF and its predictors among preterm neonates admitted to the study hospital within the study period. In this study, the overall incidence of starting TF is 2.2 per 100 person-hour observations. Among the total preterm neonates, 79.7% were initiated on TF during the follow up period and the median time for premature neonates to start TF was found to be 34.8 (IQR: 2.5-67.6) hours.

The result of this study indicates that the incidence rate of initiating TF is comparable to that of a prospective observational study done in Northwestern Ethiopia (2 per 100 person-hour observations) (22). The median time of initiating TF is lower compared to a retrospective cohort study done in Portugal (72 hours) (49), a multicenter observational study done in Africa (46 hours) (21) and another prospective study done in Addis Ababa (23). But higher than a multicenter prospective study done in China (23 hours) (34) and another study done in New Zealand (24 hours) (48).

This study demonstrated that 79.72% of the total neonates are initiated on TF. This finding is lower when compared to a prospective follow up study done in Northern Ethiopia (90.9%) (22) and another follow up study in Addis Ababa (85%) (23). This could be due to the difference in the hospital levels which are comprehensive specialized and tertiary level hospitals which are equipped with specialized NICUs and adequate and trained professionals which could provide quality service to preterm neonates with complicated medical problems compared to our study hospital (Level II) and are less likely to refer preterm neonates which in turn minimizes the number of censored cases. The difference could also be due to the different study designs (prospective vs. retrospective), study subjects and sample sizes utilized for the respective studies.

This study also found that, among the total preterm neonates, 41.92% started TF by the end of the first post natal day. This implies that majority of the preterm neonates had a delayed initiation of TF which is against the Ethiopian national feeding neonatal guideline and WHO recommendations (9). This proportion is higher compared to a cohort study done in Iran (27%) (35), an observational study done in South Africa (30.8%) (52), a follow up study in Northern

Ethiopia (22%) (22), a prospective study done in selected public hospitals in Addis Ababa (24.3%) (23) and another retrospective follow up study done in Southern Oromia region (21.93%) (69). But, it is lower when compared to an observational study done in Italy (74.11%) (46), a multicenter web based study done in hospitals in Spain (65%) (50) and a multicenter study done in Nigeria and Kenya (48%) (20). These differences could be due to differences in study designs, hospital set ups and heterogeneity in management protocols among health care facilities and practice among professionals worldwide and different regions and set ups with in the same country.

The multivariable cox regression in this study showed that, first minute APGAR score of less than 7, a birth weight of less than 1500 grams, having a hemodynamic instability, being on CPAP and being born to a PROM mother were significant predictors of delay in the initiation of TF.

The hazard of initiating TF was 2.66 times more likely among preterm neonates with a first minute APGAR score of ≥ 7 compared to those with a first minute APGAR score of < 7. This could arise from the fact that preterm neonates with low APGAR scores might need more medical attention and treatment including airway suctioning, respiratory support, fluids, medications and resuscitation which might interrupt with earlier initiation of TF. Additionally, preterm neonates with lower first minute APGAR scores had shown to have lower pressure amplitudes while sucking breast milk (70), which might prolong TF initiation and implies that these neonates need more individualized feeding plan including naso-gastric tube feeding and close follow up. This result is consistent with the findings of a prospective cohort study done in India (57), a prospective cohort study done in Northwestern Ethiopia (22) and another observational study done in Addis Ababa (23).

The hazard of initiating TF was 52% less likely among preterm neonates with a birth weight of less than 1500 grams compared to those with a birth weight of ≥ 1500. This could be due to the concern of feeding intolerance and NEC due to immature gut development in preterm neonates with a very low birth weight among professionals. This could also be due to the poor coordination of breathing, sucking and swallowing in preterm neonates with very low birth

weight (71). This finding conforms to a retrospective review of charts done in New Zealand (48), a prospective follow up study done in Addis Ababa (58) another multicenter prospective study done in Addis Ababa (33) and a facility based retrospective follow up study done in Southern Oromia (69).

Furthermore, the hazard of initiating TF was 2.08 times more likely among preterm neonates without a hemodynamic instability than those with hemodynamic instability. This might be due to the associated risk of organ dysfunction and failure in preterm neonates with hemodynamic instability and the fear of NEC and feeding intolerance in neonates with hemodynamic instability (68). This finding is consistent with an observational study done in Spain (62), a prospective follow up study done in selected public hospitals in Addis Ababa (23) and another observational cohort study done in Northwestern Ethiopia (22).

The hazard of initiating TF was 3.82 times more likely among preterm neonates who were not put on CPAP than those who were put on CPAP. Similar finding was reported in a retrospective study done in Northern America that preterm neonates on CPAP had a delayed initiation of TF (64). This could be due to the fear of readiness for enteral feeding and feeding related morbidities in the preterm neonates who are on CPAP. But, a similar study showed that delayed feeding until ceasing CPAP did not contribute to reducing feeding related morbidities and health care professionals should not hold back on initiating TF for neonates on CPAP since being on CPAP is not a contraindication for the initiation of TF (64). Another retrospective study done in Turkiye had also shown the same finding (56).

Moreover, the hazard of initiating TF was 1.59 times more likely among preterm neonates born to mothers with a diagnosis of PROM compared to those who were born to mothers without a diagnosis of PROM. This might be due to the fact that neonates born to a PROM mother are at an increased risk of developing early onset neonatal sepsis (72), which might make the condition and management of the preterm neonate more complicated.

# 7. STRENGTH AND LIMITATIONS

## 7.1. Strength

This study is addresses a topic which is not yet well covered in Ethiopia and covers a relevant and timely issue in neonatal care. Knowing the practice in the time to initiating TF and identification of the predictors could provide valuable insights to inform clinical guidelines and improve neonatal care. Therefore, the findings have huge clinical implications leading to improved feeding protocols and better outcomes for preterm infants. Furthermore, through the identification of important associations between predictors and TF initiation, the study could generate hypotheses for future prospective researches.

## 7.2. Limitations

The retrospective study design utilized might lead to selection bias since some charts were excluded due to incomplete and inconsistent information. And some important maternal and neonatal related variables including marital status, educational level, economic status, maternal medical conditions and passage meconium could not be found on the neonatal medical records which might be important confounders which should have been accounted for. Moreover, there might be a risk of poor data quality and introducing an information bias since the data utilized for this study was secondary, forcing reliance on existing medical records and there was no way of validating the data.

# 8. CONCLUSION AND RECOMMENDATIONS

## 8.1. Conclusion

In this study, a significant delay in the time to initiate TF is indicated. The multivariable cox regression revealed that first minute APGAR score, birth weight, hemodynamic instability, CPAP and PROM were significant predictors of the time to initiate TF.

## 8.2. Recommendations

**To the Ministry of Health (FMOH):** to develop a standardized feeding guideline for preterm neonates to decrease heterogeneity of practice regarding the time of initiation of TF and enforce its uniform implementation throughout the country through quality improvement initiatives and training health care professionals.

**To the regional health bureau (RHB) and administrators:** to prioritize preterm neonates' feeding and the identified predictors in health service planning and policies that support research and implementation of evidence-based practices.

**To Adare General Hospital (AGH):** to give due attention and develop targeted interventions to preterm neonates with the identified predictors and work on reducing their occurrence including, early identification and treatment of conditions causing hemodynamic instability, adequate follow up and support of mothers diagnosed with PROM in the prepartum period utilizing multidisciplinary approaches. To take the appropriate actions in early identification and development of individualized care plan for every preterm neonate with such conditions.

**To researchers in the field**: to conduct longitudinal, large scale and multicenter researches in this area in the different parts of the country.

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# 10. APPENDIXES

**Appendix I: Information sheet and informed permission form for the head of NICU**

My name is_____, I am a data extractor working on a research project led by the Principal investigator, Sosina Asrat (MD), a Master of Public health student at Pharma college Hawassa campus, School of Public health.

**The study title:** Time to initiate trophic feeding and its predictors among preterm neonates admitted to NICU of AGH, Hawassa, Ethiopia, 2024.

**Purpose of the study:** The purpose of this study is to investigate the time to initiate trophic feeding and its predictors in preterm neonates admitted to NICU of AGH. Trophic feeding is the practice of supplying small volumes of enteral milk feeds to the preterm neonate to promote the development of the immature gastrointestinal tract of the premature neonate. And its delay is associated with growth failure, poor neurological development, increased hospital stay, morbidity and mortality. Studying the time to initiate and predictors of initiation of trophic feeding in Hawassa city is of paramount importance to address the problem and for planning and implementing intervention strategies.

**Procedure and duration**: I will be reviewing the Preterm neonatal medical records who were admitted at the NICU from January 2021- December 2023 by using a checklist to provide me with pertinent data that is helpful for the study. There are 38 questions to answer where I will be filling the checklist by reviewing the neonatal medical records. The review will take about 30 minutes for each record, so I kindly request you to allow me this time for the review.

**Risks and benefits:** The risk of being reviewing in this study is minimal since the study doesn't need direct contact with the preterms. There would not be any direct payment for reviewing in

this study. However, the findings from this research will reveal important information for the institutions, health planners, and researchers.

**Confidentiality:** All the information will be kept confidential. Nothing that is recorded will be shared with anybody outside the research team, and names and other identifying information will not be included in any reports or publications. The findings of the study will be general for the study community and will not reflect anything particularly of the individual record. The checklist will be coded to keep the anonymity of the record.

**Rights:** Giving permission for this study is voluntary. You have the right to permit or not for this study. If you decide to permit the study, you have the right to terminate the study at any time if you consider something related to the study is wrong.

**Contact address:** If there are any questions or inquiries any time about the study or procedures, please contact:

**Mobile phone of investigator**: +251913101330 (Sosina Asrat).

**Email address of investigator**: abebesosina1@gmail.com

**Declaration of informed voluntary permission:** I have read the information sheet. I have clearly understood the purpose of the research, the procedures, the risks and benefits, issues of confidentiality and the contact address for any queries. I have been given the opportunity to ask any questions about things that may have been unclear. Therefore, I declare my permission to this study to be conducted in this institution with my signature as indicated below.

Name and signature of head of the Health institution _____

Signature of data extractor_____

Thank you for your cooperation!!

**Appendix II: Data extraction sheet**

Data extraction sheet to assess time to initiation of trophic feeding and its predictors among preterm neonates admitted to NICU of AGH, 2024.

**Instructions**: Circle/write the code corresponding to the answer to each question.

Date of the checklist filled (dd/mm/yyyy): _____/_____/_____

**Code No**. _____

**Table 9:** Data extraction check list to determine time to initiate trophic feeding and its predictors among preterm neonates admitted to the NICU of AGH, 2024.

| **Question code** | **Questions** | **Response** | **Skip to** |
|---|---|---|---|
| | **Part I: Questions related to the mother** | | |
| | **A. Socio-demographic characteristics of the mother** | | |
| 101 | Age (in years) | _____ | |
| 102 | Residence | 1. Urban<br>2. Rural | |
| 103 | Educational level | 1. No education<br>2. Primary<br>3. Secondary<br>4. College and above | |
| | **B. Maternal obstetric factors** | | |
| 201 | Antenatal Care(ANC) visit | 1. Yes<br>2. No | If no, skip to #203 |
| 202 | Total number of ANC visits | _____ | |
| 203 | Number of Gravidity | _____ | |
| 204 | Number of Parity | _____ | |
| 205 | Type of current pregnancy | 1. Single<br>2. Twin<br>3. Triplet<br>4. Other specify_____ | If single, skip to Q.207 |
| 206 | If 2 or 3for Q #205 which twin /triplet | _____ | |

| | | | |
|---|---|---|---|
| 207 | Current mode of delivery | 1. Spontaneous vaginal(SVD)<br>2. Cesarean section(C/S)<br>3. Instrumental vaginal | |
| 208 | Place of delivery | 1. At health institution<br>2. At home | If 2, skip to 210 |
| 209 | If the answer for Q. 208 is 1, which health institution? | 1. At the study Hospital<br>2. Outside the study Hospital | |
| 210 | Was the mother diagnosed with any maternal obstetric complication? | 1. Yes<br>2. No | If no, skip to #301 |
| 211 | What was the diagnosis? | 1. APH<br>2. Chorioamnionitis<br>3. Preeclampsia/Pregnancy induced hypertension<br>4. PROM<br>5. Others(specify)_____ | |
| | **C. Maternal medical related factors** | | |
| 301 | Did the mother have any medical disease/disorder? | 1. Yes<br>2. No | If no, skip to #401 |
| 302 | What was the disorder? | 1. HIV/AIDS<br>2. Hypertension<br>3. Diabetic mellitus<br>4. Anemia<br>5. Other (Specify)_____ | |
| | **Part II: Premature neonate related factor** | | |
| | **A. Identifications of the neonate** | | |
| 401 | Sex of the neonate | 1. Male<br>2. Female | |
| 402 | Gestational age at birth in weeks | _____ | |
| 403 | Birth weight of the preterm neonate in grams | _____ | |
| | **B. Medical related problems of the preterm neonate** | | |
| 501 | Was the neonate diagnosed with any medical problem? | 1. Yes<br>2. No | If no, skip to #503 |
| 502 | If yes, what was the diagnosis? | a. Respiratory distress<br>b. Perinatal Asphyxia<br>c. Sepsis<br>d. Jaundice<br>e. Hypothermia<br>f. MAS<br>g. PDA<br>h. Other(Specify)_____ | |
| 503 | First and fifth minute APGAR | | |

| | | | |
|---|---|---|---|
| | score respectively. | _____, _____ | |
| 504 | Did the neonate pass meconium with in the first 24 hours? | 1. Yes<br>2. No | |
| 505 | Did the neonate had an intact sucking reflex? | 1. Yes<br>2. No | |
| 506 | Did the preterm had hemodynamic instability? | 3. Yes<br>4. No | If no, skip to #508 |
| 507 | Cause of the hemodynamic instability | a. Blood group and RH incompatibility<br>b. Anemia<br>c. Polycythemia<br>d. Bleeding disorders<br>e. Blood glucose disturbances | |
| 508 | Was the neonate on CPAP | 1. Yes<br>2. No | |
| 509 | Was the neonate on antibiotics? | 1. Yes<br>2. No | |
| 510 | Was the neonate on phototherapy? | 1. Yes<br>2. No | |
| 511 | Did the neonate receive blood transfusion? | 1. Yes<br>2. No | |
| 512 | Was the neonate started on trophic feeding? | 1. Yes<br>2. No | If no, skip to #514 |
| 513 | Date and time of first trophic feeding (dd/mm/yr) | ____, ____,_____ | |
| 514 | Date and time of birth (dd/mm/yr) | ____, ____,_____ | |
| 515 | Outcome of the neonate | 1. Initiated on TF<br>2. Died<br>3. Referred<br>4. Absconded<br>5. Left against Medical advice (LAMA) | |
| | **Part III: Service related factor** | | |
| 601 | Did the neonate receive KMC (check only if neonate is < 2000 grams) | 1. Yes<br>2. No | |
| 602 | Type of milk provided | 1. Breast milk<br>2. Formula milk<br>3. Other (Specify)_____ | |
| 603 | Frequency of order revision | 1. At least every 24 hour<br>2. Greater than 24 hour | |

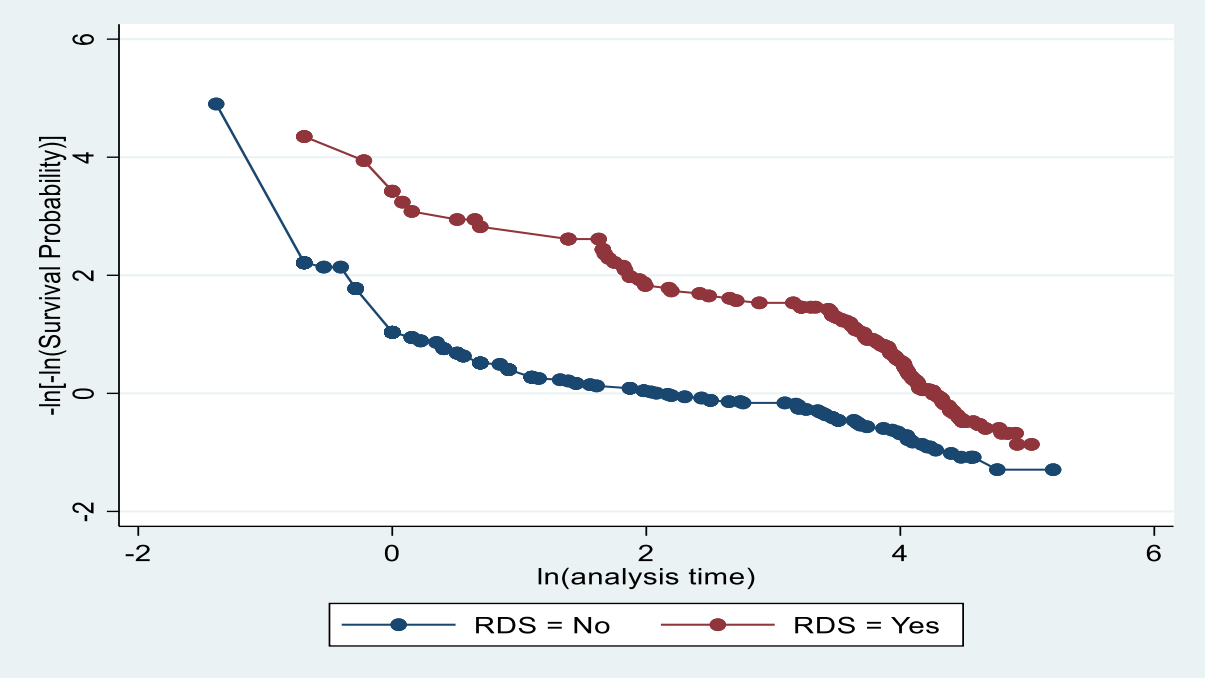
## Appendix III. Cox proportional hazard assumptions

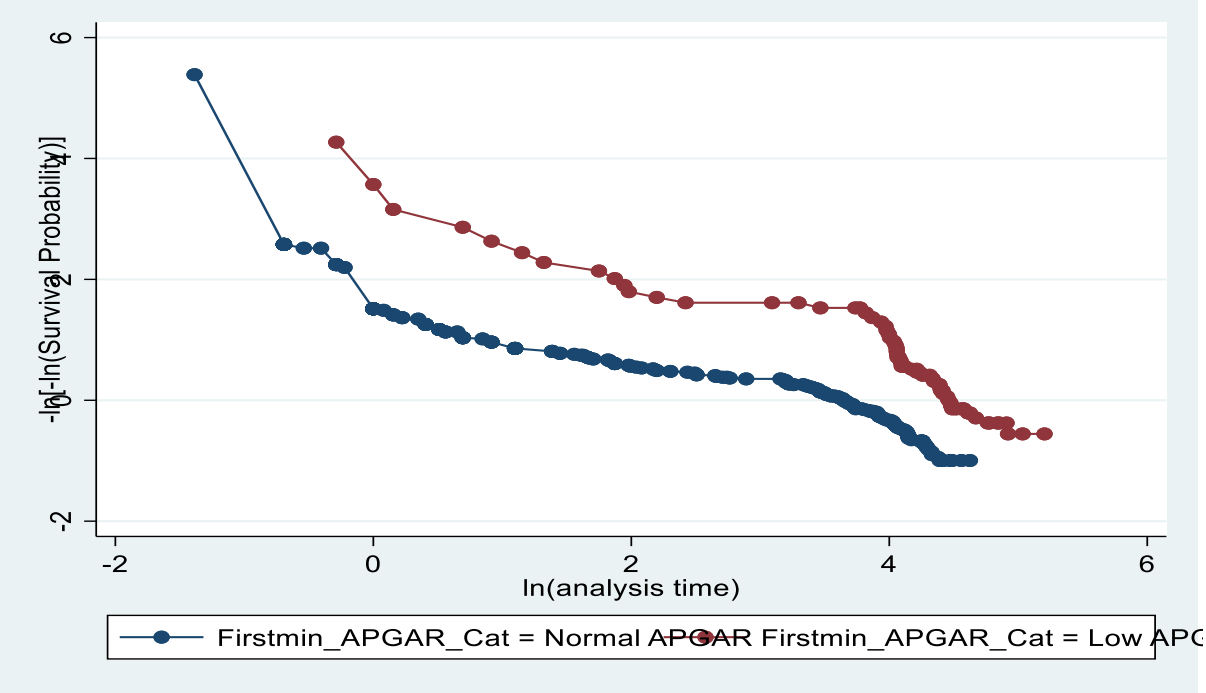
### Schoenfeld test of proportionality of hazard ratio

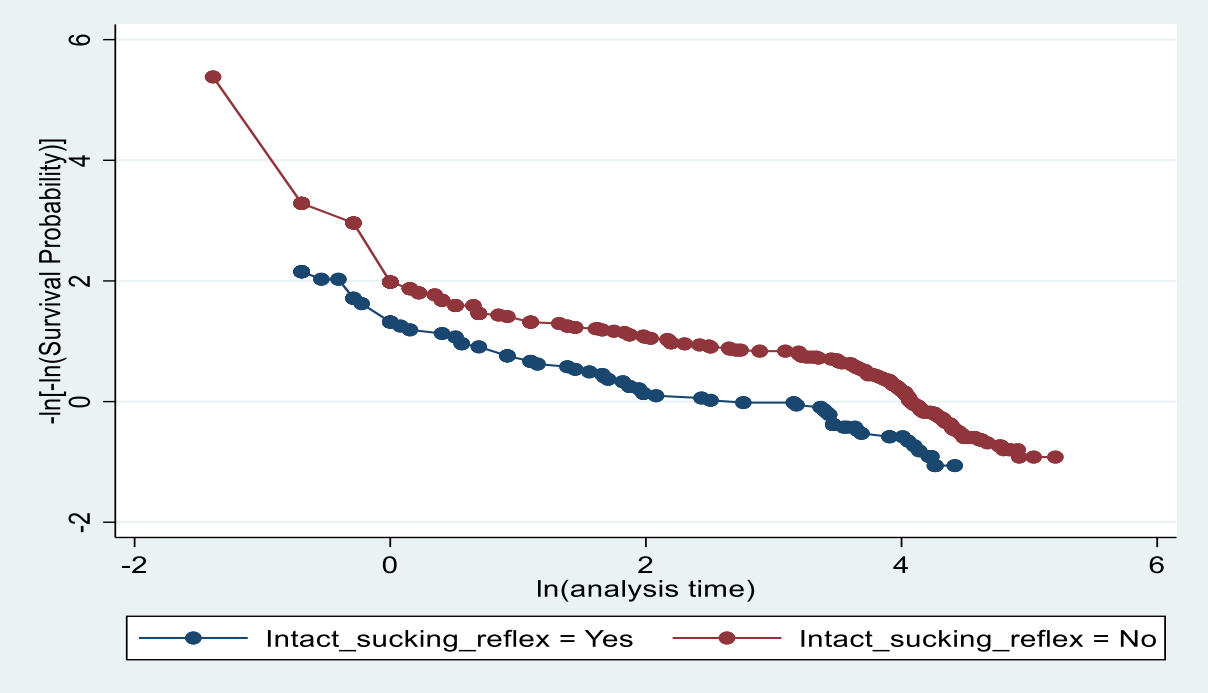
**Table 10**: Schoenfeld test of proportional hazard assumption for the study of the time to initiate TF among preterm neonates admitted to the NICU of AGH from January 2021- December 2023 (n=291).

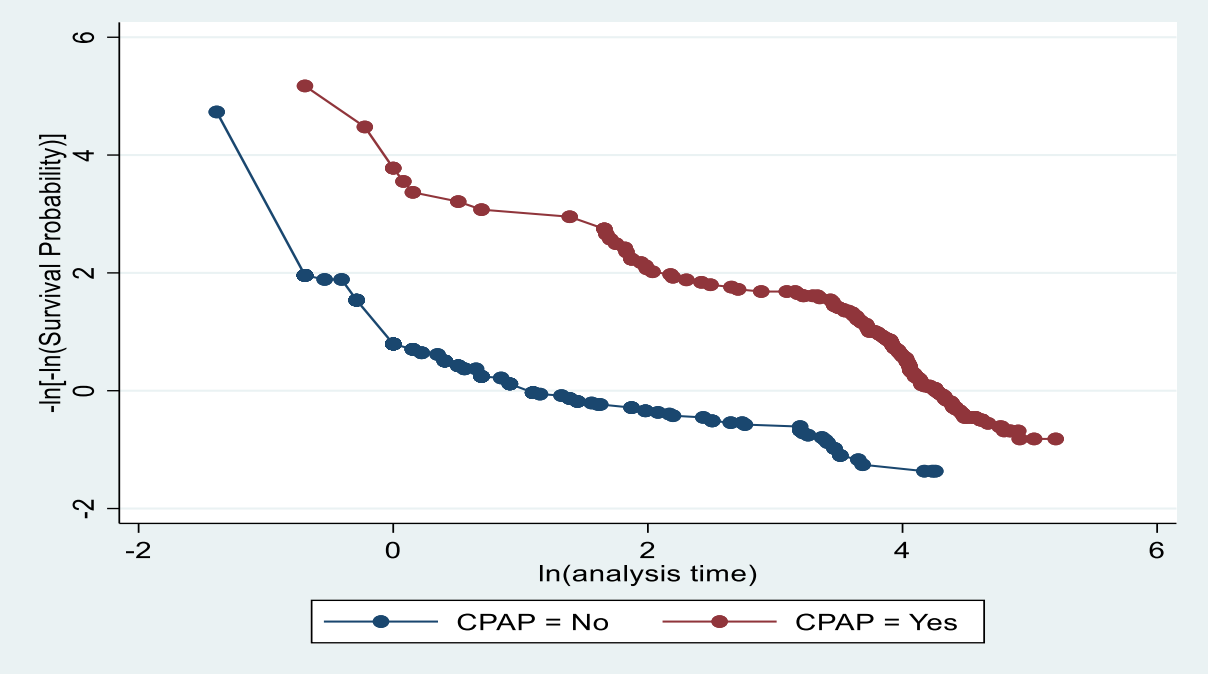
| **Predictor variable** | **rho** | **Chi2** | **df** | **Chi2 P value** |
|---|---|---|---|---|
| ANC visit | 0.00600 | 0.01 | 1 | 0.9266 |
| Health institution | -0.03499 | 0.31 | 1 | 0.5787 |
| PROM | 0.02528 | 0.16 | 1 | 0.6911 |
| Birth weight | -0.10109 | 2.18 | 1 | 0.1401 |
| RDS | -0.07172 | 1.13 | 1 | 0.2869 |
| Hypothermia | -0.02123 | 0.11 | 1 | 0.7405 |
| First minute APGAR score | -0.02804 | 0.20 | 1 | 0.6557 |
| Sucking reflex | -0.00624 | 0.01 | 1 | 0.9196 |
| Hemodynamic instability | 0.11558 | 2.79 | 1 | 0.0947 |
| CPAP | 0.07779 | 1.20 | 1 | 0.2730 |
| Global test | | 14.36 | 10 | 0.1572 |

**Log-log plots**

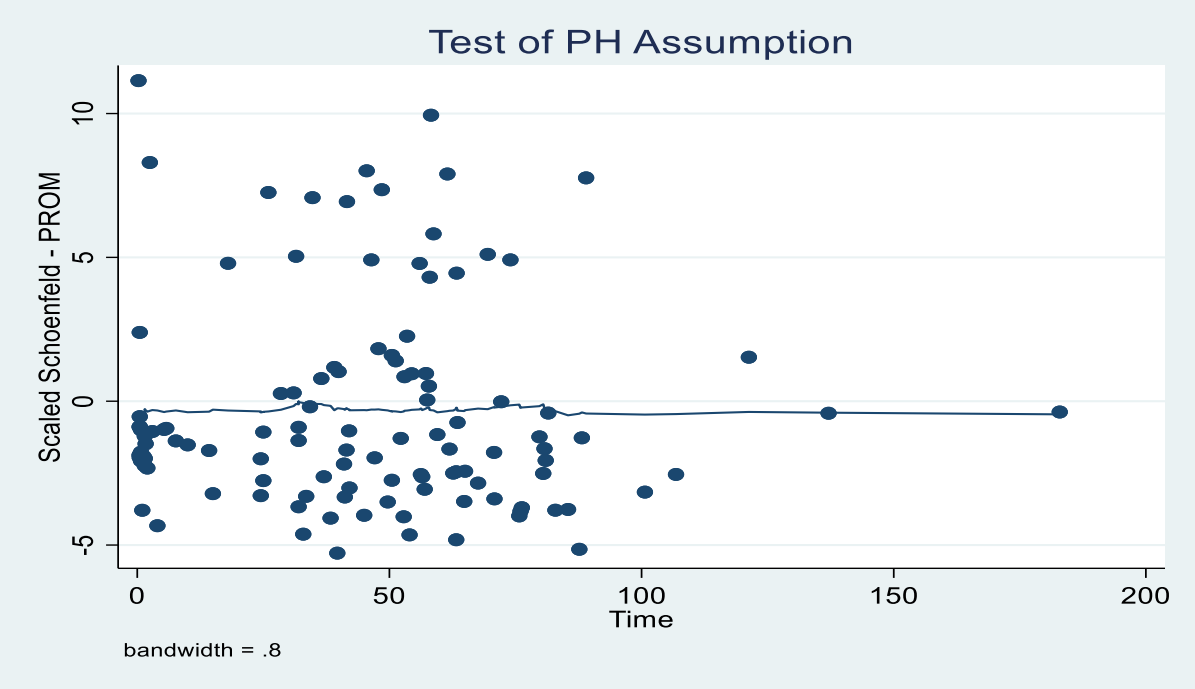


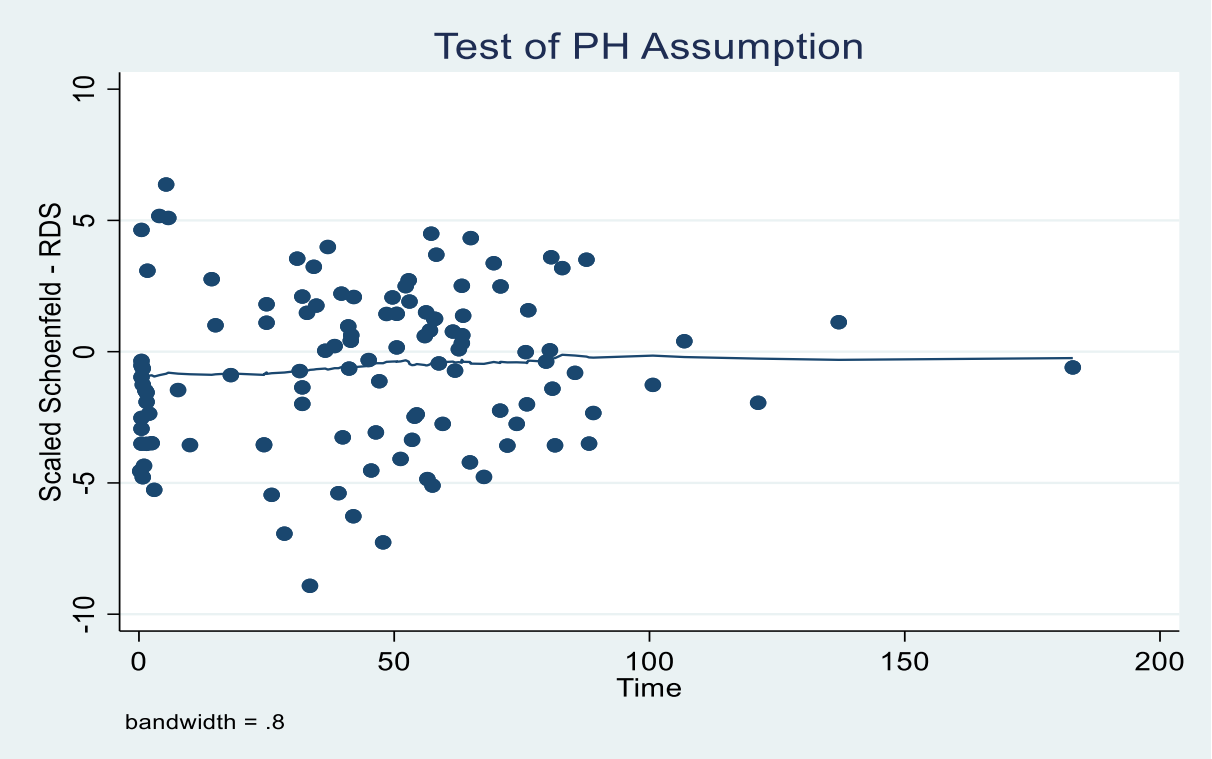



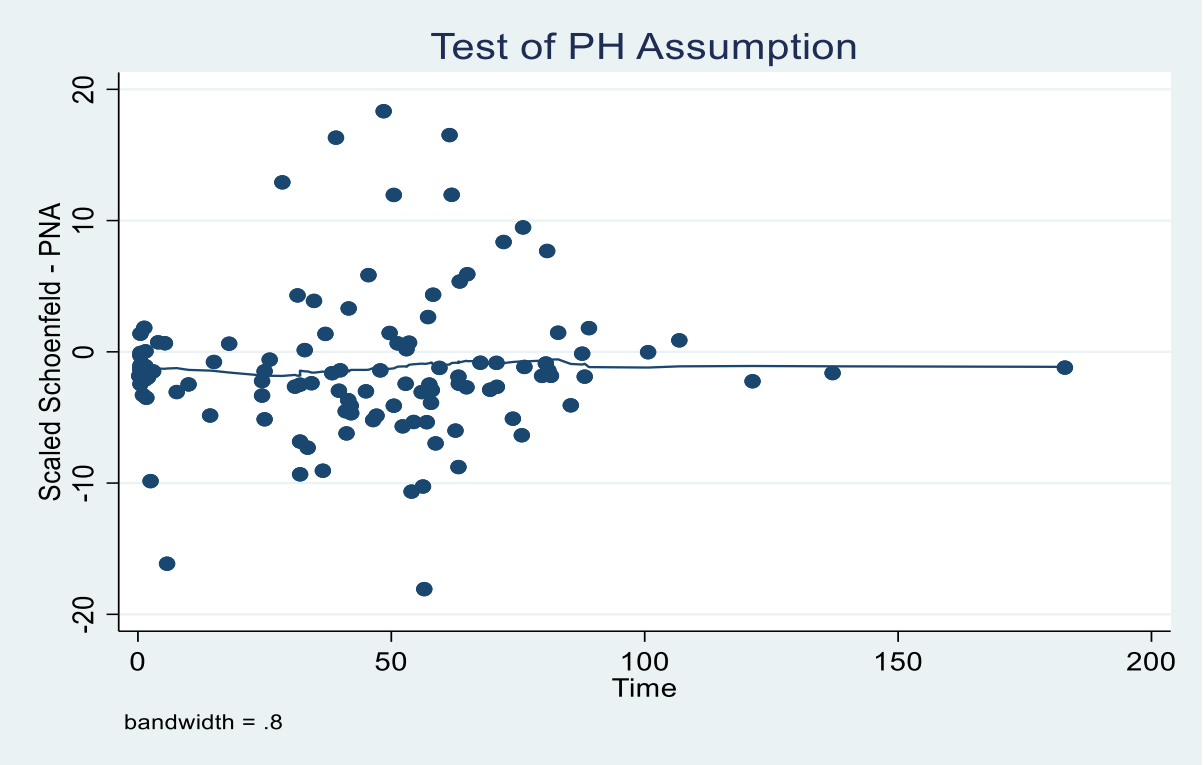

-ln[-ln(Survival Probability)]
6
4
2
0
-2
-2
0
2
4
6
ln(analysis time)
Intact_sucking_reflex = Yes
Intact_sucking_reflex = No

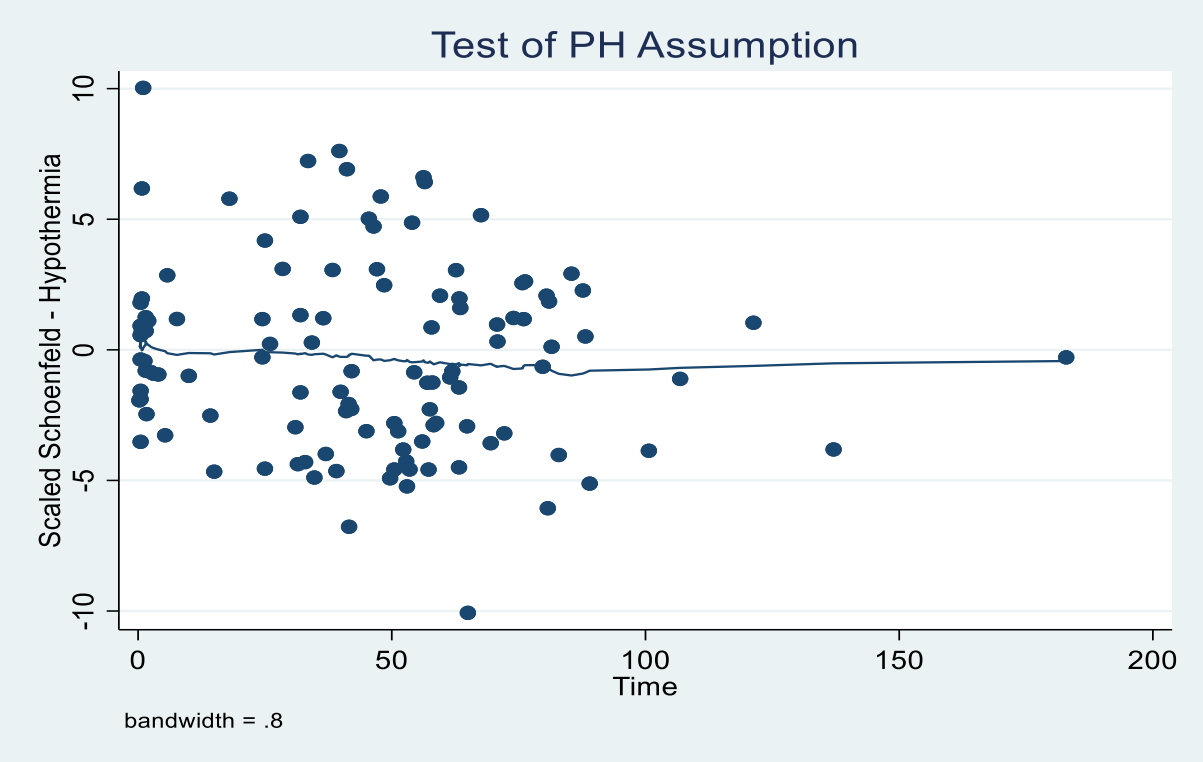

-ln[-ln(Survival Probability)]
6
4
2
0
-2
-2
0
2
4
6
ln(analysis time)
CPAP = No
CPAP = Yes

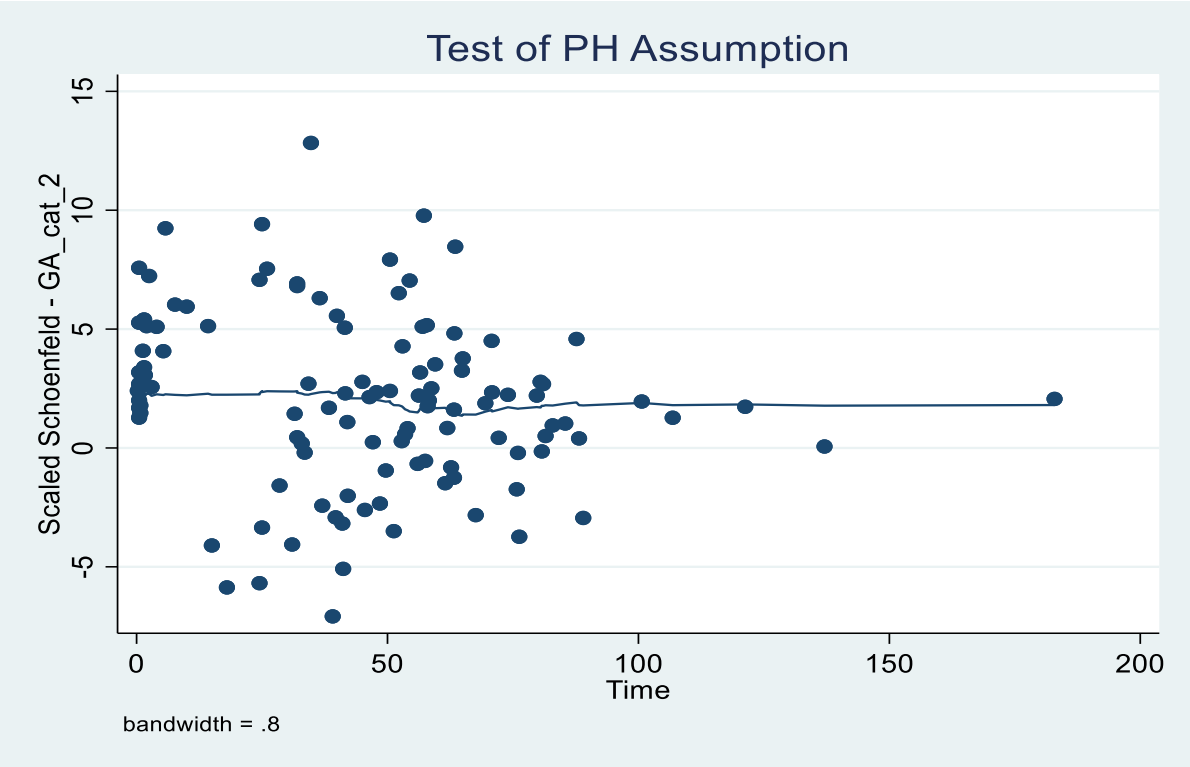
**Schoenfeld residual plots**

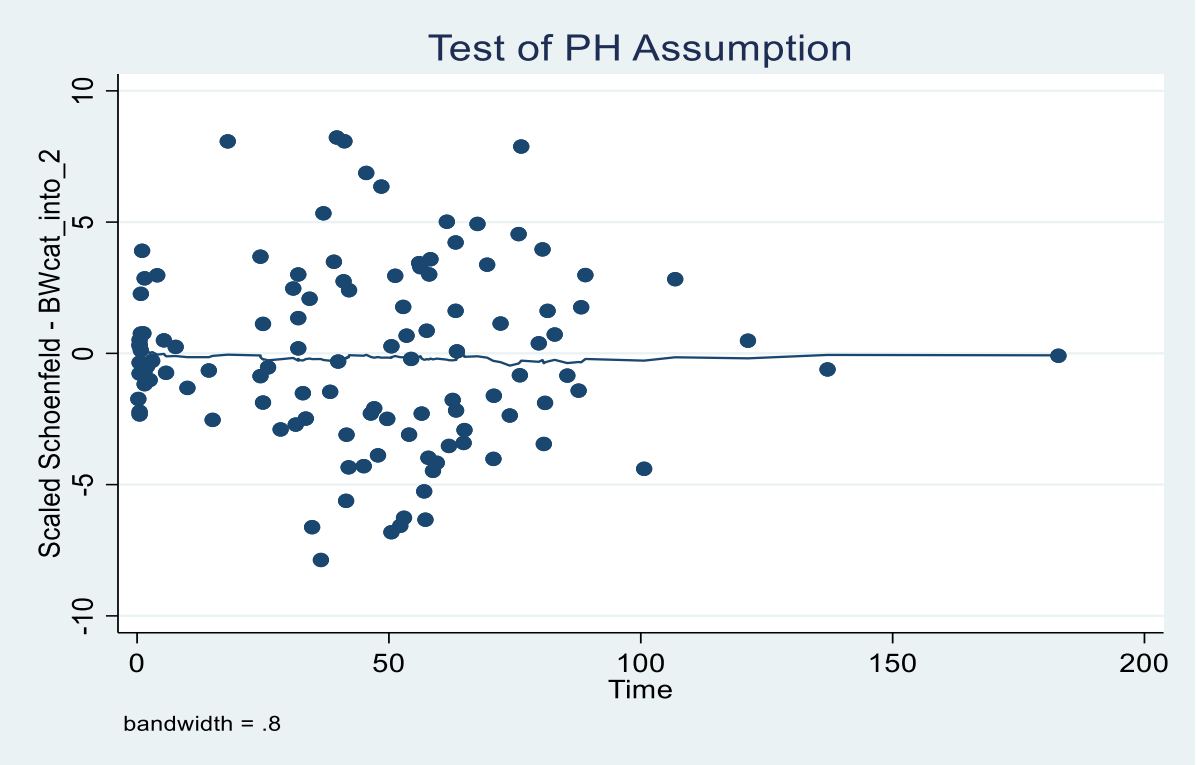



Test of PH Assumption
Scaled Schoenfeld - PNA
20
10
0
-10
-20
0
50
100
150
200
Time
bandwidth = .8


Test of PH Assumption
Scaled Schoenfeld - Hypothermia
10
5
0
-5
-10
0
50
100
150
200
Time
bandwidth = .8


Test of PH Assumption
Scaled Schoenfeld - GA_cat_2
15
10
5
0
-5
0
50
100
150
200
Time
bandwidth = .8


Test of PH Assumption
Scaled Schoenfeld - BWcat_into_2
10
5
0
-5
-10
0
50
100
150
200
Time
bandwidth = .8