Research Article

Evaluating the Predictors of Mortality in Extremely and very Preterm Neonates in a Developing Country

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Abstract: Background: Various comorbidities affect preterm infants throughout their hospitalization. Death among children under the age of five years occurs mainly due to complications developed after preterm births accounting for almost a million fatalities annually. Infants with extremely preterm births are at great risk of complications, which frequently cause death.

Objective: To identify the rate of survival and deaths in extremely and very preterm neonates in our center and to identify the commonest predictors of mortality in our preterm population.

Materials and Methods: This prospective observational longitudinal study was conducted at the Department of pediatric medicine, Liaquat National Hospital, Karachi, Pakistan, after obtaining the permission from Ethics Committee of the hospital (Ref. App # 0889 -2023-LNH-ERC), over a period of 9 months from 10th April 2023 to 10th January 2024. 169 Neonates in total were managed uniformly and followed up till discharge or death. Chi-square test was used to compare categorical variables. P-value ≤ 0.05 was taken as statistically significant.

Result: There were 53.3% male and 46.7% female patients. The majority of patients (89.3%) had very low birth weights. Most of the births were very preterm births (67.5%) followed by preterm births (20.1%), and extremely preterm births (12.4%). Death was recorded in 11 (6.5%) patients and among these patients sepsis was the most observed cause with 45.5%. Extremely preterm births and very preterm births were significantly associated with gender and birth weight, but not with survival status and predictors of mortality.

Conclusion: Very preterm was the most common birth status. Mortality was reported 6.5% cases. The most common predictor of mortality was Sepsis.

Keywords: Extremely preterm, Very preterm, Neonates, Rate of survival, Deaths, Predictors, Respiratory Distress Syndrome (RDS).

INTRODUCTION

Preterm birth (PTB) is defined by the World Health Organization as all births that occur before 37 weeks of pregnancy or 259 days after the woman's last menstruation. Extremely preterm births (EPT) (less than 28 weeks), very preterm births (28–31+6/7 weeks), moderate births (32–33+6/7 weeks), and late preterm births (34–36+6/7 weeks) are further categories for preterm births [1].

Despite the relatively small number of infant (i.e. 5.2%) born extremely preterm among total worldwide preterm births, they have a high risk of morbidity as well as mortality [2]. They also have increased risk for different complications like respiratory distress syndrome (RDS), Intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), sepsis, white matter injury (WMI), and retinopathy of prematurity (ROP), which are associated with adverse long-term outcomes [3]. The survival rate of extremely preterm newborns varied across affluent nations. It was observed in 62% newborns in England [4], in France it was 69%, [5] in Norway it was 74%, [6] however, in United State it was found as 72%, [7] according to major cohort studies of these infants' outcomes have improved in the past 20 years [2].

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Finding the risk factors enables us to screen pregnant women and develop effective measures which may help in, decreasing preterm birth [8]. It has been demonstrated that neonatal death rates rise with decreasing gestational age, from 8.2% of babies at 27 weeks to 44.2% of newborns at 23 weeks [9].

The main causes for mortality among children under five years are the complications caused due to preterm birth which accounts approximately million fatalities yearly [10,11]. Preterm delivery is a major contributor to neonatal mortality, accounting for 35% of all newborn fatalities and 18% of deaths in children under the age of five during the first 28 days of life [12,13]. Preterm babies born in high- and low-income countries have different survival rates. Among babies who were born at 24 weeks and among babies who were born at 28 weeks in nations with high income had surviving newborn period as 50% and 90% respectively. Among low income countries only 10% newborns born at 28 weeks were survived. Among babies who were delivered at 32 weeks, the rate of survival was increased up to 50%. Neonatal mortality and morbidity are more common among preterm babies who survive than term babies [10].

Infants delivered at 34 to 36 weeks are at higher risk, despite the fact that morbidity and death decrease with each successive gestational week [10]. Infant mortality in very preterm (VPT)

babies has been significantly decreased in recent years as a result of improvements in the care of extreme prematurity [14]. Worldwide, 2.5 million newborns pass away every year. Low- and middle-income countries (LMICs) account for a large proportion of these fatalities [15]. The majority of newborn fatalities, which may be prevented in 80% of cases with modifiable measures, are due to prematurity-associated problems (35%), intra-partum asphyxia-related events (23%), and sepsis (27%). Congenital abnormalities and preterm delivery were found as the most common causes of early (0–6 days) as well as late (7–28 days) neonatal fatalities in high-income countries (HICs).

It is important to identify the burden and outcome of all above mentioned problems in our institute. It will help us in enhancing our resources and timely management of future preterm case. Establishing our own institutional data of morbidities and mortalities, will help us in counseling of the parents of preterm babies.

MATERIALS AND METHODS

This study was a prospective observational longitudinal study which was conducted over a period of 9 months from 10th April 2023 to 10th January 2024, at Department of pediatric medicine, Liaquat National Hospital, Karachi, Pakistan. The research proposal was approved by the Research and Ethics Committee of the hospital,(Ref. App # 0889 -2023-LNH-ERC). The written and informed consent was obtained from the parents of enrolled babies. The calculated sample size was 156 patients, which was calculated by WHO sample size calculator by considering preterm mortality as 11.4% [16], margin of error 5% with 95% confidence interval. Considering a 10% nonresponse rate, 174 cases were approached, of which 6 patients were dropped from the study. Therefore,169 patients were included in the analysis. A neonate born before 37 weeks of gestation was considered as preterm. A neonate born between 24 and 28 weeks of gestation was labeled as extremely preterm. A neonate born between 28 till 32 weeks of gestation was considered as very preterm.

Neonates were managed uniformly as per departmental protocols and followed up till discharge or death, whichever comes earlier. No intervention was involved in the study. No additional financial burden was experienced by the participants.

STATISTICAL ANALYSIS

Data were collected prospectively in a pre-designed Performa. The confidentiality of the patient's information was maintained. Frequencies percentages were calculated to present Qualitative variables. Quantitative variables were summarized as mean±SD or median with interquartile range (IQR) as appropriate. Chi-square or Fisher-exact test was used to compare categorical variables whereas numerical variables were compared using independent t-test or Mann-Whitney U test. Binary logistic regression was applied to ascertain the factors associated with mortality. P-value ≤ 0.05 was taken as statistically significant.

RESULT

A total of 169 patients were included in the study, out of them 53.3% were male and 46.7% were female patients. The average age of patients was 3.86±3.76 days. Most of the patients (69.2%) were belonged to age <3 days. The average weight, length, and occipital frontal circumference (OFC) were 1.49±0.56 kg, 40.30±3.63 cm, and 29.08±2.13 cm, respectively. The majority of patients (89.3%) had very low birth weights. Majority of patients were from rural areas i.e. 85.8%. As far as birth status according to gestational age of total 169 patients is concerned, most of the births were very preterm births (67.5%) followed by preterm births (20.1%), and extremely preterm births (12.4%), also presented in Fig. (**1**). Table **1** showed detailed descriptive statistics of demographics and birth status for the study variables.

Table **2** represents clinical outcomes among the study population. The results showed that Respiratory distress syndrome (RDS) was most common short term outcome with 75.7%, followed by sepsis (44.4%), and necrotizing enterocolitis (NEC) (27.2%). While hypothermia was the least prevalent short term outcome with (0.6%) which was observed in only one patient. Death was recorded in 11 (6.5%) patients and among these patients sepsis was the most common observed cause accounting for 45.5% followed by prematurity (27.3%). However Respiratory distress syndrome, Hyperglycemia, and Necrotizing Enterocolitis (NEC), each were observed in one patient. Frequency distribution of outcome and predictors of outcome are presented in Figs. (**2** and **3**) respectively.

Table 1. Descriptive Statistics of Demographic Variables of Study Population.

	mean±SD
Age (days)	3.86±3.76
Weight (kg)	1.49±0.56
Length (cm)	40.30±3.63
Occipital Frontal Circumference (OFC) (cm)	29.08±2.13
	n(%)
Gender	
Male	90(53.3)
Female	79(46.7)
Age Groups	
≤3 days	117(69.2)
4-7 days	32(18.9)
>7 days	20(11.8)
Birth Weight	
Very Low Birth Weight	151(89.3)
Extremely Low Birth Weight	18(10.7)
Residential Status	
Urban	24(14.2)
Rural	145(85.8)

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Gestational Age	
Pre Term	34(20.1)
Extremely Preterm	21(12.4)
Very Preterm	114(67.5)

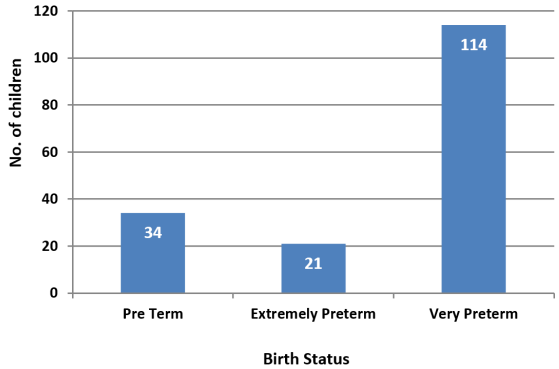

Fig. (1). Frequency Distribution of Birth Status.

Table 2. Descriptive Statistics of Clinical Outcomes of Study Population.

Outcomes	**n(%)**
Respiratory Distress Syndrome	128(75.7)
Sepsis	75(44.4)
Hypoglycemia	7(4.1)
Hyperglycemia	3(1.8)
Hypothermia	1(0.6)
Intraventricular Hemmorrhage (IVH)	20(11.8)
Necrotizing Entero Colitis (NEC)	46(27.2)
Retinopathy Of Prematurity (ROP)	8(4.7)
Chronic Lung Disease (CLD)	6(3.6)
Patent DuctusArteriosus (PDA)	8(4.7)
Survival Status	
Death	11(6.5)
Alive	158(93.5)
Predictors of Mortality (n=11)	
Respiratory Distress Syndrome	1(9.1)
Sepsis	5(45.5)
Hyperglycemia	1(9.1)
Nectrotizing EnteroColitis(NEC)	1(9.1)
Pre Maturity	3(27.3)

Table **3** presented association of extremely preterm births and very preterm births with demographic variables, mortality and predictors of mortality. The results showed that extremely preterm births and very preterm births were significantly associated with gender (p=0.003) and birth weight (p=0.000), but they were not significantly associated with age (p=0.938) and residential status (p=0.738). It was also found that extremely

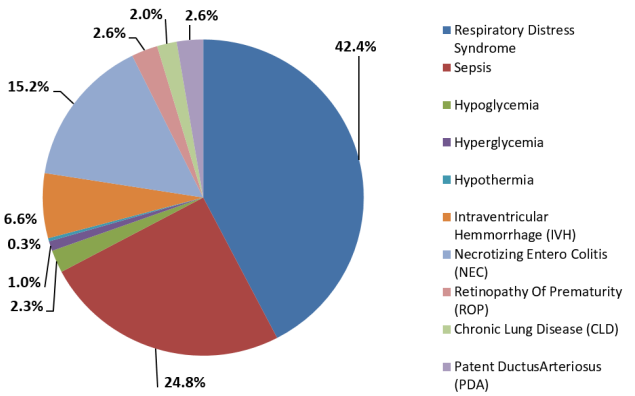

Fig. (2). Percentage of Outcomes.

preterm births and very preterm births were not significantly associated with survival status (p=0.654), and predictors of mortality (p=0.333).

It was found that males are more likely to have Very preterm in comparison of females (aOR=0.138, p=0.035) whereas children with very low birth weight are more likely to have very preterm in comparison of extremely low birth weight (aOR=104.643, p<0.001). Detailed odds are presented in Table **4**.

Table 3. Association of Extremely and Very Preterm Births with Demographic Variable, Mortality and Predictors of Mortality (n=135).

	Gestational Age n (%)		**p-value**
	Extremely Preterm	**Very Preterm**	
Gender			
Male	18(85.7)	58(50.9)	0.003*
Female	3(14.3)	56(49.1)	
Age Group			
≤3 days	13(61.9)	75(65.8)	0.938
4-7 days	5(23.8)	23(20.2)	
>7 days	3(14.3)	16(14)	
Birth Weight			
Very Low Birth Weight	6(28.6)	111(97.4)	<0.001*
Extremely Low Birth Weight	15(71.4)	3(2.6)	
Residential Status			
Urban	2(9.5)	18(15.8)	0.738
Rural	19(90.5)	96(84.2)	
Survival Status			
Death	2(9.5)	8(7)	0.654
Alive	19(90.5)	106(93)	

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Predictors of Mortality (n=10)			
Respiratory Distress Syndrome	0(0)	1(12.5)	0.333
Sepsis	0(0)	4(50)	
Hyperglycemia	0(0)	1(12.5)	
Nectrotizing Entero Colitis (NEC)	1(50)	0(0)	
Pre-Maturity	1(50)	2(25)	

Chi- square/fisher exact test was applied. *Significant at 0.05 level.

Table 4. Odds for Very Preterm Births with Demographic Variables and Mortality.

	Un-Adjusted		**Adjusted**	
	OR (95% CI)	**p-value**	**aOR (95% CI)**	**p-value**
Gender				
Male	0.173 (0.048-0.619)	0.007*	0.138 (0.022-0.866)	0.035*
Female	Ref			
Age Group				
≤3 days	1.082 (0.276-4.242)	0.910		
4-7 days	0.863 (0.180-4.134)	0.853		
>7 days	Ref			
Birth Weight				
Very Low Birth Weight	92.500 (20.908-409.238)	<0.001*	104.643 (19.407-564.235)	<0.001*
Extremely Low Birth Weight	Ref		Ref	
Residential Status				
Urban	1.781(0.381-8.322)	0.463		
Rural	Ref			
Survival Status				
Death	0.717 (0.141-3.640)	0.688		
Alive	Ref			

Binary logistic regression was applied. *Significant at 0.05 level.

DISCUSSION

In the previous 25 years, the rate of preterm births has grown by 33%, with the growth in late preterm births being the primary cause. According to the literature, there is male predominance with 55.03% of preterm births [17]. Preterm birth prevalence was found to be 11.1% globally in one of the largest data-based studies, which included 99 nations [18]. Another research included information from low- and middle-income nations and indicated an 8.2% rate of preterm deliveries [19].

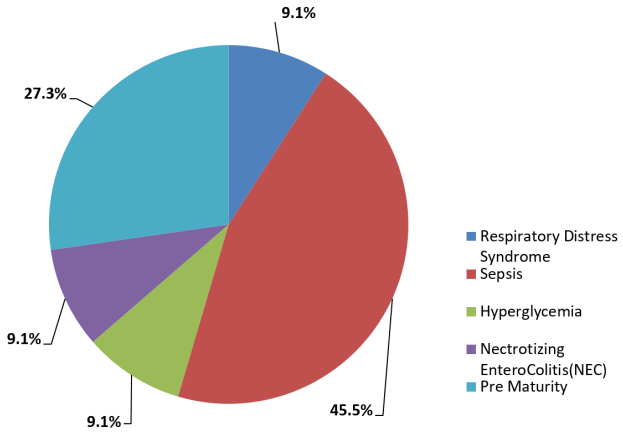

Fig. (3). Percentage of Predictors of Mortality.

In this study, the survival rate of preterm neonates was 93.5%, with a low mortality rate of 6.5%. Within the spectrum of survival rates in other industrialized nations, the study's survival rates for severely preterm newborns from 2011 to 2017 were acceptable. Some national population-based cohort studies reported that the rate of survival to discharge among 24-week live born infants was ranged from 31% to 67%. In 25-weeks live born infants it was ranged from 59% to 81% [20], compared with 34% (24 weeks) and 59% (25 weeks) in our cohort.

Death due to Respiratory distress syndrome and Intraventricular Hemorrhage had high risk of early occurrence as compared to deaths due to Necrotizing Enterocolitis tended to happen after 2nd to 3rd week of life. This was consistent with two studies that found that the development of NEC occurs after 2-3 weeks of age while infants who die from acute respiratory disease and Intraventricular Hemorrhage typically pass away during the first two to three weeks of life [21]. Due to various methodological decisions, one research did not report nearly as many fatalities as Patel *et al.* did that were ascribed to immaturity. Necrotizing Enterocolitis, Respiratory distress syndrome, and Intraventricular Hemorrhage were found as the main causes of mortality, and their cause-dependent mortality rates were identical to those seen in previous research [20]. According to research by Patel *et al.* that included RDS and BPD with respiratory issues, fewer children died from respiratory insufficiency between 2015 and 2017 compared to 2011 to 2014. This has been described previously, and it may be the outcome of the NICU's increasing use of high-frequency ventilation and more rigorous respiratory therapy [22].

Some other reasons like hypoxia and Intraventricular Hemorrhage were also observed as important causes of mortality

among late preterm babies. Preterm birth, as predicted, the most important predictor of mortality in our preterm group, independent of the reason of death. Male gender, small for gestational age, low Apgar score at five minutes, and low birth weight were among perinatal characteristics linked to a greater death rate. These outcomes are all in agreement with earlier research [23].

Prematurity, which accounts for 40% of NMR in India, is the main cause of newborn mortality, according to the MDS research [24]. Among preterm neonates born at 32 weeks, an author [25], in his study examined the reasons which are common and cause in hospital mortality. Prematurity-related problems (including respiratory disorders, CLD, Intraventricular Hemorrhage, and Necrotizing Enterocolitis; 70%) were cited as the leading cause of gestational fatalities in this group, however sepsis was 16% and neonatal asphyxia was 7.2%. Sepsis was accounted for 17% (37/221) of in-hospital fatalities in a German group of extremely LBW patients [26]. According to this study, the three most frequent causes of mortality in ELBW newborns were immaturity (gestational age 24 weeks), RDS, and sepsis. These findings confirm our conclusion that it is necessary to also investigate the major cause of mortality in preterm populations in LMIC settings [27]. Since preventative strategies vary depending on the cause of mortality, determining the cause of death in every setup is important. It will aid in providing programmatic information for anticipation and management in future cases.

LIMITATIONS

Our study is a prospective institutional study, which caters the patients predominantly from low socio-economic status and rural areas, the results may not reflect the true burden of population. Maternal illnesses contributing the neonatal outcomes are not studied in the present study. Future research is warranted in this regard.

CONCLUSION

In conclusion, the findings of the study indicated that extremely preterm birth was the most prevalent birth status in the group under consideration. 6.5% mortality was found, which is quite low. With 45.5% of all fatality cases, sepsis was identified as most common cause of death. However, there was no statistically significant link between birth status, gestational age, and death or its predictors.

AUTHORS' CONTRIBUTION

Durre Shahwar Khan: Conceptualization, Study design, Methodology, Data analysis and interpretation, Writing draft, Critical review and revision the manuscript, Final approval, final proof to be published.

Haider Abbas: Study design, Methodology, Data analysis and interpretation, Writing draft, Critical review and revision the manuscript, Final approval, final proof to be published.

Kashif Abbas: Study design, Methodology, Data analysis and interpretation, Writing draft, Critical review and revision the manuscript, Final approval, final proof to be published.

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Declared none.

CONFLICT OF INTEREST

Declared none.

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