

## Research Article

# Mortality in Low Birth Weight Infants in a Developing Country, a Case of Zimbabwe

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## Abstract

**Objective:** To determine the mortality of infants born weighing less than 2000g in a low resource setting, and identify time related risk factors for death in the first 28 and 48 days of life.

**Methods:** A prospective cohort study of 399 infants born alive weighing less than 2000g was followed up for death outcomes. Data was analyzed using STATA (USA) statistical package, survival curves were deduced using Kaplan Meyer; Adjusted Risk Ratios (RR) were deduced using generalized linear models with poison link function.

**Results:** Overall mortality rate in the first 28 days was 51.2%. Mortality in the first 12 hours of life was 33%. Mortality in the ELBW was 91.1%, VLBW – 54.4% and LBW – 28.8%. The independent risk factors for mortality in the first 12 hours of life were Respiratory Distress Syndrome (RDS) (RR 1.58 95% CI 1.039 - 2.405) and infants born to Diabetic mothers (RR 2.31 95% CI 1.46 - 3.65).

**Conclusion:** Neonatal mortality rate was very high and the majority of the deaths occurred within 12 hours of birth. Interventions to reduce mortality should target particularly treatment of respiratory distress syndrome such as use of life support mechanisms, surfactant therapy, and improve monitoring during the critical early hours of life.

**Keywords:** Mortality; Low birth weight; Infants; Zimbabwe

## Introduction

More than 20 million infants worldwide representing 15.5% of all births are born with Low Birth Weight (LBW) particularly in developing countries where, approximately 16.5% of all births are LBW. In both developed and developing countries, preterm birth is the main contributor to LBW. However, in less developed countries, Intrauterine Growth Restriction (IUGR) has significant contribution to the burden of LBW. LBW infants are 20 times more likely to die than normal birth weight counterparts, as they are more susceptible to complications in the neonatal period such as hypothermia and hypoglycemia.

Globally 6.6 million children less than 5 years old die every year and 44% of these deaths happen in the first 28 days of life [1]. Of the neonatal deaths, 60% are as a result of LBW which implies that indirectly LBW is a big contributor to neonatal mortality. An estimated 2.8 million infants are born both preterm and Small for Gestation Age (SGA) in developing countries annually. This latter group of infants are 10 – 40 times more likely to die in the first month of life [2]. Mortality in LBW infants is associated with multi-system complications that include respiratory aberrations, gastrointestinal, neurologic and cardiovascular. A LBW infant is more prone to perinatal infection and nosocomial infection than a normal weight term baby.

Studies on mortality trends and risk factors for mortality have been done in developed more than in developing countries. In a

prospective USA cohort study of 18,153 infants born with birthweight between 501g and 1500g, Fanaroff et al found that 87% of the in-fants, who died, did so by 28 days of life. The risk for mortality in the lowest birth weights was greatly influenced by sex with males being more vulnerable than females. Early on-set sepsis was an important risk factor for mortality. In another USA cohort of babies born between 22 and 28 weeks of gestation. Patel et al found that deaths occurring within 12 hours after birth were most commonly attributed to prematurity whereas death in infants that survived beyond 12 hours were most commonly attributed to Respiratory Distress Syndrome (RDS). From 15 days to 60 days necrotizing enterocolitis was the most common cause of death [3]. The results of these studies could be generalizable in the USA and most other developed countries. The pattern is likely to be altered in a developing country because of limited resources such as unavailability of ventilators and surfactant replacement therapy.

In a Turkish study of 241 VLBW infants by Centikaya et al overall mortality was 23.2%. Of those who died 17.3% were delivered by caesarian. Infants who did not receive antenatal steroids and those with incomplete steroid courses had a higher mortality rate than infants with complete or prolonged antenatal steroids [4].

Studies on the outcomes of low birth weight infants have also been reported in Sub-Saharan Africa. In Malawi, the country with the leading number of preterm births currently, a prospective study of 1496 infants born in a public hospital in Lilongwe, Ashleen et al [5]. 1,496 infants that were reported survival rate of only 7% for

ELBW, 52% for VLBW and 90% for LBW. The majority of deaths occurred within the first three days. The risk factors for mortality were not determined in this study. The survival rates were largely similar to Ballot's findings in a retrospective study at a public hospital in Johannesburg 6. In the later study the overall survival rate was 70.5%. Survival rates for weight bands below 1001g and 1001 -1500g were only 34.9% and 85.8% respectively. The predictors for survival were birth weight, gender, necrotizing enterocolitis, born before arrival and Nasal Continuous Positive Airway Pressure (CPAP) usage [6]. This is one of the few studies that looked at predictors for survival in the VLBW. Another Johannesburg study by Velaphi SC et al. showed similar survival rates of 32% among ELBW and 84% among VLBW [7]. In this study provision of antenatal care, caesarian section, female gender and an APGAR score more than five at one minute or five minutes were associated with better survival to hospital discharge. Lack of mechanical ventilation in this institution contributed to high mortality [7].

Zimbabwe has a comparable prevalence of LBW (11%) to its neighboring countries (Angola 12%, Botswana 10%, Mozambique 14%, Namibia 14%, Zambia 12%) [8]. In 2000, Kambarami et al [9]. found that in-hospital mortality rate was 39.4%. The risk factors for mortality were birth weight less than 1500g, breech delivery and unbooked pregnancies. Another prospective cohort study by Stranix L [10]. in 2000 found early neonatal death rate (death within seven days of life) to be 16.7% with the risk factors for mortality being a low five minute Apgar score, respiratory distress, prematurity, absence of growth restriction, unbooked pregnancy and breech delivery. This study explored the risk factors for mortality in infants born with weight below 2500g. The overall mortality was lower than the previous studies because of inclusion of babies with higher birth weights. Reporting on weight specific mortality would have been more informative in this study.

The number of infant deaths occurring during the neonatal period is increasing and in order for the country to improve child survival, a reduction in neonatal mortality has to be realized [11]. Although it has been established that overall mortality of LBW infants is high, the age specific risk factors for death in the first 28 days of life in these high risk infants have not been studied adequately in a low resource setting such as Zimbabwe. Knowledge of these factors will help both the clinicians and health care managers to identify and prioritize interventions that might avert unnecessary mortality.

## Subjects and Methods

A prospective cohort study, with a follow up period of 28 days was carried out at Harare Hospital Neonatal Unit from 01 August 2014 to 28 February 2015. Infants weighing less than 2000g were recruited excluding those weighing less than 500 or without consent. The calculated minimum sample size to detect a mortality rate of 39.4% (Kambarami et al) [9] at 5% significance level and 95% confidence interval was 367 newborn babies. Allowing for 10% loss to follow up and a design effect of 1.1 (catering for age specific risk factors) we enrolled 399 participants. The infants were identified from labour ward and operating room delivery registers each morning during the study period. Consecutive sampling was employed until sample size was reached. Details of the study were explained to all mothers of eligible infants.

The investigator administered both the informed consent and the questionnaire within 48 hours of delivery. Supplemental information was extracted from delivery registers and mothers' antenatal books. The investigator documented maternal demographic data, antenatal care, and newborn characteristics. Gestational age was calculated from the Last Normal Menstrual Period (LNMP), first trimester USS. In the event that the mother was not sure of dates and did not have a first trimester Ultrasound scan a New Ballard's score alone was used. The investigator examined all the infants at enrolment, then on day two and three of life and, subsequently weekly until discharge. Weighing scales were calibrated before commencement of the study and every morning. A research assistant helped with following up the infants at the outpatient review clinic.

At each review, the weight, method of feeding, the type of milk, illnesses and medication were recorded. Mothers were reimbursed bus fare every time they came for a study re-view. These fees were determined according to MRCZ approved schedule. Mothers that missed scheduled appointments were contacted on their cellular phones and a phone interview carried out. In the case of death at home, a verbal autopsy was carried out. The management of the infants followed existing guidelines on the unit

All data were checked for completeness and consistency of responses in the field before entering into Epi Info (version 4, USA) database. After data cleaning the data was exported to STATA (version 12 USA) package for analysis. Frequencies were generated to describe mother and infant demographic details. The risk factors for mortality were identified using univariate analysis initially then multivariate regression procedure to calculate adjusted relative risk estimates. Poisson generalized linear model with a logarithmic link function regression model and robust variance were used to estimate the adjusted relative risk ratios. Kaplan-Meier survival graphs were generated to determine mortality patterns.

Permission to carry out the study was obtained from the Harare Central Hospital Research Ethics Committee, Joint Research Ethics Committee (JREC) and the Medical Research Council of Zimbabwe (MRCZ). Informed verbal and written consent was obtained from mothers or fathers prior to enrollment. Data was kept confidential by limiting access to patient details. Medication was not withheld from any study participant and treatment was in accordance with the existing nursery protocols.

## Results

Data was collected for 399 infants over a seven month period from the 1st of August 2014 to the 28<sup>th</sup> of February 2015. During the study period a total of 592 infants with a weight below 2000g were admitted into the neonatal unit of whom 193 were not studied. The later included 67 who lived outside Harare and 126 whose mothers did not consent. Of those enrolled 367 (92%) completing the study. One hundred and eighty eight (188) infants died within the 28 days of follow up giving an overall mortality rate of 51% (95% CI 46% - 56%). Thirty two (8%) infants were lost to follow up. (Figure 1) below shows the number of recruited infants and those infants that were lost to follow up.

### Demographic characteristics

The mean age of the mothers was 24.23 ± 0.30 years. Three

**Table 1:** Factors associated with mortality in the first two weeks of life.

Time	13 - 24 hrs (1 day)	25 - 48 hrs (2 days)	49 - 72 hrs (3 days)	73 - 168 hrs (1 week)	169 - 336 hrs (2 weeks)
<i>Risk Ratio (95% Confidence Interval)</i>					
EGA Extreme	1.13 (0.64 - 2.01)	0.95 (0.50 - 1.77)	0.78 (0.26 - 2.30)	0.54 (0.15 - 1.93)	1.87 (0.62 - 5.60)
EGA Term	.	*2.23 (1.71 - 2.90)	.	.	.
EGA	1.16 (0.73 - 1.86)	1.1 (0.65 - 1.85)	0.88 (0.41 - 1.88)	0.63 (0.22 - 1.78)	0.45 (0.11 - 1.78)
Very preterm	1.38 (0.80 - 2.36)	1.29 (0.64 - 2.60)	*1.77 (1.14 - 2.77)	*3.14 (1.69 - 5.85)	0.54 (0.09 - 3.45)
Late preterm	1.143 (0.74 - 1.77)	0.6 (0.35 - 1.03)	1.38 (0.69 - 2.74)	0.63 (0.27 - 1.46)	2.81 (0.71 - 11.13)
Unbooked	1.03 (0.62 - 1.72)	1.52 (0.87 - 2.66)	*1.85 (1.10 - 3.12)	*2.25 (1.18 - 4.30)	0.54 (0.09 - 3.45)
HIV	0.91 (0.47 - 1.77)	1.38 (0.77 - 2.49)	0.56 (0.177 - 1.77)	1.5 (0.60 - 3.76)	*3.00 (1.43 - 6.27)
PIH	1 (0.55 - 1.82)	1.52 (0.81 - 2.88)	0.48 (0.09 - 2.60)	1.53 (0.72 - 3.22)	78 (0.13 - 4.53)
Steroids	1.32 (0.76 - 2.31)	1.06 (0.55 - 2.05)	2.06 (0.38 - 11.05)	1.5 (0.44 - 5.08)	0.23 (0.058 - 0.90)
Natural birth	1.24 (0.69 - 2.25)	1.75 (0.73 - 4.20)	0.56 (0.36 - 0.88)	1.25 (0.51 - 3.04)	0.91 (0.23 - 3.58)
Temp<36	1.5 (0.91 - 2.48)	0.7 (0.27 - 1.84)	*1.70 (1.13 - 2.56)	1.78 (0.85- 3.6)	.
Temp 36.5-37.4	0.24 (0.04 - 1.49)	0.53 (0.09 - 3.00)	*1.64 (1.12 - 2.39)	.	2.17 (0.67 - 7.05)
Temp 37.5-38.5	1.23 (0.53 - 2.85)	.	.	0.69 (0.13 - 3.70)	.
Temp>38.5	1.12 (0.64 - 1.97)	0.92 (0.53 - 1.62)	0.75 (0.26 - 2.19)	0.03 (.048 - 1.97)	*2.67 (1.39 - 5.12)
Birthweight <1000g	1.11 (0.71 - 1.73)	0.88 (0.53 - 1.47)	1.16 (0.54 - 2.53)	0.95 (0.42 - 2.17)	1.04 (0.28 - 3.84)
1000-1499 g	0.82 (0.49 - 1.38)	1.35 (0.77 - 2.38)	1.07 (0.43 - 2.64)	1.74 (0.79 - 3.83)	0.54 (0.085 - 3.44)
1500-1999 g	0.33 (0.09 - 1.18)	0.52 (0.19 - 1.46)	*1.75 (1.09 - 2.79)	0.67 (0.25 - 1.75)	1.83 (0.57 - 5.85)
Apgars 1 min 1-5	*2.59 (1.07 - 6.32)	*2.22 (1.09 - 4.51)	1.25 (0.48 - 17.53)	1.1 (0.52 - 2.34)	0.5 (0.13 - 2.00)
Apgar 1 min 5-7	0.6 (0.19 - 1.94)	0.55 (0.22 - 1.34)	.	1.42 (.68 - 2.96)	1.25 (0.35 - 4.52)
Apgar 1 min >7	0.6 (0.19 - 1.94)	1.43 (0.65 - 3.15)	.	*1.82 (1.21 - 2.72)	*2.60 (1.27 - 5.30)
Apgars 5 min 1-5	0.84 (0.49 - 1.46)	0.8 (0.45 - 1.44)	0.57 (0.17 - 1.87)	2.72 (0.99 - 7.50)	0.4 (0.13 - 1.25)
Apgar 5 min >7	1.18 (0.51 - 2.74)	0.61 (0.18 - 2.06)	.	1.12 (0.26 - 4.91)	.
Hypoglycemia	1.81 (0.79 - 4.17)	1.61 (0.60 - 4.33)	0.61 (0.42 - 0.89)	0.76 (0.34 - 1.70)	0.67 (0.18 - 2.46)
Hypothermia	.	.	.	1.5 (0.37 - 10.92)	5 (0.73 - 34.12)
Eclampsia	1.35 (0.82 - 2.22)	*1.90 (1.09 - 3.31)	1.75 (0.68 - 4.48)	1.74 (0.79 - 3.83)	1.04 (0.28 - 3.83)
RDS					

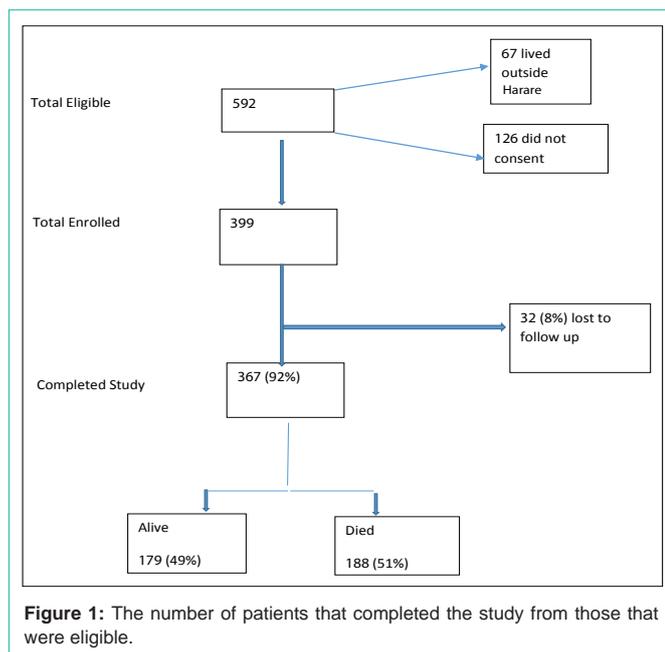
**NB** \*is highlighting the statistically significant; hrs - hours

hundred and sixty (98.09%) of the mothers had at least grade 7 level of education. Eighty one (22.07%) were HIV positive. Three hundred and sixty seven infants (215 male and 152 female) had complete follow up data. The overall mean weight at birth was 1400.88g  $\pm$  19.93. Ninety two infants (24.2%) were extremely premature (less than 28 weeks gestation), 176 (46.3%) very pre-term infants (28 – 32 weeks), 102 (26.8%) late preterm (between 32 weeks and 37 weeks gestation) and 10 (2.6%) were born at term gestation (more than 37 completed weeks). The majority (70%) of the infants were Appropriate for Gestational Age (AGA). More than half (70.1%) had a temperature less than 36.5°C on hospitalization whilst 63.5% had respiratory distress.

## Mortality

The Overall mortality rate over 28 days was 51.2% (95% CI 46.0%-56.0%). Twenty four percent of the infants who deceased were between 28 and 32 weeks of gestation. Thirty four percent of those that died had hypothermia on admission and 38% had respiratory distress on admission. Gestational age, hypothermia on admission, respiratory distress on admission, apnea on admission were associated with mortality.

Mortality rate was highest in the first 12 hours of life during which 33% of the infants died. More than half of the deaths 99 (53%) occurred in the first 48 hours of life. The Kaplan Meier survival curve



below (Figure 2) shows the probability of dying at various postnatal ages. Irrespective of sex (since the Kaplan Meier graph arms are crossing) the probability of dying is highest in the first week of life (the first 200 hours) and decreases as age in-creases.

The probability of death further decreases at 2 weeks up to the end of the neonatal peri-od. The mortality rates for the weight band categories were as follows: 91% for weight less than 1000g, 54% for weight between 1000g and 1499g, and 29% for weight between 1500g and 1999g.

### Time specific factors associated with mortality

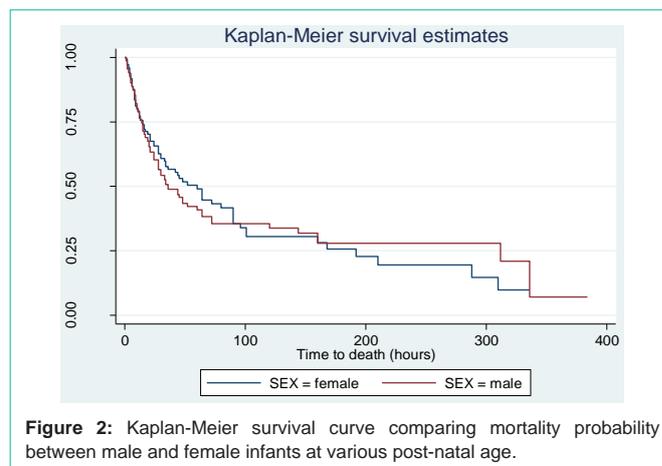
In a univariate analysis for risk factors for mortality at different time points i.e. <12 hours, 13 - 24 hours, 25 - 48 hours, day three to seven, second week, third week and fourth week. In the first 12 hours of life infants with RDS had a relative risk of dying of RR 1.44  $p = 0.040$  (95% CI 1.02 - 2.04). Infant born to a diabetic mother also a significant risk of dying within the first 12 hours of life RR 1.93  $p = 0.000$  (95% CI 1.65 - 2.26). After adjusting for confounders respiratory distress syndrome RR 1.58 (95% CI 1.039 - 2.405), and infant of a diabetic mother RR 2.31 (95% CI 1.46 - 3.65) were independent risk factors for mortality.

Table 1 gives the adjusted relative risk ratios obtained by multivariate analysis.

Time specific relative risks for all the study factors in the first 2 weeks of life. After control-ling for confounders using multivariate analysis only the following factors were signifi-cant at respective specific times: at 13 - 24 hours (1 day), only Apgar 1 min 5-7 score; at 25 - 48 hours (2 days), only EGA Term, Apgar 1 min score 5-7 score and RDS; at 49 - 72 hours (3 days), only EGA Late preterm, HIV, at 73 - 168 hours (1 week), only EGA Late pre-term, HIV, Apgars 5 min 1-5 score, PIH, Birth weight <1000g and Apgars 5 min 1-5 score.

## Discussion

The current study found that the overall mortality in the first



28 days of life among infants born weighing less than 2000g was very high 51% (95% CI 46% - 56%). Most of the deaths (52.6%) happened in the first 48 hours of life. This mortality was higher than the mortality rate of 39.4% reported by R Kamba rami in 2000 [9]. However, Kambarami's study was restricted to in hospital mortality whereas the current study also included post dis-charge mortality [12]. In another public hospital in Lilongwe Malawi, a low resource country, the calculated mortality rate was 93% in ELBW infants, 48% in VLBW infants and 10% for LBW infants 5, these figures are similar to this study.

In developed countries mortality in low birth weight infants especially in the extreme low birth weight infant has been decreasing [13]. Owing to the improvement of care that includes the routine use of surfactant and the respiratory support measures such as CPAP and mechanical ventilation. The average mortality in VLBW in the developed countries is as low as 15 - 28% depending on the hospitals level of care [14]. As indicated in Table 5, 60% of the deaths in the current cohort occurred in the first 72 hours of life. This rate is much lower than 82% mortality which was found at a public hospital in Lilongwe for the same period of time [5]. Further analysis on the risk factors for mortality in the first 12 hours of life showed that the significant independent risk factors for mortality were respiratory dis-tress syndrome and infants born to diabetic mothers. Infants with RDS often need inten-sive care nursing with ventilatory support and surfactant replacement therapy. At the unit that the study was carried out these lifesaving interventions were not available leaving a lot of infants without the appropriate care and at risk of dying. Infants that were born to diabetic mothers succumbed to death more in the first 12 hours and further research is required for these group of infants. RDS was also an independent risk factor for mortality between 25 hours and 48 hours. A few studies have looked at the factors associated with mortality, in a study done in Malawi at a public hospital RDS was one of the factors that contributed to a high mortality in the first three days of life [15]. In the developed countries RDS is no longer a factor associated with mortality because of the wide use of surfactant replacement therapy either as prophylactic treatment or therapeutic. The use of continu-ous positive airway pressure has also reduced mortality from RDS [16].

This study showed that the late preterm infants had a high risk of dying from day 3 of life to the end of the first week. Mortality in the

late preterm is not surprising because of their low birth weight they are at risk of complications commonly hypothermia, hypoglycemia and infections [17]. At the unit the study was carried out late preterm infants are often nursed in an open cot whilst waiting for an available bed for the mother to start KMC. This delay in starting KMC could predispose them to other complications such as hypothermia and nosocomial infections.

APGAR scores were predictors of mortality in the first 24 hours in this study especially low APGARs at 1 minute. A low APGAR was also found to be a predictor of early neonatal death in a study that was done in Brazil [18]. APGAR scores in these low birth weight in-fants are indicators for the need of resuscitation and therefore emphasis should be put on resuscitating all infants appropriately [5].

Although autopsies were not done on the infants that died the causes of mortality were established clinically as complications of prematurity, anemia, necrotizing enterocolitis and sepsis, this brings a limitation to the findings. The risk of dying for infants born to mothers that had PIH was high in the second week of life RR 3.00 (1.43 to 6.27) and this could be explained by the fact that these infants often have intrauterine growth re-striction. Studies have shown that their risk of dying is more than in infants who are appropriate for gestational age. They are at increased risk of necrotizing enterocolitis, thrombocytopenia and temperature instability and could explain the deaths in the second week of life.

Neonatal mortality in infants less than 2000g is very high at Harare Maternity Unit. The majority of the deaths happen within the first 48 hours of life with highest mortality being in the extremely low birth weight infants. The probability of dying declines with increasing postnatal age. The independent risk factors for mortality were RDS and hypoglycemia in the first 12 hours of life. Hypoglycemia can be prevented easily by initiating feeds early and close monitoring especially in the first 12 hours of life. RDS remains a significant cause of mortality in the first 48 hours of life at Harare Maternity Unit. This highlights the need to capacitate the neonatal intensive care unit with adequate life support mechanisms such as CPAP machines, ventilators and surfactant. This study also showed that the late preterm infants and the IUGR infants had an increased risk of dying in the second week of life. This may highlight the need to relook at the discharge weight criteria.

## Conclusion

Neonatal mortality was high (51%) in infants with weight less than 2000g in the Maternity Unit. The majority of the deaths (52.6%) happen within the first 48 hours of life with high-est mortality (91%) for weight less than 1000g, being in the extremely low birth weight in-fants. The probability of dying declines with increasing postnatal age. The independent risk factors for mortality were RDS and hypoglycemia in the first 12 hours of life. Hypoglycemia can be prevented easily by initiating feeds early and close monitoring especially in the first 12 hours of life. RDS remains a significant cause of mortality in the first 48 hours of life at Harare Maternity Unit. This highlights the need to capacitate the neonatal intensive care unit with adequate life support mechanisms such as CPAP machines, ventilators and surfactant. This study also showed that the late preterm infants and the IUGR in-fants had an increased risk of dying in the second week of life. This

may highlight the need to relook at the discharge weight criteria and avoid too early discharges in these in-fants should be avoided.

## Conflict of Interest Statement

All authors, declare no conflict of interest.

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