# Survival time and its predictors among preterms in the neonatal period post-discharge in Busoga region-Uganda June – July 2017

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## ABSTRACT

**Introduction:** Globally, out of 15 million babies born preterm each year, one million die. In Uganda, preterm deaths contribute 30% of the neonatal mortality rate. There is a paucity of information on the most critical time to conduct high impact interventions among neonate born preterm especially post-discharge from hospital. We determined the survival time to mortality and its predictors among preterm infants in the neonatal period post-discharge from hospital. **Methods:** We conducted a prospective cohort study in which 128 preterm infants were recruited from six hospitals including Jinja Regional Referral, St. Francis Buluba, Kamuli mission, Iganga, Kamuli and Bugiri district hospitals were prematurity was confirmed using gestation age and birth weight. Initially, background characteristics of the participants were assessed and then followed prospectively until 28 days. Kaplan-Meier survival analysis was used to estimate survival probabilities while time to preterm mortality was described using the 5thpercentile. Cox proportional hazards regression was used to determine predictors of survival. **Results:** Overall, 8% (10/128) of the preterm infants died; the 5th percentile survival time was 17 days. There was a 6-fold increase in hazard to mortality among preterm infants who had Kangaroo Mother Care (KMC) compared to those who did not (adjusted HR: 6.4, 95%CI: 1.7 – 24.5), a 5-fold increase in the hazard to preterm mortality among preterm infants born to HIV positive mothers compared to their counterparts who had HIV negative mothers (adjusted HR: 4.9, 95%CI: 1.1 – 22.2); and a 4-fold increase in the hazard to preterm mortality among preterm infants who were not exclusively breastfed compared to those who were exclusively breastfed (adjusted HR: 4.4, 95%CI: 1.1 – 18.3). **Conclusion:** Among babies who died, death occurred in the first 17 days while factors negatively associated with preterm survival included; not practicing Kangaroo Mother Care, not being breastfed exclusively and being born to an HIV positive mother. We recommend follow-up care for preterm infants following hospital discharge, implementation of prevention of mother to child transmission of HIV and exclusive breastfeeding of preterm babies.

## Introduction

Globally, 15 million babies are born preterm each year. Of these, 1 million die shortly after birth while most of those that survive suffer physical and cognitive disabilities [1]. Over 60% of all preterm births take place in sub-Saharan Africa and Asia [2]. Although great innovations and improvements have been made in reducing under-five mortality, over two million newborns die every year from preventable causes mainly related to prematurity [3,4]. Moreover, preterm birth rates are increasing and currently responsible for over 35 percent of the world's neonatal deaths [5]. While almost half of all childhood deaths occur in the neonatal period (0 – 28 days after birth), babies born preterm are between 6 and 26 times more likely to die during the first four weeks of their lives than babies born at term [3].

The estimated preterm birth rate in Uganda is 13.6 per 1000 live births. However, most of the preterm deaths are experienced in the neonatal period after the preterm has been discharged from hospital [6]. Despite efforts to reduce the neonatal mortality rate (NMR), the Uganda Demographic and Health Survey (UDHS) reports an NMR which has stagnated at 27 per 1000 live births in 2011 and 2016 UDHS surveys [7,8]. Given the contribution of preterm birth to the NMR, there is paucity of information on the most critical time to conduct high impact interventions among neonate born preterm – with an overall effect of reducing the NMR.

In sub-Saharan Africa, the risk factors for preterm mortality are hypothermia, respiratory distress syndrome, high vulnerability to severe infection and difficulty feeding [9–11]. Over the years, low cost recommended measures such as practice of Kangaroo Mother Care (KMC) (which involves continuous skin to skin contact in an effort to improve thermoregulation), exclusive breastfeeding and home visits have been implemented to reduce the risk of preterm mortality [5,11–13].

Given that majority of preterm deaths occur in the neonatal period [2], and these contribute over 30 percent to the NMR. In addition to the paucity of information on risk factors for preterm mortality in Uganda. There was a need to determine the time within the neonatal period when majority of preterm infants die – especially after discharge from hospital in order to guide Ministry of Health and her partners on the most effective time period to plan interventions for maximum survival among preterm infants born in hospital. We sought to determine the survival time to preterm mortality and its predictors in the neonatal period post-discharge from hospital.

## Methods

### Study area

The study was conducted in six health facilities in Busoga region. Busoga sub-region, located in Eastern Uganda occupies an area of approximately 10,000 square kilometers. According to the 2014 national census, the region has a population of 3.8 million people and is home to >40% of the people in Eastern region and covers 10 districts including Bugiri, Buyende, Iganga, Jinja, Kaliro, Kamuli, Luuka, Mayuge, Namayinga and Namutumba. Busoga region has a high maternal mortality ratio (MMR) of 438 per 100,000 live births and NMR of 38 per 1000 live birth which are poor indicators compared to National MMR of 336 per 100,000, NMR of 27 per 1000 respectively [8]

### Study setting

Busoga region hosts the Preterm Birth Initiative (PTBI) which is currently being implemented by Makerere University School of Public Health in partnership with University of California San Francisco. In a bid to improve preterm outcomes, the PTBI established a number of interventions in addition to a follow-up system for all preterm infants born in six hospitals in the region including Jinja Regional Referral Hospital, St. Francis Buluba and Kamuli Mission Hospitals and Iganga, Bugiri and Kamuli general hospitals. Prior to discharge, preterm infants are assessed to ensure they are fit to be discharged and if so, their caregivers are taught to take care of preterm while those who deemed not fit for discharge are retained for further management – all preterm infants at the six hospitals

that were deemed fit for discharge between June and July 2017 were included in this study.

## Study design

We conducted a prospective cohort study. All preterm infants born between June and July 2017 from six district hospitals were included in the study.

## Data collection

*Recruitment*: healthy preterm infants (fit to be discharged) from hospital were recruited and baseline characteristics and measurements were obtained. Prematurity was confirmed by gestation age (<37 weeks) using a standardized neonatal examination tool. We adjusted age of the preterm infants (by subtracting the number of days born premature from the chronological age)

*Follow-up*: Preterm infants were followed up weekly for the first 28 days of life (neonatal period). At each visit, the outcome (preterm survival or mortality), time to survival and predictors of survival were assessed. Using phone contact information from the PTBI registry, caregivers were reminded to attend follow up visits with their preterm infants. Those who were not accessible through phone contacts were physically traced using other available information from PTBI database. Preterm infants with poor indicators (especially poor weight gain per day) were referred to the nearest district or regional referral hospital for further management. These were identified when screening preterm infants for eligibility to participate in this study and at subsequent follow up visits.

*Quality control*: we recruited research assistants based on their ability to administer study tools in either Lusoga or Luganda. In addition to the research assistants, we recruited study nurses from each of the six hospitals were the study was conducted. These were trained prior to data collection.

## Data processing and analysis

*Dependent variables*; the dependent variable was survival of babies born preterm which was dichotomized (survived or did not survive). The time event variable was time to preterm mortality. Preterm infants who were lost to follow-up were censored. However, we incorporated their total time contribution to the study when computing the total follow-up time. We computed the $5^{th}$ percentile survival time because the median survival time had not yet been achieved by the end of the study.

*Independent variables*; The independent variables included; caregiver's essential newborn care practices (cord care, thermal care, breast feeding, personal illness prevention and control practices), socioeconomic (education level, employment status, income level, type of residence), environmental (sanitation and hygiene care, presence of tobacco smoker in the house, indoor cooking), maternal characteristics (age of caregiver, parity and caregiver's knowledge on preterm care), Annex1.

*Predictors of Preterm Survival*: Cox proportion hazard analysis was used to explore the association between independent characteristics and time-to death at bivariate and multivariate analyses. Hazard ratios were obtained. The model was built using a forward stepwise approach (i.e. forward selection of variables followed by backward elimination). The inclusion criteria were characteristics with $p$-value $\leq 0.2$ at bivariate analysis as recommended by Bendel and In Lee [14,15]. Characteristics with $p$-value $< 0.05$ were reported as predictors of preterm survival. All variables in the multivariable model were subjected to hazard proportion assumption violation tests using the log-log plots and the global proportion hazard tests. From both tests, the proportional hazards assumption was not violated.

*Censoring*; preterm infants that were lost to follow up were censored. However, the total time they contributed to the study was incorporated during analysis of results.

## Ethical Considerations

Institutional Review Boards (IRB) approval was obtained from Makerere University School of Public Health Higher Degrees Research and Ethics committee and Uganda National Council of Science and Technology prior to conducting the study. Permission was obtained from the respective hospital medical superintendents. In addition, prior to participation in the study, a detailed informed consent (with a summary of the study, its risks and benefits of the study in the local language) was obtained from caregivers of preterm neonates. During interviews, confidentiality was maintained. The data collected from the participants were de-identified, kept under key and lock. The electronic dataset was password-protected and only accessible to the research supervisor and the Principal investigator. All preterm infants with poor indicators were referred for medical attention.

## Results

### Socio-demographic characteristics of preterm infants and caregivers

Overall, 128 preterm infants (Jinja Regional Referral: 36, St. Francis Buluba: 9, Kamuli Mission: 11, Iganga district: 18, Bugiri district: 23 and Kamuli district: 21 general hospitals) were included in the study. Of the 128 preterm infants, 35.2% (45/128) were male. Censoring was conducted at varying stages of follow up - for instance; five percent of preterm infants were censored in the first week of follow up, six percent were censored after two weeks of follow up, 28 percent of preterm infants were censored at three weeks while the majority (60.2 percent) of the preterm infants were followed for the entire four weeks. The total time that participant contributed to the study was thus incorporated at analysis.

The mean age of preterm infants at discharge was 4 days (SD +/- 3 days). The mean weight was 1.8 kg (SD +/-0.6 kg). Of the caregivers, 5.5% (7/128) were positive for HIV. The majority of the caregivers 66.4% (85/128) had post primary education level (Table 1). Overall, 7.8% (10/128) of preterm babies did not survive. The total time at risk was 2567 days while the mortality rate was 0.39 per 100-person days. The 5th percentile survival time to mortality was 17 days.

### Survival time to preterm mortality over the 28-day follow-up period

Most of death occurred at 7 days (60%), 20% (2/10) occurred at 21 days and 20% (2/10) at 28 days. The proportion of preterm babies that survived at 7 days was 0.95 (95%CI: 0.90 -0.99). No death was registered at 14 days. However, the proportion who survived at 21 days was 0.93 (95%CI: 0.87 – 0.97) while 0.89 (95% CI:0.80 – 0.95) survived at 28 days (Figure 1).

### Factors associated with Preterm Survival

Preterm infants who were not on KMC had a 5-fold increased hazard to mortality compared to their counterparts on KMC (unadjusted hazard ratio (HR): 5.4, 95% CI: 0.1 – 0.7). Similarly, preterm infants born to mothers with primary or no education had a 4-fold increased hazard to mortality compared to those born to mothers with post-primary education (Unadjusted HR: 4.3, 95% CI: 1.1 – 16.3). There was an 8-fold increase in the hazard to preterm mortality among preterm infants born to HIV positive mothers compared to those born to HIV negative mothers (Unadjusted HR: 7.9, 95% CI: 2.0 – 30.7). Preterm infants who were not exclusively breastfed had a 5-fold increase in the hazard to preterm mortality than those exclusively breastfed (Unadjusted HR: 4.6, 95% CI: 1.2 – 18.0). Preterm infants whose mothers had a good nutrition status (mid-upper arm circumference (MUAC) ≥24.5cm) had a 75% reduction in the hazard to preterm mortality than those whose mothers had poor nutrition (MUAC <24.5cm), Unadjusted HR: 0.3, 95%CI: 0.1 – 0.9.

### Predictors of Preterm mortality

In the adjusted model containing practice of KMC, Mother's age group, Education level, mother's HIV status, breastfeeding practices and mother's nutrition status (MUAC); we found a 6-fold increase in hazard to mortality among those who had KMC compared to those who did not(adjusted HR: 6.4, 95%CI: 1.7 – 24.5);, a 5-fold increase in the hazard to preterm mortality among preterm infants born to HIV positive mothers compared to their counterparts (adjusted HR: 4.9, 95%CI: 1.1 – 22.2); and a 4-fold increase in the hazard to preterm mortality among preterm infants who were not exclusively breastfed compared to those who were (adjusted HR: 4.4, 95%CI: 1.1 – 18.3)

## Discussion

We found that majority of the deaths among preterm infants occurred in the first week of life. This is consistent with a systematic review where authors found that majority of neonatal deaths in developing countries occurred in the first week [16].The preterm mortality rate in this study (0.39 per 100 person days) is lower than findings from a nationwide population study in Ghana where mortality for infants below 2.5Kg was 2.25 per 100 person days [17]. The possible reason for this was, that preterm infants in this study were followed for at most 28 days whereas follow-up period in the study in Ghana was one year. O'Leary *et al* in the aforementioned in the above study reported very high illness rates among the infants and poor health seeking behavior among caregivers with small, fragile and ill patients. This could have contributed to the higher mortality rate when compared with caregivers of preterm infants in this study who generally perceived their preterm infants to be extremely vulnerable and thus sought care whenever they were ill.

We also found that not using KMC, not exclusively breastfeeding and being born to an HIV positive mother were predictors of preterm mortality. Hypothermia due to poor body temperature regulation has been cited as one of the cardinal risk factors for preterm mortality [5,9,10]. Moreover, KMC on the other hand is a very effective low-cost intervention to prevent hypothermia among preterm infants [18–20].

Findings from this study showed that preterm infants that were not on KMC in the neonatal period had a 4-fold increase in the hazard to mortality compared with their counterparts who received KMC. Most of those that were not on KMC were preterm infants whose mothers had had a caesarian delivery and therefore could not practice KMC. This is consistent with findings from Waiswa *et al*. who found that regardless of the place of birth of a neonate, KMC resulted into better outcomes and therefore could be scaled up by involvement of community health workers through home visits [12].

There was a 5.6-fold increase in the hazard to preterm mortality among preterm infants born to HIV positive mothers compared to those born to HIV negative mothers. Findings from this study are comparable those in Kenya in which authors found a 4-fold increase in the risk to mortality among infants born to HIV positive mother compared to those born to HIV negative mothers [21]. Preterm infants on replacement feeding had a 4.3-fold increased hazard to preterm mortality compared with their counterparts who were exclusively breastfed. Our findings are consistent with a study by Kagaayi *et al* who found that replacement feeding was associated with a 6.1 increase in mortality [22,23]. These findings may be generalized to Busoga region because all hospitals in the region were included in the study.

## Conclusion

Among babies who died, death occurred in the first 17 days while factors negatively associated with preterm survival included; not practicing KMC, not being breastfed exclusively and being born to an HIV positive mother. We recommend that the Ministry of Health and partners should implement evidence-based integrated newborn care programs for preterm babies that includes follow-up care following hospital discharge, prevention of mother to child transmission of HIV and with emphasis on exclusive breastfeeding.

## Availability of data and materials

Data and materials can be made available by the corresponding author based on reasonable request.

## What is known about this topic

- Previous studies in the same area have; estimated the preterm birth rate; identified risk factors of preterm birth and predictors of mortality of preterms while in the health facility among others
- Majority of the work done in this topic focus on the period while the child born preterm is still in the health facility - most of these studies are not in Uganda
- This study provides more information about preterms especially after discharge from a health facility

## What this study adds

- Determines the most critical time to conduct high impact interventions among neonate born preterm especially post-discharge from hospital
- We determined the survival time to mortality and its predictors among preterm infants in the neonatal period post-discharge from hospital


## Acknowledgments

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## Competing Interests

The authors declare no competing interests


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## Authors´ contributions

CO conceived the idea and designed the study; led data analysis and interpretation; developed the first draft of the manuscript and made all revisions based on co-authors comments and suggestions. RM, OA, YA, FM critically revised the manuscript for important intellectual content; ensured the requirements of submission of the manuscript are met. JK, OA, RM contributed towards analysis and data interpretation; revision and editing of the manuscript. CK, CN, AM, AK contributed towards review for expert opinion and revision of manuscript for important intellectual content. JK, PW supervised the study from design to writing of the manuscript. All authors read and agreed to final version of the manuscript for publication.

## Tables and Figures

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**Table 3**: Multivariable Cox Regression Analysis for Predictors of Preterm Mortality in the Neonatal Period Post-discharge from Hospital, Busoga Region June and July 2017

**Figure 1**: Kaplan-Meier Survivor function for preterm infants over the 28-day follow-up period

## Annex

**Annex 1**: Measurement of Variables

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| Table 1: Socio-demographic characteristics of preterm infants and caregivers, Busoga region, June – July, 2017 (N = 128) | | |
|---|---|---|
| **Characteristics** | **Frequency** | **Percentage** |
| **Preterm** | | |
| Sex | | |
| Female | 83 | 64.8 |
| **Maternal** | | |
| Age | | |
| <20 | 31 | 24 |
| 20-34 | 52 | 40 |
| 35+ | 64 | 36 |
| Marital status | | |
| Married | 116 | 90.6 |
| Not married | 12 | 9.4 |
| Education level | | |
| Post primary | 85 | 66.4 |
| Primary or no education | 43 | 33.6 |
| Occupation | | |
| Business person | 32 | 25.0 |
| Salaried | 17 | 13.3 |
| Peasant | 41 | 32.0 |
| Unemployed | 38 | 29.7 |
| Residence | | |
| Urban | 34 | 26.6 |
| Rural | 94 | 73.4 |
| Religion | | |
| Muslim | 36 | 28.1 |
| Christian | 92 | 71.9 |
| HIV status | | |
| Negative | 121 | 94.5 |
| Positive | 7 | 5.5 |

| Table 2: Bivariate Cox Regression Analysis of predictors of Preterm mortality in the Neonatal Period Post-discharge from Hospitals, Busoga region, June – July, 2017 | | | | | |
|---|---|---|---|---|---|
| **Characteristics** | **Categories** | **Preterm survival** | | **Unadjusted model** | |
| | | **Survived n (%)** | **Did not survive n (%)** | **HR (95%CI)** | ***p*-value** |
| **Sex of preterm** | Male | 42 (35.6) | 3 (30.0) | Ref | |
| | Female | 76 (64.4) | 7 (70.0) | 1.3 (0.33 – 4.96) | 0.730 |
| **Practiced kangaroo mother care** | No | 24 (20.3) | 6 (60.0) | Ref | 0.009* |
| | Yes | 94 (79.7) | 4 (40.0) | 0.18 (0.05 – 0.66) | |
| **Mother's age group** | <20 | 25 (21.2) | 6 (60.0) | Ref | 0.104 |
| | 20-34 | 48 (40.7) | 3 (30.0) | 0.32 (0.08 – 1.24) | |
| | 35+ | 45 (38.197.83) | 1 (10.0) | 0.11 (0.01 – 0.89) | 0.039* |
| **Marital status** | Married | 108 (91.5) | 8 (80.0) | Ref | |
| | Not married | 10 (8.5) | 2 (20.0) | 2.6 (0.56 – 12.14) | 0.220 |
| **Educational level** | Post-primary | 80 (67.8) | 3 (30.0) | Ref | |
| | Primary or no education | 38 (32.2) | 7 (70.0) | 4.3 (1.14 – 16.33) | 0.030* |
| **Occupation** | Business person | 30 (25.4) | 2 (20.0) | Ref | |
| | Salaried | 16 (13.694.12) | 1 (10.0) | 0.85 (0.08 – 8.95) | 0.890 |
| | Peasant | 37 (31.4) | 4 (40.0) | 1.56 (0.28 – 8.84) | 0.610 |
| | Unemployed | 35 (29.7) | 3 (30.0) | 1.13 (0.19 – 6.78) | 0.890 |
| **Residence** | Urban | 32 (27.1) | 2 (20.0) | Ref | 0.630 |
| | Rural | 86 (72.9) | 8 (80.0) | 1.4 (0.32 – 6.4) | |

| Table 2: Bivariate Cox Regression Analysis of predictors of Preterm mortality in the Neonatal Period Post-discharge from Hospitals, Busoga region, June – July, 2017 | | | | | |
|---|---|---|---|---|---|
| **Characteristics** | **Categories** | **Preterm survival** | | **Unadjusted model** | |
| | | **Survived n (%)** | **Did not survive n (%)** | **HR (95%CI)** | ***p*-value** |
| **Mothers HIV status** | Positive | 4 (3.4) | 3 (30.0) | Ref | 0.003* |
| | Negative | 114 (96.6) | 7 (70.0) | 0.12 (0.03 – 0.49) | |
| **Breastfeeding** | Exclusive | 80 (67.8) | 3 (30.0) | Ref | 0.020* |
| | Non-exclusive | 38 (32.2) | 7 (70.0) | 4.6 (1.2 – 18.0) | |
| **Mothers MUAC** | Good nutrition (≥24.5) | 91 (77.1) | 4 (40.0) | Ref | 0.020* |
| | Poor nutrition (<24.5) | 27 (22.9) | 6 (60.0) | 4.08 (1.15 – 14.46) | |
| **Anything applied to cord** | No | 20 (17.0) | 3 (30.0) | Ref | 0.310 |
| | Yes | 98 (83.1) | 7 (70.0) | 2.0 (0.52 – 7.79) | |
| **Passive smoking** | Yes | 12 (10.2) | 2 (20.0) | Ref | 0.310 |
| | No | 106 (89.8) | 8 (80.0) | 0.45 (0.06 – 2.11) | |
| **Preterm sleeps in ITN†** | No | 13 (11.0) | 3 (30.0) | Ref | 0.410 |
| | Yes | 105 (89.0) | 7 (70.0) | 0.28 (0.07 – 1.10) | |
| **Visit by a CHW**** | No | 97 (82.2) | 7 (70.0) | Ref | 0.270 |
| | Yes | 21 (17.8) | 3 (30.0) | 1.0 (0.28 – 3.40) | |
| **Know Danger signs of preterms** | No | 63 (53.4) | 5 (50.0) | Ref | 0.260 |
| | Yes | 55 (946.6) | 5 (50.0) | 0.5 (0.14 – 1.76) | |
| ***Statistically significant at 95% CI, ITN: Insecticide Treated Net ** CHW: Community Health Worker** | | | | | |

| **Table 3: Multivariable Cox Regression Analysis for Predictors of Preterm Mortality in the Neonatal Period Post-discharge from Hospital, Busoga Region June and July 2017** | | | |
|---|---|---|---|
| **Characteristics** | **Categories** | **Adjusted model** | |
| | | HR (95%CI) | P-Value |
| **Practiced kangaroo mother care** | Yes | Ref | |
| | No | 6.4 (1.65 – 24.45) | 0.007* |
| **Mother's age group** | <20 | Ref | |
| | 20-34 | 1.17 (0.22 - 6.057) | 0.846 |
| | 35+ | 0.27 (0.03 - 2.220) | 0.201 |
| **Education level** | Post primary | Ref | |
| | Primary or no education | 1.54 (0.33 – 7.14) | 0.579 |
| **Mothers HIV status** | Negative | Ref | |
| | Positive | 4.87 (1.07 – 22.19) | 0.041* |
| **Exclusive breastfeeding** | Exclusive | Ref | |
| | Not exclusive | 4.4 (1.07 – 18.34) | 0.040* |
| **Mothers MUAC** | Good nutrition (≥24.5cm) | Ref | 0.077 |
| | Poor nutrition (<24.5cm) | 3.3 (0.88 – 12.3) | |
| ***Statistically significant at a 95% CI** | | | |

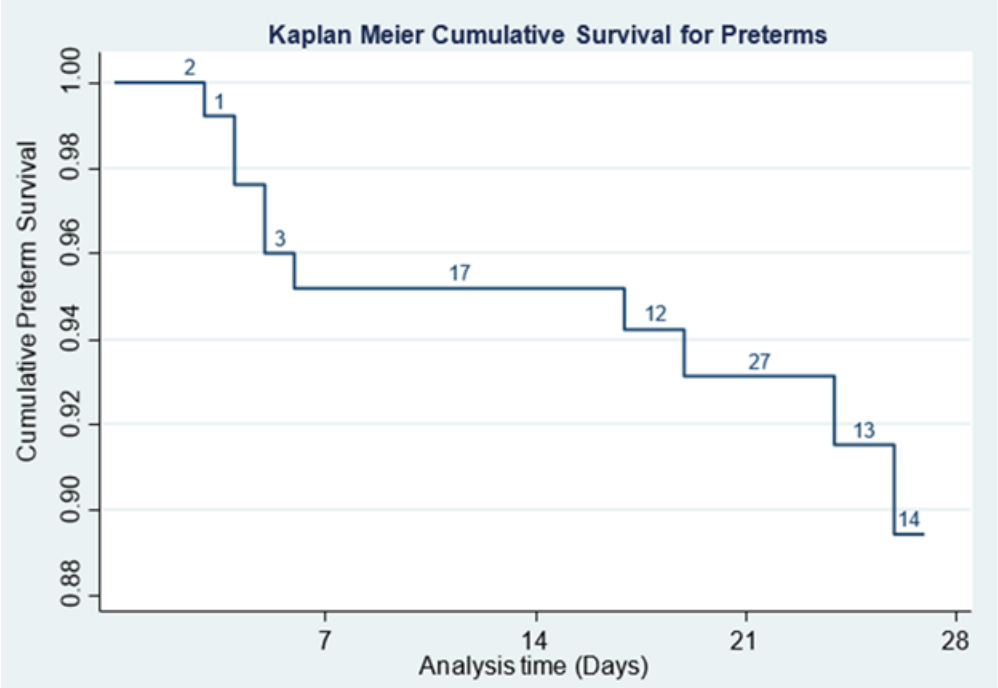


**Figure 1:** Kaplan-Meier Survivor function for preterm infants over the 28-day follow-up period

| ANNEX 1: Measurement of Variables | |
|---|---|
| **Variables** | Measurement |
| **Time to mortality** | ▪ Time was measured in days<br>▪ The age of the preterm was based on Adjusted age (age of the baby based on the due date) and not chronological age (age of the baby from the day of birth). This was computed by subtracting the number of days or weeks of premature from the chronological age |
| **Caregiver's practices;** | Cord care, thermal care and breastfeeding among others. These were measured at nominal scale i.e. yes / no or exclusive or not-exclusive breastfeeding. |
| **Socioeconomic determinants** | |
| **Education level** | Measured at nominal scale i.e. post-primary and primary or no education |
| **Occupation** | These were classified as; business person, salaried, peasant and unemployed |
| **Type of residence** | These were grouped as either urban or rural |
| **Environmental determinants; Passive smoking and Indoor cooking** | These were measured at nominal scale i.e. yes / no |
| **Maternal determinants** | |
| **Know Danger signs of preterms** | These were measured at nominal scale i.e. yes / no |
| **Parity; Age of caregiver** | Measured at the ratio scale. Caregivers were asked to mention their age at the last birth date (in complete years) and parity. These were grouped at analysis |
| **Mother's MUAC** | Measured at ratio scale. However, at analysis, responses were grouped as either poor nutrition (<24.5) or good nutrition (≥24.5) |