

## Original Research Article

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# Mortality profile of extreme to very preterm infants in an extramural tertiary care neonatal unit of a teaching hospital in Southern India: a retrospective study

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## ABSTRACT

**Background:** Neonatal deaths account for 47% of all deaths in children younger than 5 years globally. More than a third of deaths are due to preterm related complications. Understanding the factors contributing to preterm deaths and pattern of mortality is needed to implement interventions that are essential in improving neonatal survival.

**Methods:** This was a retrospective study done in neonatal intensive care unit, Institute of Child Health (ICH) and Hospital for Children, Chennai, a tertiary care regional center. All preterm (<32 weeks) deaths registered in the neonatal medical records from 1<sup>st</sup> of January 2018 to 31<sup>st</sup> of December 2018 were analysed. Primary causes of deaths were analysed by two consultants. When there were more than one cause contributing to responsible for death the most significant problem was taken as the cause of death.

**Results:** Overall neonatal mortality was 312 (14.2%) of 2189 neonates. Out of 148 admissions in the study population mortality was 74.2% (26 of 35) for extreme preterm (<28 weeks) infants and 42.7% (48 of 113) for very preterm (28 to 32 weeks) infants. Predominant causes of death were sepsis 44.5% (33), prematurity-related complications 37.8% (28) followed by congenital anomalies 12.1% (9) and miscellaneous causes 2.7% (2). Respiratory Distress Syndrome (RDS) and Intra Ventricular Haemorrhage (IVH) attributed to 75% (21/ 28) of deaths among prematurity-related complications.

**Conclusions:** This study identified sepsis; prematurity related complications were the predominant causes of mortality in the extreme to very preterm population. Understanding the specific causes of preterm mortality would help to implement interventions to promote their survival.

**Keywords:** Extreme preterm, Mortality, Sepsis, Very preterm

## INTRODUCTION

Every year nearly 15 million babies are born prematurely (before 37 completed weeks of gestation).<sup>1,2</sup> The rate of preterm birth ranges from 5% to 18%. The UNICEF outlined that among the under-five year olds, 69% of the deaths were attributed to neonatal deaths. Prematurity was responsible for 31% of the neonatal deaths.<sup>3</sup> Prematurity was the leading cause of death in the first month of life and was a factor in greater than 75% of early deaths in the

neonatal period.<sup>4</sup> Very preterm infants born at less than 32 weeks account for nearly 12.9% of all preterm births. However, they accounted for more than 50% of infant deaths and neurodevelopmental disabilities.<sup>5-7</sup>

According to the recent MDS (Million Death Study) report, prematurity is accounting for 40% of NMR in India.<sup>7</sup> Deaths from prematurity is increasing over the last 16 years (2000-2015) which has hampered achieving the Millennium Development Goal-4 by year 2015. According

to global and national statistics India has to bring down prematurity-related deaths in order to reduce NMR to 12 per 1000 live births by 2030.<sup>8,9</sup> Inspite of advances in neonatal intensive care, mortality is very high among preterm infants less than 32 weeks. There are still possibilities for reducing mortality in these infants.<sup>10,11</sup> Hence authors want to analyse the specific causes of death among extreme to very preterm infants admitted in unit.

## METHODS

This is a retrospective hospital based observational study done in the department of Neonatology, Institute of child Health, Chennai. The period of the present study was January 2018 to December 2018. After obtaining approval from the Institutional Ethics Committee (IEC) necessary permissions were taken from the hospital authorities. Medical records of preterm neonates (<32 weeks) died from 1st of January 2018 to the 31 of December 2018 were reviewed and admission details were obtained in a predesigned proforma.

Data regarding the demographic profile, diagnosis at the time of admission, incidence of deaths due to sepsis, outcomes in terms of mortality, duration of stay, referral center and mode of transport were analysed.

Preterm deaths (<32 weeks) will be classified into one of these categories based on the uniform definitions for mortality as put forth by the NNPD collaboration; Prematurity-related complications; Sepsis (including pneumonia and meningitis); Congenital disorders; Birth Asphyxia; Miscellaneous group (cause not classified by above or not established).<sup>12</sup>

Death is considered to be due to prematurity or its complications if the underlying cause of death is Respiratory Distress Syndrome, Bronchopulmonary dysplasia, Necrotizing Enterocolitis, Patent Ductus Arteriosus, Severe grades (grade III or IV) of periventricular-intraventricular hemorrhage. When more than one cause responsible for death the most significant problem was taken as the cause of death. In all deaths, the authors were able to come to a consensus agreement on the single most important cause of death.

### Statistical analysis

All collected data was tabulated and statically analysed by using SPSS software.

## RESULTS

Out of the 2189 admissions 148 (6.7%) babies were less than 32 weeks of gestation. Among them 113 (5.1%) were very preterm neonates and 35 (1.5%) were extremely preterm neonates. Overall neonatal mortality was 14.2% (312/2189) (Table 1). The mortality was 50% (74/148) in the study population. Out of total 312 deaths 26 (8.3%)

were extreme preterm infants and 48 (15.3%) were very preterm infants.

Of the total 74 deceased 34 (45.9%) were males and 40 (54%) were female infants with a male: female ratio of 0.85:1. Among the 74 deaths 42 babies were extremely low birth weight (<1000 grams) and 28 babies were between 1000-1500 grams and 4 babies were above 1500 grams. There were 20 (27%) multiple births, 14 (18.9%) small for gestational age, 15 (20.2%) had hypothermia and 4 babies had hypoglycaemia on arrival. The leading causes of death in the extreme to very preterm infants were sepsis 33 (44.5%), prematurity related complications 28 (37.8%) followed by congenital malformations 9 (12.1%) and birth asphyxia 2 (2.7%) and miscellaneous 2 (2.7%).

Among the 33-culture proven sepsis 24 had grown gram negative pathogens, 4-gram positive organisms and 5 fungal pathogens. Most common organisms isolated were *klebsiella* (27%), *pseudomonas* (18%), *acinetobacter* (12%) and *candida* (15%). Among extreme preterm prematurity related complications 65.3% (15/26) was the single most common cause of mortality followed by 26.9% (7/26) sepsis.

Respiratory distress syndrome 40% (6/15) and intraventricular hemorrhage (grade 3 and above) 46% (7/15) attributed to 50% (13/26) of death in extreme preterm infants (Table 2). Prematurity related complications and sepsis the mean duration of stay was 2.6 days and 24.6 days respectively.

Among very preterm infants sepsis attributed to 54% (26/48) of mortality followed by prematurity related complications 27% (13/48). Respiratory distress syndrome and intraventricular hemorrhage (grade 3 and above) the mean duration of stay was 1.5 days and 2.9 days respectively. The mean duration of stay was 11.9 days in sepsis related mortality. Most common organisms isolated were *klebsiella* 6 (23%) of 26, *pseudomonas* 5 (19%) of 26 followed by *candida*, *staphylococcal aureus* and *Escherichia coli*.

Among the 74 deaths 51 babies (68.9%) were referred from private institutions and 21 babies (28.3%) were from government institutions and 2 babies were from home. Out of 51 babies from private institutions 14 babies were from private medical college hospitals and 37 babies were from private hospitals.

Among the 21 babies from Government institutions 14 babies were from government medical college hospitals and 5 babies were from GH and 2 babies were from urban health centers (Table 3). All babies from government institutions availed the state run 108 ambulance services. Among the state-run ambulance service 89% (34/38) babies were shifted by neonatal 108 ambulance service.

Over all 44.5% (33/74) babies were transported by private ambulances, 51.3% (38/74) babies shifted by government

ambulances and self-transport was 4% (3/74) (Table 4). Out of 33 babies transported by private ambulance 57.5% (19/33) babies had shock, 24% (8/33) babies had

hypothermia, 2(6%) babies had hypoglycaemia and 18% (6/33) babies required intubation at Emergency Room.

**Table 1: Number of admissions as per gestational age during study period.**

| January to December 2018 | Total | <28 Wks | 28 to <32 Wks | 32 to <34 Wks | 34 to <37 Wks | > 37 wks |
|--------------------------|-------|---------|---------------|---------------|---------------|----------|
| Admission                | 2189  | 35      | 113           | 153           | 300           | 1588     |
| Mortality                | 312   | 26      | 48            | 48            | 32            | 158      |

**Table 2: Distribution of deaths among prematurity related complications.**

| Prematurity related complications (28) | Extreme preterm (15) | Very preterm (13) | Total (28) |
|--|----------------------|-------------------|------------|
| Respiratory distress syndrome          | 6                    | 4                 | 10 (35.7%) |
| Intraventricular haemorrhage           | 7                    | 4                 | 11 (39.2%) |
| Necrotising enterocolitis              | 1                    | 4                 | 5 (17.8%)  |
| Broncho pulmonary dysplasia            | Nil                  | 1                 | 1 (3.5%)   |
| Patent ductus arteriosus               | 1                    | Nil               | 1(3.5%)    |

Among the 38 (51%) of 74 babies shifted by government ambulances 15.7 % (6/38) babies required intubation, 26% (10/38) babies had shock, 10% (4/38) babies had hypothermia and one had hypoglycaemia at Emergency Room.

Authors received three babies who used own vehicles of which one was from private hospital and 2 were from home. All of them were hypothermic, 2 had shock, one had hypoglycemia and 2 babies got intubated in Emergency Room.

Maximum number of deaths 45.9% had occurred during the early neonatal period (0 to 6 days) followed by 35.1% during late neonatal period (7 to 28 days) and 18.9% occurred after 28 days of life.

**Table 3: Neonates required stabilization at emergency room.**

| Mode of Transport    | Intubated at ER (13) | Shock on arrival (31) | Hypothermia on arrival (15) | Hypoglycaemia on arrival (4) |
|----------------------|----------------------|-----------------------|-----------------------------|------------------------------|
| Private Ambulance    | 6                    | 19                    | 8                           | 2                            |
| Government Ambulance | 6                    | 10                    | 4                           | 1                            |
| Own vehicle          | 1                    | 2                     | 3                           | 1                            |

**Table 4: Age on arrival from various referral centers.**

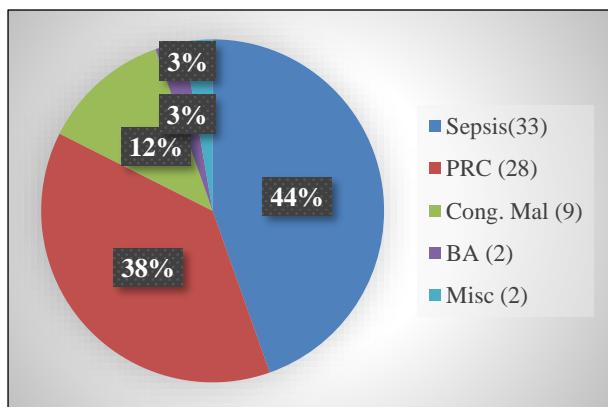
| Age on arrival | Extreme preterm (n=26)   |                            | Very preterm (n=46)      |                             |
|----------------|--------------------------|----------------------------|--------------------------|-----------------------------|
|                | Private Institution (22) | Government Institution (4) | Private Institution (29) | Government Institution (17) |
| < 6 Hours (29) | 12                       | 1                          | 9                        | 7                           |
| 6-24Hours (16) | 6                        | 1                          | 6                        | 3                           |
| 1-7 Days (12)  | 2                        | 1                          | 7                        | 2                           |
| >7 Days (15)   | 2                        | 1                          | 7                        | 5                           |

## DISCUSSION

Overall neonatal mortality was 14.2% whereas mortality was 50% in infants less than <32 weeks admitted in NICU.

In Delhi Neonatal Infection Study (DeNIS) cohort done in three inborn level-3 NICUs had mortality of 45.4% among infants of less than 33 weeks was similar to this study.<sup>13</sup> In this study mortality among extreme preterm infants was

74.2% and 42.4% in very preterm infants. The most significant predictor of death was gestational age regardless of the cause of death similar to studies done by Kong X et al, and Basiri et al.<sup>14,15</sup> Mortality was 56.7% in babies less than 1000 gms which is comparable to National Neonatal Perinatal Database (NNPD) (55%) data and study by Cupen K et al.<sup>16</sup> Studies done by Malik S et al, Baruah MN et al, and Katz et al, showed that small for gestational age was associated with increased risk of mortality.<sup>17-19</sup> The prevalence of Small for Gestational Age (SGA) in preterm infants less than 33 weeks was 9.6% as per National Neonatal Perinatal Data from intramural centres.<sup>12</sup> Whereas being an extramural unit authors had higher incidence (18.9%) of small for gestational age in babies. These infants are at 10-40 times increased risk of dying in the first 28 days of life.<sup>20</sup> Other contributory factors that were associated with a higher mortality were hypothermia (20%) and multiple births (27%).<sup>14</sup> Study by Wolf et al, reported that very preterm multiple birth infants had a substantially higher mortality than singletons.<sup>21</sup> The leading causes of death in this study were sepsis (44.5%), prematurity related complications (37.8%) followed by congenital malformations (12.1%). In Goat Lung Surfactant Extract (GLSE)-Plus cohort done in five inborn level-3 NICUs sepsis was implicated in 41% of deaths followed by prematurity-related complications accounting for 39.7% of all deaths in neonates between 26-32 weeks gestation which was similar to this study (Figure 1).<sup>22</sup>



**Figure 1: Mortality profile in preterm infants (<32 weeks).**

Prematurity-related complications and sepsis contributed to 53.5% and 19.8% of deaths in the National Neonatal Perinatal Database (NNPD) cohort, 51.0% and 25.0% in the DeNIS cohort respectively from preterm deaths of less than 33 weeks died in intramural centers. Ours being an exclusive extramural unit could explain the high sepsis related mortality (44.5%) as authors are receiving very sick babies treated at various hospitals (50% of babies were from private hospitals, 38% of infants were from medical college hospitals) with different antibiotics usage. Kajal Jain et al, M. Jeeva Sankar et al, Sushma Nangia et al et al, analysed the three large prospective multicentric inborn cohorts (National Neonatal Perinatal Database (NNPD) of India, Delhi Neonatal Infection Study (DeNIS)

cohort and Goat Lung Surfactant Extract (GLSE)-Plus cohort) and concluded that 20-40% of preterm neonates less than 33 weeks gestation admitted to Indian NICUs were died of sepsis.<sup>23</sup> Their conclusion was that in verbal autopsy based analysis would have classified all deaths in preterm infants <33 weeks gestation to be directly related to prematurity related complications. Whereas analysis of hospital-based medical certification attributed prematurity related complications as a cause of mortality in only 40-50% of babies. A study done in rural India based on verbal autopsy tools estimated that among 179 neonatal deaths attributed to prematurity, nearly a half (95/179) had an overlap with sepsis.<sup>24</sup> There are inherent uncertainties exist in indirect verbal autopsy-based tools.

In this study gram negative organisms (*klebsiella*, *pseudomonas* and *ace natobacter*) and fungal pathogen attributed to 72% and 15% of all sepsis related deaths. As per Delhi Neonatal Infection Study Group nearly one-fifth of neonates with sepsis die in the hospital and these deaths rise up to 50% in those with culture proven sepsis.<sup>13</sup> Antibiotics are essential, however liberal antimicrobial use has been associated with increased adverse neonatal outcomes. A study from California showed substantial variations in antibiotic use that was not related to proven infection was prevalent especially among community and intermediate NICUs.<sup>25</sup> In mortality among sepsis authors had 15% mortality was due to fungal sepsis. This could be attributed to prolonged NICU stay and broad-spectrum antibiotic usage. The majority of deaths (75%) relating to sepsis died after first week reflecting that these babies stay longer in the hospital and consume more resources. This finding assumes great significance in unit with high level of gram negative and fungal sepsis. Authors need to develop optimum strategies to allocate proportionate resources, antimicrobial policies, liberal use of consumables to tackle these sepsis related deaths.

In this study prematurity related complications attributed to 37.8% of deaths of which intraventricular hemorrhage (39.2%), respiratory distress syndrome (35.7%) and necrotising enterocolitis (17%) were predominant causes. A Study from Canada by Ijab Khanafer- Larocque et al, showed the incidence of severe IVH was 9.7% and study by Stoll BJ et al, and Bolisetty S et al, had incidence of severe IVH between 10 and 17%.<sup>26-28</sup> Severe IVH (grade 3 and above) attributed to 14.8% mortality in this study. Expected cause for this was due to associations between being out born and death due to IVH.<sup>29</sup> In this study 84% of extreme preterm infants were referred from private institutions of which 46% of them reached emergency room within 6 hours of life. 53% of them had shock and 15% of them died within 12 hours of arrival.

Hospital level of neonatal care is an extremely important factor for outcomes. Mortality are higher in hospitals without a Neonatal Intensive Care Unit (NICU) (Finnstrom, Olausson et al,) compared to those with a NICU. A meta-analysis of 30 years of published data had shown that birth in a level III hospital led to a 40%

reduction in neonatal and post-discharge mortality of very preterm infants (Lasswell, Barfield et al).

All babies from Government institutes were shifted by the state-run ambulance service of which 89% of babies shifted by state run neonatal 108 ambulances. Only 33% of babies from private institutes had availed the state-run ambulance service. Authors need to increase the awareness among the private units regarding the availability of well-equipped 108 ambulance service to shift neonates from private institutes to government centers. When analysing the Emergency room data authors observed that infants shifted by government ambulance services had lesser incidence of shock 26% Vs 57.5%, hypothermia 10% Vs 24% and emergency room intubation 15.7% Vs 18% when compared to private ambulance services. Authors had 13.5% mortality occurred within 24 hours of admission. Authors had received 62% of babies within 24 hours of life. Early neonatal period (0 to 6 days) mortality was 45.9%. Infants who had respiratory distress syndrome and intraventricular hemorrhage had died within the first week of life and 24.4% deaths secondary to sepsis had occurred in the first week of life. As per world health report three-quarters of neonatal deaths occur in the first week, and more than one-quarter occur in the first 24 hours.<sup>30</sup> Hence authors need to give specific attention in the early neonatal period as advised by in India's recently launched Newborn Action Plan 25.<sup>31</sup> Significant percentage (35.1%) of babies were died during late neonatal period (7 to 28 days) and 18.9% of babies were died after 28 days of life. Infants diagnosed with sepsis, necrotising enterocolitis, Broncho pulmonary dysplasia died later. Authors had very few deaths attributable to NEC (6%) and BPD (1%). This could be due to very high early neonatal mortality. 75% sepsis related deaths occurred after first week. The varying timing of death provides insight into the prolonged vulnerability of these infants to infection. In a prospective study by Baqui et al, showed 50% of neonatal deaths secondary to sepsis occurred in the first week and 30% occurred in the second week and 20% in 3-4 weeks.<sup>32</sup>

Although analysed retrospectively the major strength of this study was that detailed investigations were available to ascertain the exact cause of death for every infant. This study had some limitations. This was a hospital based retrospective study, the results from this study could not be a complete reflection of the problem in the community. Being an exclusively out born unit authors are receiving significant percentage of babies referred from NICUs (38%) attached with medical college hospitals. Many preterm neonates in India are managed in level-2 units (Special Neonatal Care Units) with limited resources. The cause-specific mortality proportion may be different in these settings. Authors used retrospective evaluation based on standardized definitions to identify the specific cause of death. Authors are not practising autopsy as a routine. Hence determining a single cause of death when multiple causes playing a role was difficult. Authors have analysed only the medical records of extreme and very preterm babies who had died during the study period. Ideally,

authors should have analysed medical records of all extreme and very preterm infants admitted during the study period over one year. Authors did not analyse the perinatal risk factors such as chorioamnionitis, duration of premature rupture of membrane, pregnancy induced hypertension, antenatal steroid uptake and delivery room practices in detail. In sepsis authors did not analyse data regarding percentage of babies with first culture, second culture positivity.

## CONCLUSION

Authors need to implement the concept of organizing optimal perinatal neonatal care services. It is essential to create awareness among the care givers regarding the importance of keeping high risk deliveries particularly less than 32 weeks in centres with level III NICU care, whenever feasible prefer intrauterine transport, strengthening the uptake of antenatal steroids, provision of quality delivery room practices like ensuring the availability of continuous positive airway pressure, T Piece resuscitator and timely referral to higher centres for early surfactant using neonatal 108 ambulance services may help to reduce mortality in preterm birth complications.

Encourage the team to practice regular hand hygiene, ensuring the availability of antiseptic hand rub solutions at the bed side, effective implementation of IMNCI for early diagnosis of danger signs, encourage the team to do quality improvement initiatives to address their challenges in implementing asepsis routine and timely intervention and referral to tertiary care centres, feedback between referral centres and continuous monitoring of the change in practice would result in better outcome in sepsis related mortality.

The high mortality also due to result of limited resources, manpower and knowledge and attitude. Authors also suggest the need of preparedness of the units in terms of staff training and developing proper infrastructure and administrative support to allocate proportionate resources to take care of this high-risk infants.

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