

# Mortality rate and associated factors among preterm babies born in Moshi, north – Tanzania: A prospective cohort study

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## Research article

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# Abstract

**Introduction** Globally, approximately 15 million babies are born before term each year. Of these, more than 1 million die within the first 28 days of their life. Understanding the mortality rate and its predictors during neonatal period among preterm babies is crucial to help designing interventions to avert the situation. This study aimed to determine the neonatal mortality rate and associated factors among preterm babies born in Moshi Municipality, Tanzania. **Methodology** A prospective cohort study was conducted in three hospitals in Moshi Municipality from December 2016 to May 2017. All live births at gestational age of <37 weeks and those of <24 hours were studied. Babies who died prior to gestation age assessment and those whose mother did not consent were excluded. Cox regression model was used to estimate maternal and fetal factors associated with neonatal mortality. A p-value of <0.05 was considered statistically significant. **Results** A total of 311 of preterm babies were recruited from 265 mothers and were followed for 28 days. The neonatal mortality rate was 6.5 deaths per 1,000 preterm live births (95% CI: 4.83-8.61). It was higher among extremely preterm babies compared to very preterm ones (HR: 38.24; 95% CI: 16.62-87.96) versus (HR: 8.01; 95% CI: 3.96-16.20) respectively. Apgar score of <7 at 1st minute (HR: 14.03; 95% CI: 7.27-27.06), respiratory distress syndrome (HR: 8.14; 95% CI: 4.27-15.54) and antepartum hemorrhage (HR: 3.32; 95% CI: 1.49-7.39) were significantly associated with neonatal mortality. **Conclusion** Preterm birth complication is the major cause of neonatal death in the study setting. Interventions to address the identified risk factors may reduce neonatal mortality among preterm babies.

## Introduction

Globally, it is estimated that about 130 million babies are born every year. Of these, 15 million (11.5%) are born preterm of which more than 1 million die within their first 28 days of life [1]. Prematurity has been reported as a leading cause of child death globally. The rate of preterm births has been reported to increase in most countries but it is higher in low-and-middle income countries than developed countries (25% versus 5%) respectively. Southern Asia and Sub-Sahara Africa account for almost 60% of global preterm births burden and majority of these babies are moderate preterm, very preterm with few extreme preterm [1, 2].

Preterm birth is the major cause of perinatal morbidity and mortality as it has been reported to contribute up to 85% of all early infant deaths [3]. Preterm survivors suffer long-term life consequences including neuro-developmental impairment escalating the risk of cerebral palsy, learning impairments, visual disorders and affecting long term physical health leading to high risk of communicable diseases and poor growth [4].

Numerous factors contribute to preterm birth including early induction of labor or caesarian section, ordinary causes which comprise multiple pregnancy, infections and maternal conditions such as diabetes mellitus, hypertension and eclampsia [4, 5].

Majority of preterm babies die within the first 24 hours of their lives, making it the riskiest period. However more than three-quarter of these deaths can be averted by simple feasible, cost-effective interventions. These include stabilization, prevention and early treatment of infection, preventing hypothermia as well as early introduction of breast milk and further intensive neonatal care [2, 4, 6, 7]. Other interventions include helping the baby breath [8], provision of antenatal steroid and kangaroo mother care [5, 7]. Despite these interventions being in place, neonatal mortality rate is still high in Tanzania accounting for 19 deaths per 1000 live births [7]. Studies in Tanzania revealed direct complications of prematurity accounting for 18% of all the neonatal deaths where most of these babies die in the first 7 days of life [9]. However, the death among preterm within the first 7 days of life is as high as 39% [10]. In Tanzania and Sub-Sahara Africa, there is limited information on the factors associated with preterm mortality. Understanding the mortality rate among preterm and associated maternal and fetal risk factors is important to help designing appropriate interventions to avert the situation and will also accelerate the attainment of SDG 3 which aim to reduce newborn deaths to <12 deaths per 1000 live births by 2030. This study aimed at determining the neonatal mortality rate and associated factors among preterm babies born in Moshi municipality, Tanzania.

## Materials And Methods

### Study Design and setting

A prospective cohort study which was conducted from December 2016 to May 2017. During the study, all preterm babies who were born alive in the three hospitals located in Moshi Municipality were included in the cohort and followed up on day 1, day 3, day7, day 14 and day 28 of life. Follow-up parameters were adapted from the Tanzania Kangaroo Mother Care guideline [11] and were slightly modified to fit the study design. During the follow-up period, a reminder call was done to each participant 2 days before the follow up date through their mobile phones particularly for those who were not admitted in the respective hospitals.

The study participants were newborns from labour ward, obstetrics ward, neonatal ward, Kangaroo Mother Care (KMC) wards and neonatal follow up outpatient clinic. Labour ward was where most deliveries occurred and where most of the gestation age assessments were conducted. In the obstetrics and neonatal wards, most of cohort recruitment and interviews were done as well as follow up of the study participants. Follow up of participants was also done in KMC wards and Neonatal outpatient follow up clinic sites. We included all live births whose delivery took place at the study areas and aged <24 hours of life. Babies whose mothers refused to consent and those who died before gestational age assessment were excluded.

This study was conducted at three different hospitals in Moshi Municipality, north- Tanzania. These hospitals included Kilimanjaro Christian Medical Centre (KCMC), Mawenzi Regional Referral Hospital and Saint Joseph Hospital. KCMC is a tertiary zonal and teaching hospital with more than 450 bed capacity and serves a population of over 11 million individuals. It has a neonatal unit serving more than 50

neonates daily. On average, the hospital attends approximately 3000 deliveries annually and receives women from a diversified geographical area. Referrals account for approximately 20% of all deliveries that occur in the hospital. Mawenzi is the regional public referral hospital for Kilimanjaro region. It has about 300 bed capacity and provides a range of services across several departments. The hospital caters for about 300 outpatients each day. Saint Joseph Hospital is a district designated hospital with about 200 out-patients every day and about 300 inpatients. Approximately 1,084 deliveries occur annually in this facility.

### **Sample size estimation and sampling procedure**

The sample sizes for each hospital was based on the number of deliveries that occur per year in the selected hospital. Six months recruitment period lead to a total of 1500 newborn to be recruited at KCMC. At Mawenzi hospital, a total of 1,084 births were estimated to be assessed for gestation age while at St. Joseph hospital, 600 live births were estimated to be assessed. Women with <37 weeks of pregnancy were recruited in the cohort. Therefore, a total of 3,184 live births were estimated to be recruited during the study period.

### **Schematic flow of the study participants' recruitment**

There were 3354 deliveries from December 2015 to May 2017 in the study hospitals (Figure 1). A total of 265 mothers with their 311 newborns were legible and recruited.

### **Data collection**

The study variable included both newborn and maternal characteristics. The newborn variables included gestational age, sex, birth weight, birth order, diagnosis, and Apgar score. Maternal characteristics included age, gravidity, parity, area of residence, education level, medical history, peri-natal history, family history of diabetes mellitus, drugs used, hypertensive disorders in pregnancy, urinary tract infection, malaria and ante partum hemorrhage (APH). This information was collected using a pre-tested questionnaire. Gestational age assessment was done using the method described elsewhere [12]. Data collection was done by interview and physical examination of the newborns.

### **Statistical Analysis**

Data analysis was performed using STATA version 14. Numerical variables were summarized using measures of central tendency with their corresponding measures of dispersion. Frequency and proportions were used to summarize categorical variables. Cox regression models were used to estimate maternal and fetal factors associated with neonatal mortality. Kaplan –Meier survival curve was used to describe survival experiences of study participants and Log rank test was used to compare survival experience among groups of participants. A p-value <0.05 was considered statistically significant.

# Results

## Characteristics of study participants

A total of 311 preterm neonates were studied (Table 1). Majority (75.9%) were late preterm. More than half (53.1%) were females and nearly half (50.8%) of the neonates were delivered vaginally and had birth weight ranging from 1500 – 2499 grams (55.9%). Most of them had an Apgar score  $\geq 7$  in the 1<sup>st</sup> and 5<sup>th</sup> minutes.

(see Table 1 in the Supplementary Files)

## Characteristics of mothers with preterm neonates

A total of 265 mothers with preterm neonates were studied (Table 2). The overall mean age was 27.09 (SD=6.59) years. Nearly half (44.9%) were aged between 25-34 years. More than half (55.1%) lived in rural areas and had para 2-4 (55.9%) and had less than four (4) ANC visits (55.5%).

(see Table 2 in the Supplementary Files)

## Mortality Risk of Preterm Neonates

A total of 311 preterm babies were followed-up to 28 days. The end point was either death within 28 days of life, censoring due to lost to follow up or alive up to 28 days of life (Figure 2). During the first day of life, 20 neonates died. At day 3 of life of each neonate, a total of 273 neonates were at risk of death. On day 7, a total of 264 were at risk. On day 14 of life, 252 were at risk and on day 28, a total at risk were 246 preterm neonates.

## Neonatal complications of preterm babies

Respiratory Distress Syndrome (RDS) was the most frequent complication constituting about 26%, followed by multiple conditions (11.3%) and suspected early onset neonatal sepsis (EONS) (10.6%). Neonates with multiple conditions had either RDS and sepsis/congenital anomaly or RDS and EONS. Other conditions were infrequently observed (Figure 3).

## Maternal complications of preterm mothers

The most frequent complication was urinary tract infection (UTI) 94 (35.5%) followed by Premature rupture of membrane (PROM) (20%) and Pre-eclampsia (15.9%). Other complications such as epilepsy, chorioamnitis, puerperal psychosis, post-partum hemorrhage (PPH) and hypertension were infrequently reported (Figure 4).

## Frequency and mortality of preterm births

A total of 3,271 live births were assessed with their gestation age. Of these, 311 were preterm. This corresponds to frequency of preterm birth of 10%. During the follow-up, 292 preterm babies had completely known survival status. Forty-six (16%) preterm babies died within the follow up period. Most (95.7%) of deaths occurred during the hospital admission and 4.3% of deaths occurred at home post hospital discharge. Over forty-percent (43.5%) of deaths occurred within the first 24 hours of life. Three quarters (76%) of the deaths occurred within the first 7 days of life and 24% from day 7 to day 28 of life. Sixteen percent of those who had gestation age (GA) of < 32 weeks but >28 weeks died, while 95% of those with GA <28 weeks died. Only 5% of those with GA > 32 weeks died.

## Neonatal Mortality Rate among preterm babies

Neonatal mortality rate of the participants has been shown in Table 3. The overall neonatal mortality rate was 6.5 deaths per 1,000 live preterm births (95% CI: 0.48-0.86). Before the event (death) had occurred, the total time contributed by all individuals was 71.3 person years.

We further calculated neonatal mortality according to neonate characteristics (Table 3). Extreme preterm babies (GA <28weeks) had the highest mortality rate of 200 deaths per 1,000 preterm live births (95% CI: 113.58 - 352.17). Mortality rate of preterm babies with birth weight of <1 Kilogram was 94 per 1,000 preterm live babies (95% CI: 52.10-169.80). Nevertheless, preterm babies with Apgar score of < 7 in the 5<sup>th</sup> minute had higher mortality rate than those with Apgar score of <7 in the 1<sup>st</sup> minute of life [87.21(95% CI: 52.58 - 144.66) versus 40.93 (95% CI: 28.61 - 58.54) per 1000 live preterm live births respectively]. Furthermore, neonatal mortality rate among preterm babies with birth asphyxia was higher compared to those with respiratory distress syndrome [37.15 (95% CI: 21.20-65.42) versus 21.68 (95% CI: 15.33-30.66) per 1,000 live preterm births] respectively.

(see Table 3 in the Supplementary Files)

## **Overall survival time estimate**

The probability of survival rapidly decreased from day 1 to day 2, and thereafter, then it remained constant. The last event occurred on day 24 of life. Since the survival function did not fall below 50%, the median survival time could not be estimated. Instead, a restricted mean was calculated. The overall mean survival time was 24 days (Figure 5)

## **Survival time estimate in different groups**

Preterm with GA<28 weeks had lowest survival probability compared to other gestational age groups. Most of them died within the first 24 hours with median survival time of 1 day. Preterm neonates with GA between 32-36 weeks had highest survival probability and their restricted mean survival time was 26.9 days.

Preterm with birth weight<1000grams had higher mortality compared to those who had >1,000 grams. Their median survival time was 2 days. Majority of deaths were observed on day 1 and 2 with the last death occurring on day 20. Neonates with birth weight 1,000<1,500 grams had mean survival time of 18.2 days their survival probability decreased over time and the last neonate died on day 20. Preterm neonates with birth weight 1500 - 2,500 grams had a constant survival probability and their mean survival time was 26.1 days. However, those neonates with birth weight 2,500 grams and above had better survival probability and their mean survival time was 27.7 days. This corresponds with the survival probability for neonates with GA 32-36 weeks.

Preterm neonates with Apgar score <7 in the first minute died more on day 1 followed by day 2. Their survival probability decreased over time with median survival time of 14 days as compared to those with Apgar >7 in the first minute whose probability of survival was constant over time. Likewise, those with Apgar score <7 in the 5<sup>th</sup> minute died more on day 1 and their probability of survival decreased thereafter with time and their median survival time was 2 days. Those with Apgar score >7 in the 5<sup>th</sup> minute of life had almost a constant survival probability over time. In all the sub categories tested, the proportional hazards assumption for cox regression were seen to hold. Log rank test was significant at p<0.05 for gestation age, birth weight, and 1<sup>st</sup> and 5<sup>th</sup> minute Apgar score. This indicates difference in survival experience between categories in question (Figure 6)

## **Neonatal characteristics associated with neonatal mortality among preterm babies**

In crude analysis, gestation age <32 weeks, 1<sup>st</sup> and 5<sup>th</sup> minute Apgar score <7, respiratory distress syndrome and birth asphyxia were significantly associated with neonatal mortality among preterm babies.

In multivariable analysis, only variables which were significant in the crude analysis were included in the final model. Gestation age < 32 weeks, 1<sup>st</sup> min Apgar score < 7 and respiratory distress syndrome were found to be independent predictors of neonatal mortality among preterm babies. Extreme preterm neonates had 9 times higher hazard of dying (HR: 9.21; 95% CI: 2.54-33.47) than those with gestation age 32-37 weeks. Very preterm neonates (28-32 weeks) had 3 times higher hazards of dying (HR: 3.42; 95% CI: 1.34-8.69) compared to moderate/late preterm ones (32-37 weeks). Preterm neonates whose 1<sup>st</sup> min Apgar score was < 7 had 6 times higher hazards of dying (HR: 6.12; 95% CI: 2.76-13.58) compared with those with 1<sup>st</sup> min Apgar score of > 7. Preterm neonates with RDS had 2 times higher hazards of dying (HR: 2.54; 95% CI: 1.02-6.34) than those without RDS (Table 4).

(see Table 4 in the Supplementary Files)

### **Maternal Factors Associated with Neonatal Mortality among Preterm babies**

Adjusted analyses for maternal factors leading to mortality of preterm babies has shown only APH to be the independent predictor for mortality whereby women who experienced it had three times [3.32 (95% CI: 1.49-7.39)] more hazards to appreciate the deaths of their newborns compared to those who did not experience APH. Other factors were not statistically significant at  $p < 0.005$  as seen in Table 5 below.

(see Table 5 in the Supplementary Files)

## **Discussion**

In the current study, the neonatal mortality rate among preterm babies is 6.5 deaths per 1,000 live preterm births. This rate was lower compared to the previously reported in the USA by Basso & Wilcox [13]. The difference in findings could be explained by the differences in study participant's age and sample size. In rural setting of Bangladesh with dense population the neonatal mortality rate has been shown to be as high as 70.1/1000 live preterm in different levels of health facilities [14]. The rural settings that the study was done might explain why the rate differs from the current study which was conducted in the urban area with improvised medical facilities.

Respiratory distress syndrome (RDS) was significantly associated with increased mortality. Similar findings have been reported in Mwanza, Tanzania [10]. This could be due to the fact that the Mwanza study and our study were carried out in similar settings of the tertiary hospitals with lack of advanced neonatal care and lack of surfactant administration. Another reason could be that most cases were referral with complications. However, in Brazil, RDS was not significantly associated with preterm mortality during the neonatal period [18]. This might be explained by advancement of medical facilities

and preterm care in their hospital as well as surfactant administration and proper close monitoring of preterm babies.

Antepartum hemorrhage was the maternal factor that was significantly associated with preterm mortality. The finding is consistent with a study in Italy [19]. The similarities between the two studies are likely to be explained by the fact that APH itself is a cause of preterm delivery with complications that might cause mortality to the neonate due to multiple morbid conditions. However, in a hospital-based study in Nigeria, ante partum hemorrhage was not significantly associated with neonatal mortality among preterm babies [20]. The difference may be explained by the fact that information of the study population was obtained from secondary data source, hence higher chances of missing information. For this reason, the effect of APH on preterm mortality might have been underestimated.

In Australia, it was found that there was no association between APH and preterm mortality [17]. The differences might be explained with close monitoring antenatally with adequate administration of corticosteroids to enhance fetal lung maturity as well as early transfer to advanced tertiary level hospital of preterm babies. Moreover, immaturity has been described as the dominant predictors of deaths among preterm neonates.

The present study has number of strengths. Firstly, it was a prospective cohort study, that data was collected in a timely manner hence minimizing chances of missing information. Also, the use of mobile phone reminder call during follow up minimized the chances of lost to follow-up. Secondly, recruitment of participants was based on gestation age assessment which prevented the bias of using birth weight criterion as a proxy of prematurity in center-based approach. Thirdly, the study areas were catchment areas of different population from even outside Moshi, hence external validity of results.

Despite the strengths of our study, some limitations also need to be taken into account while interpreting our findings. Most of neonatal conditions diagnosed in the ward were picked based on clinical diagnosis. This may lead to differential or misclassification bias. Also, the mean survival time was high. This may be underestimated because largest observed analysis time was censored. There may be confounding effect or effect modification of both birth asphyxia and 5<sup>th</sup> minute APGAR score of less than 7 on neonatal mortality

## Conclusions

The burden of preterm deaths in our setting is high. This calls for more interventions to rescue deaths among very preterm babies who are believed to have higher chances of survival than extreme preterm babies in developing countries. More close monitoring post 48 hours is crucial to prevent preterm deaths. APGAR score <7 in the first minute of life was significantly associated with neonatal mortality among preterm babies, thus forecasting preterm mortality is possible using variables up to APGAR score in first minute of life. RDS was also significantly associated with neonatal mortality among preterm. This calls for urgent interventions to diagnose and treat RDS. Ante partum hemorrhage was the only maternal

independent predictor of neonatal mortality among preterm babies. Thus current and further interventions to prevent deaths from APH should be advocated from all levels of health care.

Strengthening care in preterm babies especially the very preterm by improving close monitoring in the 1<sup>st</sup> day of life and throughout neonatal period is crucial.

## **Abbreviations**

ANC: Antenatal clinic, APH: Ante partum haemorrhage, GA: Gestational age, HIC: High- income countries, HIV: Human immunodeficiency Virus, KCMC: Kilimanjaro Christian Medical Centre, MDGs: Millennium Development Goals, NEC: Necrotizing enterocolitis, PROM: Premature Rupture of Membrane

## **Declarations**

### **Acknowledgement**

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### **Funding**

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### **Availability of data and materials**

The data may be shared upon reasonable request

### **Authors Contributions**

RC, FM, CST and MJM primarily responsible for conceptualizing and scheming this study. RC, CST and FM: Conducted the study; MJM & CST performed data analysis; RC: Drafted the manuscript. All authors provided significant intellectual inputs in editing, revising and approving the manuscript before submission.

### **Competing Interest**

Authors declared to have no competing interest

## Ethical Consideration

Ethical clearance with reference number **957** was obtained from Kilimanjaro Christian Medical University College Clinical Research Ethics Review Committee. Permission to conduct the study was obtained from the respective hospital directors and heads of respective departments. Informed consent was signed before the enrolment of subjects. Those who did not consent were provided with equal care. During follow-up time, participants found with any clinical condition were provided with routine medical care as per respective hospital's guideline.

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## Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

## Figures

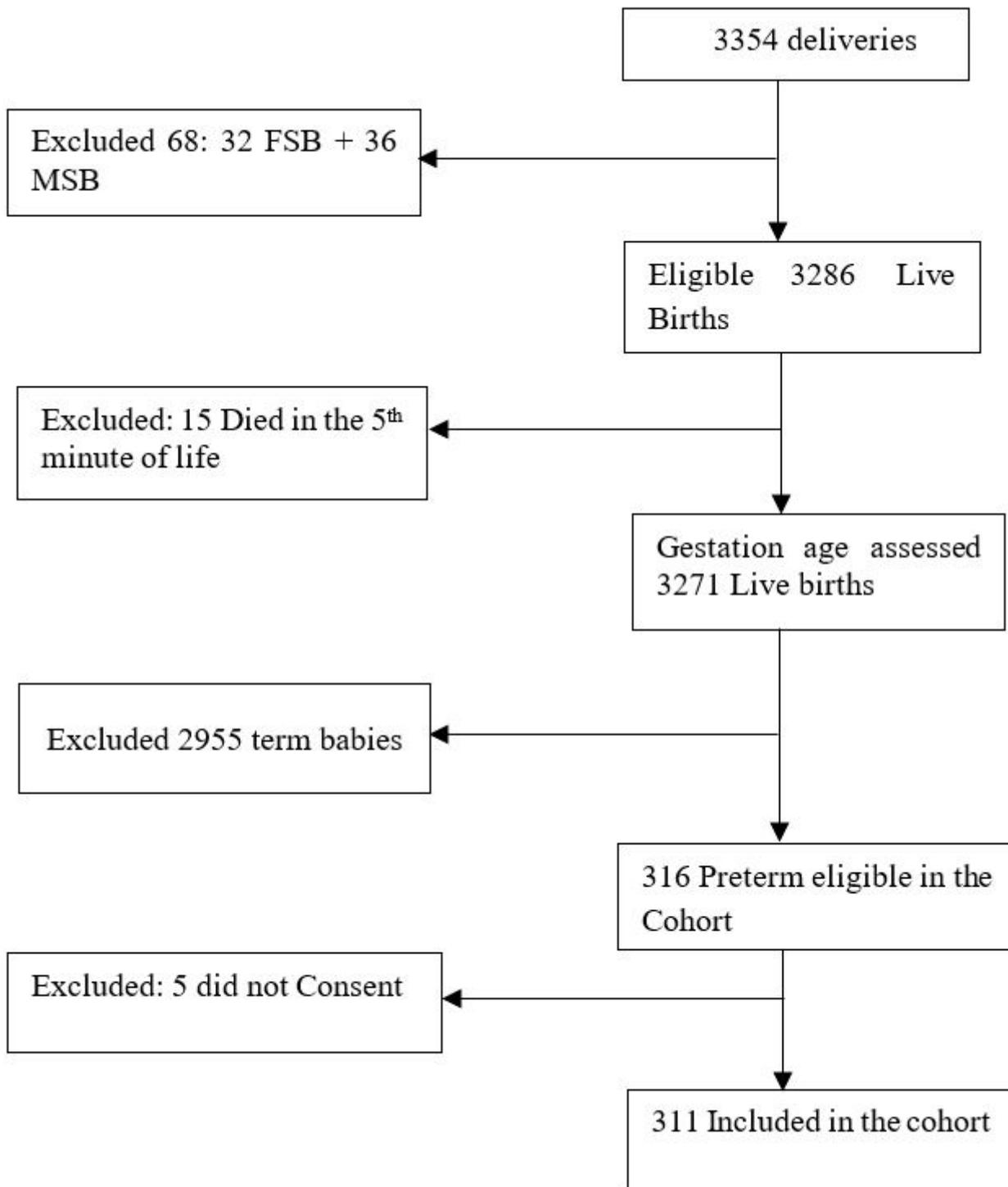
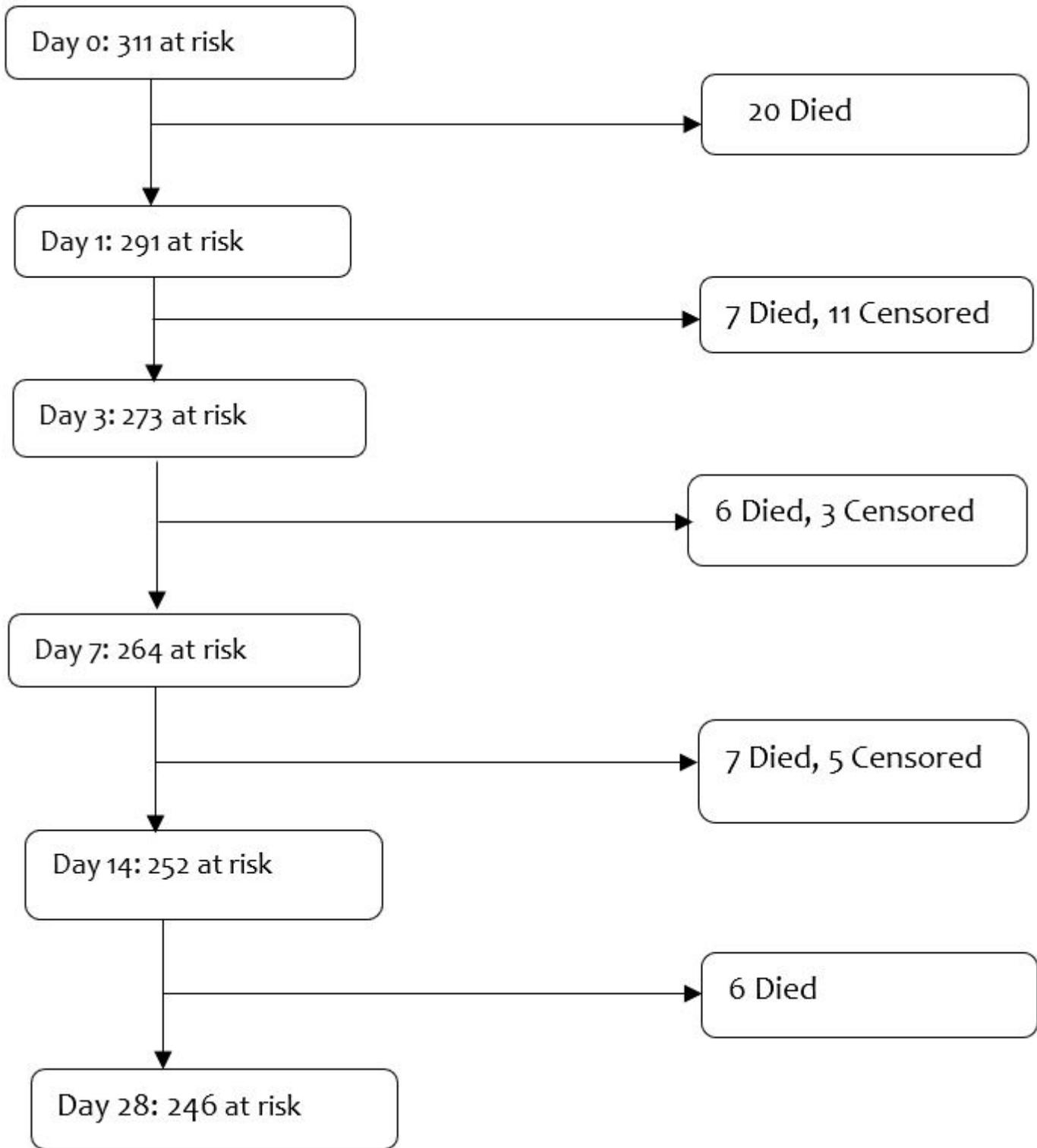


Figure 1

Schematic diagram for selection of study participants



**Figure 2**

Risk of mortality for preterm neonates

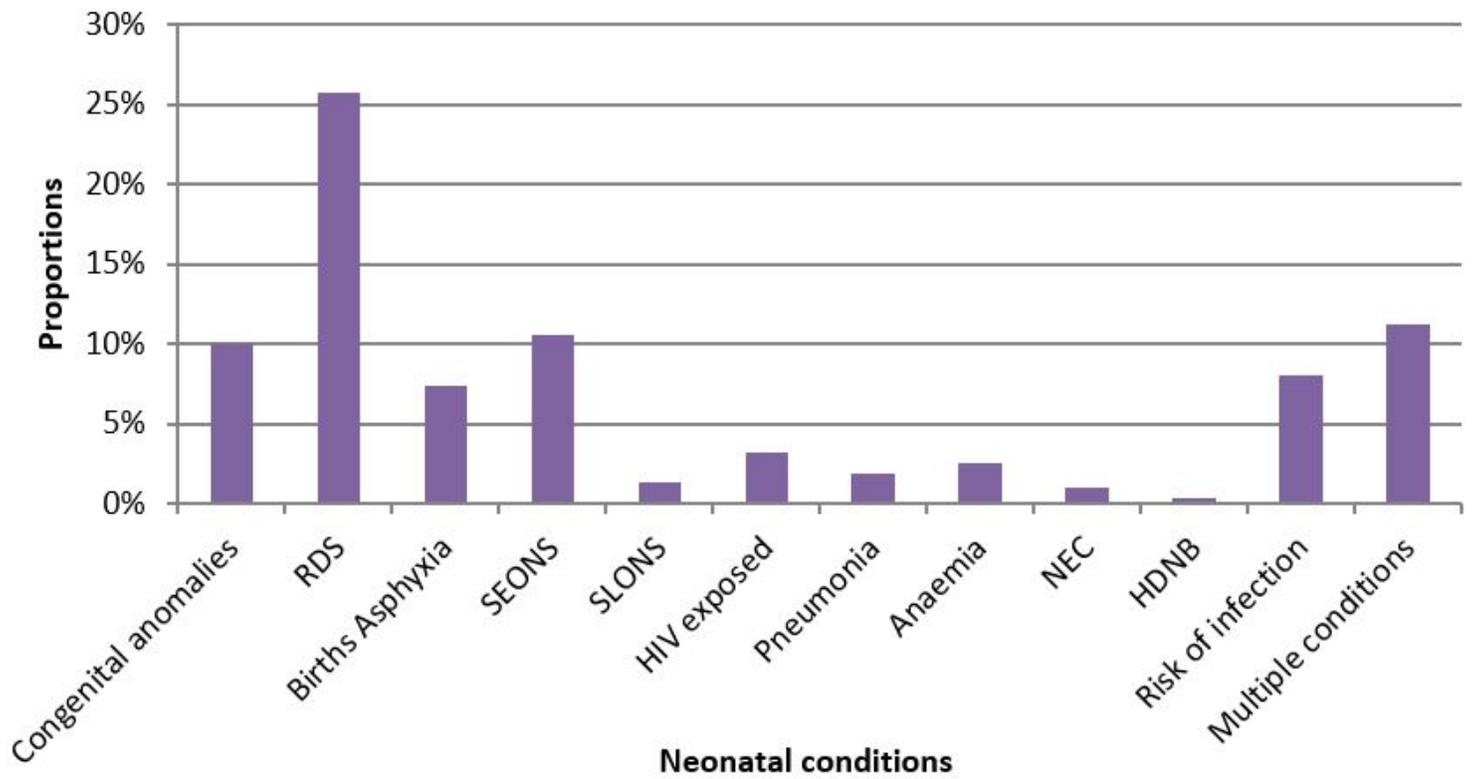


Figure 3

Proportions of neonatal complications in neonates

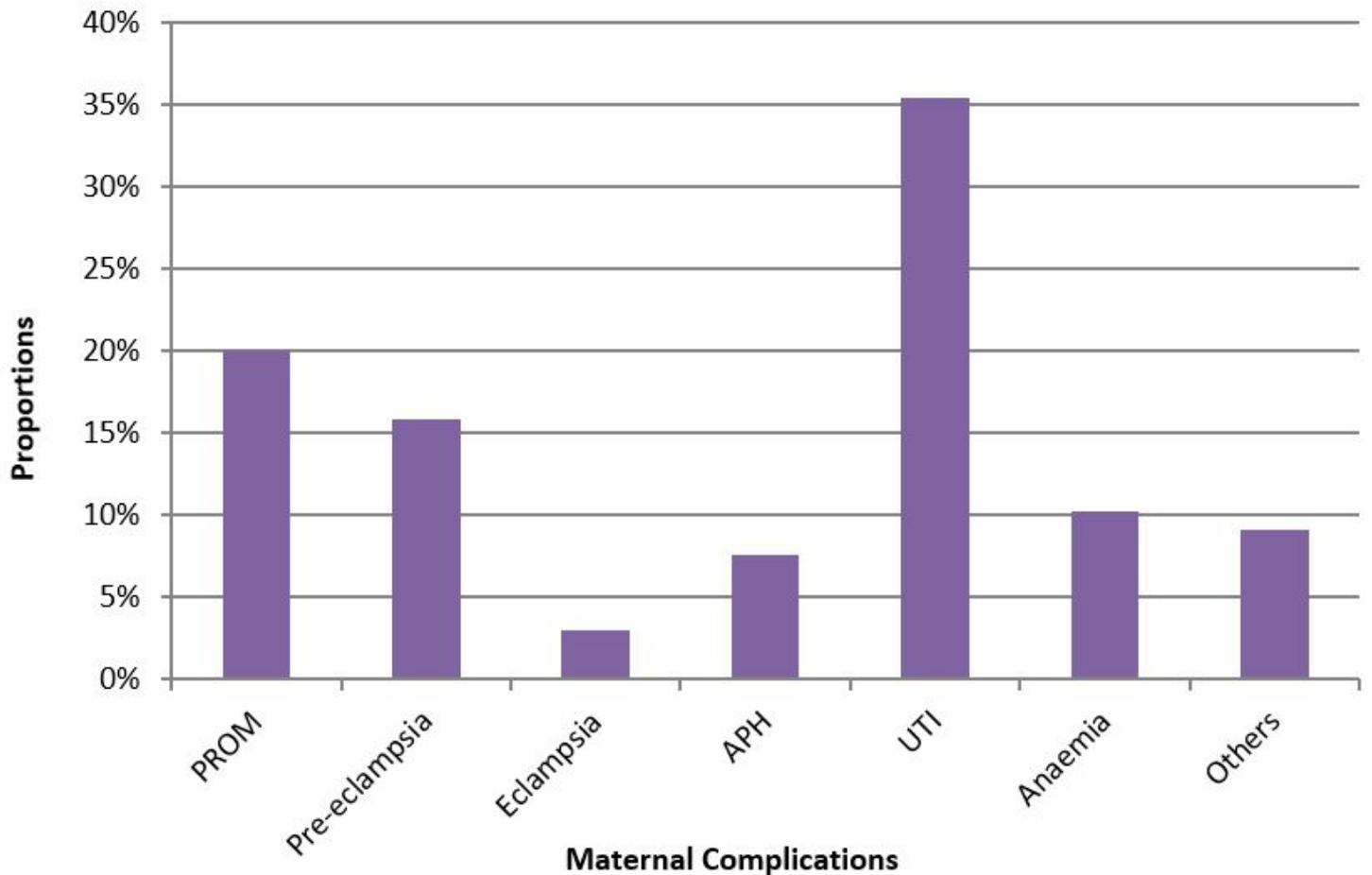


Figure 4

Maternal complications for mothers who delivered preterm

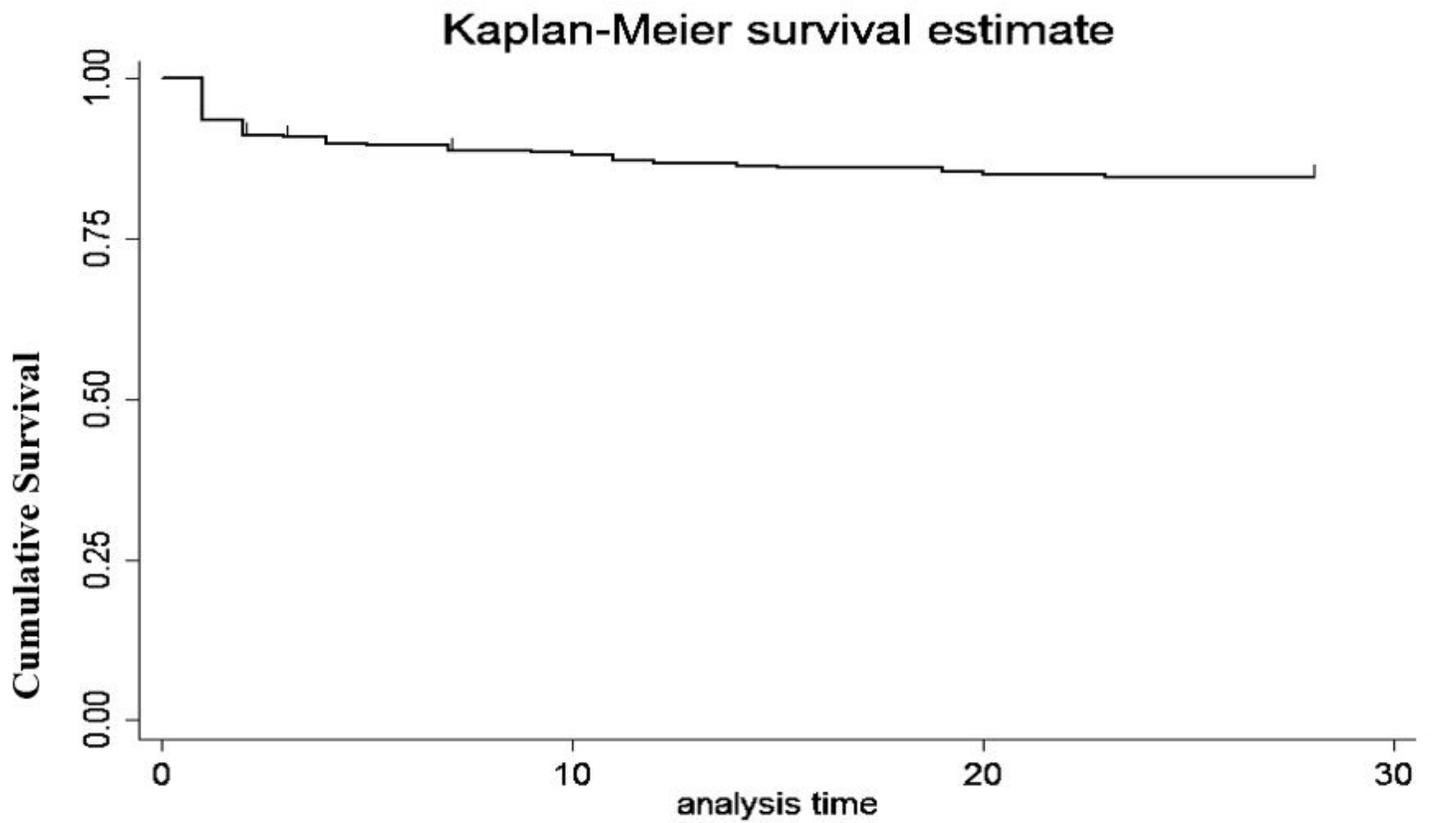
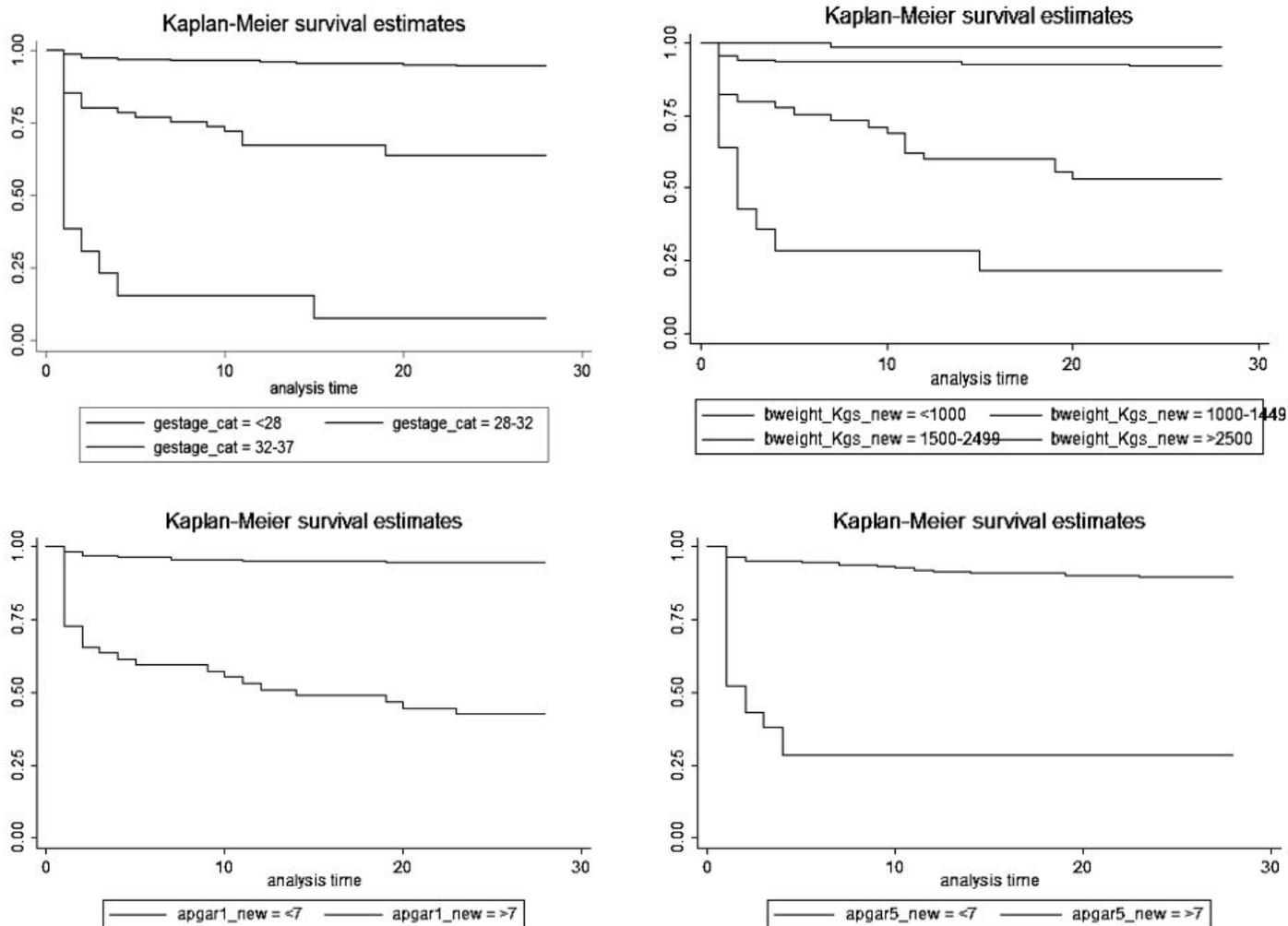


Figure 5

Total survival estimation time for preterm neonates



**Figure 6**

Kaplan-Meier survivor curves of Preterm Mortality by different categories.

## Supplementary Files

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