

Survival and Risk Factors of Extremely Preterm Babies (< 28 weeks) in the Three Iranian Hospitals

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Abstract- The present study aimed to evaluate the survival rate of extremely preterm infant (<28 weeks), predictive factors, and the risk of mortality in three training hospitals of Tehran city to make better decisions to improve public health and reduce neonatal mortality. This prospective, cohort study was conducted during 2014 to 2015. Infants with the gestational age ≤ 28 weeks were enrolled. Their information was collected by using data collection forms and clinical risk index for infants. Infants were followed up until one month after the birth, and their outcomes were determined. *Chi-square* test was used for survival analysis. Binary Logistic regression was also applied to find out the factors associated with infants' survival. Among the 325 followed up infants, 166 (51%) were intra-uterine fetal death (IUFD), and 159 (49%) remained alive after birth. The infants' overall survival rate was 62 (39%) within one month after birth. Multivariate Logistic regression analysis indicated that three factors of birth weight, gestational age (GA), and fifth minute Apgar score had a negative significant relationship with the survival rate of infants ($P < 0.05$). Receiving corticosteroid and female neonatal can had a positive significant relationship with the survival rate of infants ($P < 0.05$). The survival rate of preterm infants was 39%. Younger maternal age, lower neonatal birth weight, and GA can increase the risk of neonatal mortality. Also, receiving corticosteroid and female gender of neonate can decrease the risk of neonatal mortality. These items were important that affected infants' survival and could be considered in predicting it in neonatal intensive care units.

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Introduction

Premature delivery is defined as birth before the 37th week of gestation. The majority of preterm deliveries take place between gestational weeks 24-37. Extremely preterm, (EPT) which is the primary focus of this discussion, is less than 28 weeks gestational age (1) and represent fewer than 2% of all births and up to half of the infant deaths (2). Prematurity remains a global health problem. Although preterm birth has actually decreased in the United States over the past five years, worldwide rates have increased over the last decade (1,3-5).

The etiology is multifactorial; it is associated with the general level of healthcare, the quality of obstetric care and several gestational and maternal factors including maternal age, the presence of multiple

pregnancies, nutrition, smoking and multiple other obstetric or medical conditions developing during gestation (6).

In general, morbidity and mortality of infants delivered prematurely may markedly exceed morbidity and mortality of those born in the term. Specifically, neonates born with extremely low birth weight are prone to develop a variety of both short-term and long-term postnatal medical conditions. Short-term conditions include, e.g., idiopathic respiratory distress syndrome (IRDS), bronchopulmonary dysplasia (BPD) or necrotizing enterocolitis (NEC) (7), while long-term sequel may include respiratory disorders including bronchial asthma, growth retardation, short-bowel syndrome or cerebral palsy (8-11).

In the last few decades, there has been a major

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improvement in both postnatal morbidity and survival rate of premature infants. This success has been even more marked in the case of neonates born with less than 500 g birth weight (9-11).

Viability is often defined as the gestational age at which there is a 50% chance of survival with or without medical care. Viability in developed, high-income countries of the world is somewhere between 22-24 weeks, whereas viability is closer to 34 weeks gestational age in low- and middle-income countries (12-14).

Recent data from several sources show advances in survival for EPT infants in the US and other international developed nations, although each decreasing GA week has considerable effects on mortality, particularly for infants born at 22-25 weeks of GA (15-19).

We investigated the preterm infant's survival in the hospital NICU (neonatal intensive care unit) and measured their mortality or neonatal morbidity, and association of survival with neonatal and maternal risk factors predicting mortality for neonates born with less than 28 weeks of birth age during the entire study period (one month after birth).

Materials and Methods

This prospective cohort study was conducted from March 2014 to March 2015 in three NICUs of Tehran city, Iran. The very preterm Infants included all pregnant women residing in Tehran and delivering very preterm infants, born at <28 weeks of gestation.

Inclusion criteria

The inclusion criteria were gestational age ≤ 28 weeks.

Exclusion criteria

The exclusion criteria consisted of severe fetal malformations.

Ethical considerations

After submitting the study in Maternal, Fetal and Neonatal Research Center and getting permission from Ethics Committee of Tehran University of Medical Sciences (Approval No 93-01-91-25431), informed written consent was obtained from parents of the infants.

During a one year study period, we assessed outcome data from all 325 neonates born with age less than 28 weeks in the three Centers with the three-level services (With NICU). These NICUs were selected based on their similarity in equipment and facilities, as

well as care provided for the preterm infants.

Gestational age was calculated based on the date of the last menstrual period and ultrasonographic screening during the first trimester of pregnancy (crown-rump length). Those with unknown LMP were excluded.

Birth Weight (BW) was measured within 1 hour of birth (20), and a full course of antenatal corticosteroid was defined as dexamethasone administered intramuscularly in 4 doses of 6 mg every 12 hours for pregnancies with threatened preterm birth (21).

Baseline characteristics were extracted from hospital recorded files. A special questionnaire was designed to record required information of preterm infants in the NICU including birth weight, gestational age at birth, Apgar score, gender, need for resuscitation in the delivery room, need for surfactant, need for mechanical ventilation, causes of preterm birth, disease history in the mother and cause of infant death such as respiratory distress syndrome, sepsis or congenital anomalies.

To investigate the survival and factors predicting mortality for neonates born with age less than 28 weeks during the entire study period, we assessed several clinical parameters comparing their relative frequencies among survivors versus mortality cases. For this purpose, we divided cases representing the entire study period into alive (live in one month) and mortality group. A large number of clinical parameters were available for assessment as potential predictors for clinical outcome. These included maternal factors, obstetric data, and neonatal factors.

Among maternal factors, maternal age and parity, the number of prior gestations, previous assisted reproductive technique (ART) treatments were all assessed. Among obstetric factors, the presence of multiple pregnancies, gestational age at delivery, type and reason for preterm delivery, method of delivery, birth weight, and neonatal gender were investigated. Among neonatal factors prenatal steroid prophylaxis treatment, 1 and 5 min Apgar score, occurrence of neonatal complications like pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), postnatal echocardiography results, presence of persistent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC). Death and the survival rate were the main clinical parameters assessed.

Data are expressed as mean \pm SD and number (percentile). Statistical significance for differences was tested by Student's *t*-test or Mann-Whitney U-test depending on the normal distribution of continuous data.

Categorical data were analyzed by Chi-square test and Fisher exact test. A *P* value less than 0.05 was considered as statistically significant. Binary Logistic regression analysis was used to estimate interaction of variable that.

These variables were selected prior to inclusion on the basis of a significant association between two groups.

Potential confounders including maternal age (years), gestational age (week), neonatal weight (gr), sex of neonate (female), corticosteroid and need to resuscitation were selected as a priori for inclusion in the logistic regression model for assessment of the relation to odds of survived neonates ($P \leq 0.05$)

Multivariate binary logistic regression was used to estimate Odds ratio (OR) and 95% confidence interval (CI) for the associations between the risk factors of female neonatal sex, gestational age, neonatal birth weight, mother's age, need to resuscitations and received corticosteroid in pregnancy with neonatal survival in univariate analyses ($P \leq 0.05$).

All the statistical analyses were performed using

SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 325 neonates less than 28 weeks were screened during 2014-2015.

One hundred fifty-nine out of the total of 325 neonates were born alive and, 62 out of 159 neonates (39%) were alive one month after the birth. Survival rate (one month after the birth) was 39 % (Table 1). The majority in the alive group (53 or 85.5%) had the weight less than 1000 g, and 9 (14.5%) had the weight of 1000-1499 g. Also, among the 62 alive infants, 37(60%) were female, and 25 (40%) were male. Female neonates were more than male counterparts in alive group ($P=0.003$).

Twenty-five of alive infants (40%) were born through normal vaginal delivery (NVD) and 37 (60%) by cesarean section (C/S). Cesarean section was reported higher in the alive group more than mortality group ($P=0.001$) (Table 2).

Table 1. The status of the neonate at the birth time <28 week

		Number(n=325)	Percent
The status of the birth	Alive	159	49
	Mortality	166	51
The status after one month (N=159)	Alive	62	39
	Mortality	97	61

Also, 23 mothers (37%) in the alive group received, and 15 mothers in mortality group (15.5%) did not receive any corticosteroids during the pregnancy. The alive group received corticosteroid more than mortality group ($P=0.002$).

There were no statistically significant differences between two groups regarding the multiple pregnancy ($P=0.73$), type of pregnancy ($P=0.31$), neonatal complication ($P>0.05$), But there were significant differences regarding the sex of neonate ($P=0.003$), gestational age ($P=0.0001$), neonatal weight ($P=0.0001$, receiving Corticosteroid (before delivery) ($P=0.002$), and Apgar in first and fifth minute after delivery ($P=0.0001$) between the two groups of alive neonates versus mortality neonates (Table 2, 3).

Comparing of variables between mortality cases versus surviving infants for one month after the birth, we found that among infants who died, maternal age was significantly higher in alive neonates (29.5-5.4 years) more than in mortality group (27.4-6.1 years;

$P=0.03$)

Gestational age at delivery was significantly lower for the mortality group (gestational age=25.5-1.2SD weeks) versus the survivor group (26.5-1.1SD weeks; $P=0.0001$)).

According to multivariable logistic regression modeling (Table 4), female neonatal sex, gestational age (GA), birth weight, maternal age and receiving corticosteroid, which was significantly associated with neonatal survival. The adjusted OR proved a statistically significant association between female neonatal sex (OR=0.20, 95% CI: 0.06-0.69, $P=<0.010$), GA (OR=2.07; 95% CI: 1.15-3.74, $P=0.015$) and maternal age (OR=1.15, 95 % CI: 1.04-1.2, $P=0.0005$) with neonatal survival.

It means that younger maternal age, lower neonatal birth weight, and GA can increase the risk of neonatal mortality. Also, receiving corticosteroid and female neonate can decrease the risk of neonatal mortality or increase the neonatal survival rate.

Table 2. The frequency of qualitative variables in the studied samples (Babies who were born alive)

Variable		Alive N=62 (n,%)	Mortality N=97 (n,%)	P
Multiple pregnancy	No	42(68)	70(72)	0.735
	Yes	20(32)	27(28)	
Sex:	Female	37(60)	35(36)	0.003
	Male	25(40)	62(64)	
Type of pregnancy	Spontaneous	54(87)	77(80)	0.319
	IVF	2(3)	11(10)	
	IUI	2(3)	4(14)	
Type of delivery	other	4(7)	5(5)	0.0001
	Normal vaginal delivery	25(40)	67(70)	
	Cesarean	37(60)	30(30)	
Neonatal weight (gr)	<1000	53(85.5)	64(66)	0.006
	1000-1499	9(14.5)	22(23)	
	>1500	0	11(11)	
Gestational age (week)	23≤	2(3)	3(3.5)	0.0001
	24-26	44(71)	33(34.5)	
	26-28	16(26)	61(62)	
The mother risk factor	-Diabet	3(5)	4(4)	0.830
	-Hypertention	5(8)	6(6)	0.649
	-Chorioamnionitis	0	4(4)	0.157
	PVL	1(2)	1(1.5)	0.779
	NEC	5(10)	2(3)	0.117
	IVH	2(3)	3(3.5)	0.222
	BPD	1(2)	1(1.5)	0.779
Neonatal complication	RDS	28(58)	30(42)	0.096
	Sepsis	1(2)	2(3)	0.802
	ROP	4(6)	1(1)	0.122
	Hydrocephaly	1(2)	0	0.222
	Apnea	3(6)	5(7)	1
	Need to resuscitations	22(35)	59(61)	0.001
Receiving of Corticosteroid(before delivery)	Yes	23(37)	15(15.5)	0.002
	No	39(63)	82(84.5)	

bronchopulmonary dysplasia (BPD), postnatal echocardiography results, presence of persistent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC)

Table 3. The Mean±SD of quantities' variables in the studied samples

Variable	Mortality neonate N=97	Alive neonate N=62	P
	Mean±SD	Mean±SD	
Mother Age (Year)	27.4±6.1	29.5±5.4	0.034
Gravida(n)	1.3±0.57	1.3±0.57	0.661
Number of abortion	0.37±0.75	0.25±0.59	0.252
Gestational age (week)	25.5±1.2	26.5±1.1	0.0001
Neonatal weight (gr)	8.5±191	1085±573	0.0001
Apgar (First minute)	4.1±1.18	±2.2 6.5	0.001
Apgar (five minutes)	6±1.8	8±2	0.001

Discussion

The aim of this study was to investigate the infants' survival rate and related factors. The results indicated

that 39% of extremely preterm infants in NICUs of three training hospitals in Teran remained alive one month after birth. In a study conducted by Munack *et al.*, (22), 53.1% of the infants born at 23-37 weeks gestation were alive after 120th day of their life or their discharge from the hospital. Another study, which was carried out in Thailand and had difference with the present study, reported 81% survival rate for infants with less than 25 weeks gestation (23).

In Isfahan, Iran, among 194 infants aged lower than 30 weeks gestation, 125 (64.4%) expired during hospitalization (24). In another study by Alleman *et al.*, (25) performed during 2006-2009, 11-26% hospital mortality was reported among infants with ≥ 25 weeks of gestation in various centers. Velaphi *et al.*, (26) showed that the survival rates of the infants with 26, 27, and 28 weeks of gestation were 38%, 50%, and 65%, respectively.

In a study by EXPRESS Group in Sweden, overall perinatal mortality was 45% ranged from 93% at 22 weeks to 24% at 26 weeks (27). In a Swedish cohort between 1990 and 1992 on neonates born at 23 and 24 weeks of gestation died in the delivery room and those survival to one year were only 8% and 28%, respectively (28).

In a prospective, national, population-based study in France in 2011, 31.2% of neonates born at 24 weeks and 93.36% of those born at 27-31 weeks survived. The authors explained that although the survival rate in extremely low gestational age is improved, their long-term outcomes need more studies (29).

The differences between these results and ours could be attributed to gestational age and different study settings. In a prospective study in Isfahan /Iran in 2013-2014, 71.2% of neonates born ≤ 32 weeks with birth weight ≤ 1500 g survived (30).

Also, inconsistent with our study, Nayeri study on all neonates weighing ≤ 1500 g, born in Vali-e-Asr hospital (2001-2004) showed that the highest mortality rate among neonates of lowest gestational age was 68% in neonates ≤ 26 weeks of gestational age (31).

The reported mortality rate in the present study was higher than other results, which could be related to infants' lower gestational age. Wide disparities in the risk-adjusted mortality and morbidity of very preterm infants across countries and neonatal units suggest that large improvements are possible using current medical knowledge (32-36).

The fact that survival rates for babies born at 24 weeks and above have increased and the cutoff point for providing active treatment for those born under 24

weeks remains "extremely argumentative (37).

Various neonatal and maternal variables have been identified affecting premature neonatal mortality completely matched with previous findings. As the main independent variable, female neonatal sex, gestational age (GA), birth weight, maternal age and receiving corticosteroids were significantly associated with neonatal survival. Younger maternal age, lower neonatal birth weight, and GA can increase the risk of neonatal mortality. Also, receiving corticosteroids and female gender can decrease the risk of neonatal mortality or increase the survival rate. The present study results were not consistent with the study conducted by Khani (38), in which no significant relationship was found between receiving corticosteroids by mother and neonatal survival.

Although, the present study results were consistent with the Vincer (39) in Canada, that receiving corticosteroids by mother was one of the predictors of infant's survival. The results of a study by Ravelli *et al.*, (40) in Poland showed a significant relationship between infants' mortality rate and lack of receiving corticosteroids by mothers, male gender, and old mothers. Also, Basu showed that mortality rate could be increased with decreased birth weight and gestational age, vaginal bleeding, failure to administer steroid antenatal, Apgar score equal to or less than 5 at one minute, apnea, gestational age, neonatal septicemia and shock (41).

Moreover, Velaphi *et al.*, (42) in a study carried out in Africa indicated that cesarean section and female gender are linked with infants' good survival. Variation in the results of our study with other studies is probably related to different related environments of the countries that affected the variables.

The major reasons for infants' mortality, as shown in our study, had no significant differences in two groups of alive and mortality. But, Velaphi *et al.*, (26). Fallahi *et al.*, (42) considered respiratory distress syndrome as the major reason for infants' mortality.

Indredavik *et al.* showed that lower birth weight, shorter gestational age, and intra-ventricular hemorrhage were risk factors for neurodevelopmental problems (43). Moreover, Almeida *et al.*, survey and according to the multivariate analysis, gestational age of 23-27 weeks, maternal hypertension, 5th minute Apgar less than 6, presence of respiratory distress syndrome and network center of birth were associated with early intra-hospital neonatal deaths (44).

A retrospective, the population-based analysis showed that high quality of neonatal care provided at

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birth might reduce neonatal mortality in very preterm infant (45).

It seems that wide variations in mortality rate among premature neonates are due to the time definition of prematurity and occurrence of one or a set of causing maternal and neonatal parameters. Therefore, detecting and management of these predictive factors can improve planning practical programs for pregnancy, proper prevention of life-threatening complications in mother's and newborn's wards and raising personal responsiveness to the care of mothers and infants.

Also, current advances in science and technology, also progress and upgrading in perinatal care services have brought on a significant increase in the survival of very preterm babies in developed countries (37,46) and premature babies born in high-level neonatal intensive care units (NICUs) have a better chance of survival than those born in hospitals without such facilities (45,46).

So, the results of this study provide evidence-based information to health policymakers to evaluate the best policy approaches for efforts on reducing infant mortality.

The limitations of our study were that the involved centers equipped with NICU and analysis of outcomes until one month after the birth. To get a more clearly defined clinical picture, multi-center studies of planned follow-up will be needed. Also, in the present study; many mothers present late in labor and do not attend antenatal care. Therefore, there may be limited opportunities for obstetricians to administer steroids. To examine the performance of different centers and to bridge the gaps among different infants' survival prediction, it is recommended that effective factors of infants' survival rate be investigated comparatively in different settings through future studies.

The survival rate of preterm infants was (39%). Younger maternal age, lower neonatal birth weight, and GA can increase the risk of neonatal mortality. Also, receiving corticosteroids and female gender can decrease the risk of neonatal mortality. These items were important for affected infants' survival and could be considered in predicting it in NICUs.

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