

Neonatal Mortality and its Main Determinants in Premature Infants Hospitalized in Neonatal Intensive Care Unit in Fatemieh Hospital, Hamadan, Iran

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Background: Neonatal mortality is one of the main indicators of health and welfare of population. Prematurity is one of the most important causes of neonatal mortality. We determined mortality rate and its main indicators among premature neonates in our region with the aim of making good decisions to improve public health and reduce neonatal mortality.

Objectives: We aimed to determine mortality rate and its main indicators among premature neonates in our region with the aim of making good decisions to improve public health and reduce neonatal mortality.

Patients and Methods: Four-hundred and ninety-two consecutive premature neonates hospitalized in neonatal intensive care unit entered this cross-sectional study. The study information was extracted from hospital recorded files.

Results: Neonatal death rate was overall 27.4%, which was significantly higher in gestational age subgroup of less than 28 weeks compared with other gestational age subgroups. The most prevalent etiologies of neonatal death were respiratory distress syndrome (73.8%), congenital abnormalities (13.8%) and sepsis (5.4%), respectively. Preeclampsia and history of multiple pregnancies were more prevalent in non-survived neonates. According to multivariable regression modeling, low gestational age, low birth weight, low Apgar scores, need for intensive supports, history of disease in mother, occurrence of pneumothorax, multiple gestation and preeclampsia could all strongly predict occurrence of death in premature infants.

Conclusions: Approximately one quarter of premature neonates had early mortality, which can be predicted by low gestational age, low birth weight, low Apgar score, need to intensive supports, postpartum complications, multiple gestation and history of maternal illnesses.

Keywords: Infant Mortality; Intensive Care Units; Prematurity; Predictions

1. Background

Neonatal period is a critical time for infant survival. Fetal life as the main period of human development is a continuous period potentially influenced by various genetic, environmental, and social factors (1). In this period, many physiological adaptation processes necessary for extra-uterine life are formed. Thus, the fetus is very vulnerable with high rates of mortality and morbidity. Neonatal mortality rate is often used as a standard for the development of health care systems as well as achieving optimal educational and social conditions (2, 3). Neonatal mortality rate is directly associated with high risk pregnancy and therefore the major reasons for neonatal death can be revealed in relation to complications of risky pregnancy including prematurity, intrauterine growth retardation,

congenital abnormalities and other disabilities (3-5).

Every year more than four million neonates die worldwide and more than ten thousand deaths occur in the first day of life (6). Almost all cases of deaths occur in low-income or middle-income countries (7). Neonatal mortality is largely preventable and has been considerably reduced in developed countries using proper techniques and appropriate preventive approaches (8-10). Therefore, in addition to determining the rate of infant mortality, identifying factors associated with neonatal death may lead to the prevention of life-threatening neonatal events (11). In fact, preventive health education, prenatal cares, nutritional planning, social supports, identifying potential risk factors and obstetric cares can effectively reduce early

neonatal death in neonatal period (12). In this context, prematurity has a major role and its proper management results in increasing infant survival (13). About 15 million infants are born preterm each year worldwide and the incidence is rising (14). In the United State, prematurity causes approximately one third of infant deaths (15).

Unfortunately, we are still far from international standards for prevention and management of neonatal mortality, especially in premature state. In a recent report in our country, the most important cause of newborn death was prematurity in about 64% of affected cases (16). However, mortality rate in premature infants in different areas of the country remained unknown. Furthermore, the main determinants of premature infant death are already questioned.

2. Objectives

Thus, we aimed to determine mortality rate and its main indicators among premature neonates in our region to make better decisions to improve public health and reduce neonatal mortality.

3. Patients and Methods

Fifty-hundred consecutive premature neonates hospitalized in neonatal intensive care unit at Fatemeh hospital in Hamadan, Iran during 2012 entered this cross-sectional study. The definitional criterion of prematurity was gestational age below 37 weeks based on last menstrual period (LMP). Thus, those with unknown LMP were excluded. In this regard, 492 neonates were finally evaluated. Baseline characteristics were extracted from hospital recorded files. A special questionnaire was designed to record required information of preterm infants in the neonatal intensive care unit (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. Results were reported as mean \pm standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups were compared using Student's t-test or Mann-Whitney U test for continuous variables and chi-square test (or Fisher's exact test if required) for categorical variables. Predictors exhibiting a statistically significant relation with neonatal death in Univariate analyses (with a P Value $>$ 0.1) were taken for a Multivariable logistic regression analysis to investigate their independence as predictors. P values of 0.05 or less

considered statistically significant. All the statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

4. Results

The average of gestational age was 31.97 ± 2.99 weeks ranged 23 to 36 weeks. Mothers had the mean age of 27.59 ± 6.08 years ranged 14 to 50 years. The mean of neonatal weight at birth was 1810.15 ± 665.00 grams. Average of first and fifth minutes Apgar scores were 6.43 ± 1.92 (median 7.0) and 7.79 ± 1.73 (median 8.0), respectively. One-hundred and forty-one infants (28.7%) were the result of multiple pregnancies. Table 1 describes premature neonates and compares baseline characteristics between survived and death premature neonates. Except for mother's age and infection status as complication, which were both comparable in the two survived and non-survived neonates, other characteristics such as gestational age less than 28 weeks, low weight at birth, low first and fifth minutes Apgar scores, need for intensive supports including mechanical ventilation, instillation of surfactant, resuscitation at delivery room, history of disease in mother and occurrence of pneumothorax were all more observed in non-survived group. Moreover, male to female ratio was significantly higher in dead neonates than survived ones.

As shown in Table 2, the most frequent causes of preterm labor were premature rupture of membranes (11.2%) followed by preeclampsia (9.3%), multiple pregnancy (8.5%) and fetal distress (7.5%). Neonatal death rate was overall 27.4% (134 of 489 neonates), which was significantly higher in gestational age subgroup of less than 28 weeks compared with other gestational age subgroups ($P < 0.001$). The most prevalent etiologies of neonatal death were respiratory distress syndrome (73.8%), congenital abnormalities (13.8%) and sepsis (5.4%), respectively. Regarding etiologies of preterm labor, preeclampsia and history of multiple pregnancies were significantly more prevalent in non-survived neonates; however, two survived and non-survived patients were similar in other causes including premature rupture of membranes, fetal distress, oligohydramnios, eclampsia and previous history of various disorders in mothers (Table 2). According to multivariable logistic regression modeling (Table 3), low birth weight, need for intensive supports including resuscitation and ventilation, occurrence of pneumothorax, pregnancy complications such as preeclampsia and fetal distress could all strongly predict occurrence of death in premature infants. Moreover, male gender was associated with increased risk of death in these neonates.

Table 1. Baseline Characteristics in Survived and non-Survived Neonates

Characteristics	All Neonates (n = 492)	Survived Neonates (n = 358)	Non-Survived neonates (n = 134)	P Value
Age of gestation, wk				< 0.001
< 28	68 (13.8)	24 (6.7)	44 (32.8)	
28 - 32	185 (37.6)	130 (36.3)	55 (41.1)	
> 32	239 (48.6)	204 (57.0)	35 (26.1)	
Weight at birth, gr				< 0.001
<1000	64 (13)	11 (3.1)	53 (39.6)	
1000 -1500	128 (26)	97 (27.1)	31 (23.1)	
1501 - 2000	137 (28)	108 (30.2)	29 (21.6)	
2001 - 2500	89 (18)	80 (22.3)	9 (6.7)	
> 2500	74 (15)	62 (17.3)	12 (10.0)	
Mother age, y				0.789
<15	1 (0.2)	1 (0.3)	0 (0.0)	
15 - 35	429 (87.2)	311 (86.9)	118 (88.1)	
> 35	62 (12.6)	46 (12.8)	16 (11.9)	
First minute Apgar score				< 0.001
0 - 3	42 (8.6)	6 (1.7)	36 (26.9)	
4 - 6	172 (34.9)	111 (31.0)	61 (45.5)	
7 - 10	278 (56.5)	241 (67.3)	37 (27.6)	
Fifth minute Apgar score				< 0.001
0 - 3	20 (4.1)	4 (1.1)	16 (11.9)	
4 - 6	71 (14.4)	31 (8.7)	40 (29.9)	
7 - 10	401 (81.5)	323 (90.2)	78 (58.2)	
Gender of neonate				< 0.001
Male	305 (62.8)	209 (58.4)	96 (71.6)	
Female	181 (37.2)	144 (40.2)	37 (27.6)	
Need to resuscitation	115 (23.4)	34 (10.0)	81 (60.4)	< 0.001
Need to surfactant	124 (25.2)	38 (10.6)	86 (64.2)	< 0.001
Need to ventilation	177 (35.9)	52 (14.5)	125 (93.3)	< 0.001
Complicated by infection	36 (7.4)	24 (6.7)	12 (8.9)	0.404
Complicated by pneumothorax	31 (6.3)	4 (1.1)	27 (20.1)	< 0.001
History of disease in mother	26 (5.3)	10 (2.8)	16 (11.9)	0.001

Table 2. Etiologies of Preterm Labor in Survived and Non-Survived Groups

Etiology	All Neonates (n = 492)	Survived Neonates (n = 358)	Non-Survived Neonates (n = 134)	P Value
PROM	55 (11.2)	39 (10.9)	16 (11.9)	0.754
Fetal distress	37 (7.5)	26 (7.3)	11 (8.2)	0.737
Oligohydramnios	6 (1.2)	4 (1.1)	2 (1.5)	0.718
Preeclampsia	46 (9.3)	22 (6.1)	24 (17.9)	< 0.001
Multiple pregnancy	42 (8.5)	40 (11.1)	2 (1.5)	< 0.001
Eclampsia	1 (0.2)	0 (1.1)	1 (0.7)	0.69
Mother's disease	3 (0.6)	0 (1.1)	3 (2.2)	0.355

Table 3. Odds Ratio for Neonatal Mortality According to the Risk Factors ^a

Risk Factors	OR (95% CI)	P Value
Weight at birth, gr		
< 1000	30.2 (2.3 ~ 390)	0.009
> 2500	1	
Pregnancy complications		
Fetal Distress	46.1 (5.9 ~ 358)	< 0.0001
Pre eclampsia	9.3 (1.6 ~ 52)	0.011
Gender of neonate		
Male	5.7 (1.9 ~ 16)	0.001
Female	1	
Need to resuscitation		
Yes	6.4 (1.6 ~ 25.7)	0.008
No	1	
Need to ventilation		
Yes	48 (14 ~ 162)	< 0.0001
No	1	
Complicated by pneumothorax		
Yes	10.4 (1.7 ~ 62)	0.009
No	1	

^a ORs and 95% CIs were calculated by performing logistic regression analysis to determine the risk of neonatal mortality according to the presence of maternal and neonatal risk factors.

5. Discussion

The purpose of the present investigation was to assess neonatal in-hospital mortality and its main indicators in a sample of premature neonates in Hamadan, a big province in west of Iran. In this survey, prematurity was defined as gestational age below 37 weeks. Recently, a steadily decreasing trend of infant mortality rate has been shown worldwide; however, change in neonatal mortality, especially in premature status, remained partially constant. Prognosis of prematurity in these neonates generally depends on birth weight, gestational age, disease severity in the first hours of life and other-related pathophysiological conditions causing a wide range of neonatal premature mortality in various regions and countries. We documented a mortality rate of 27.4% in our studied premature neonates. In most similar studies, a wide varied mortality rate was documented ranged from 23% to 29% (17-19). In a study by Dong and colleagues in China, in-hospital mortality decreased from 29.8% in 2002 - 2005 to 28.1% in 2006 - 2009 with a significant trend (20). Our obtained mortality rate was inconsistent with global rate published in recent studies, however some recent reports documented dramatically higher rate of premature neonatal mortality based on definitional time of prematurity. In a study by EXPRESS Group in Sweden, overall perinatal mortality was 45% ranged from 93% at 22 weeks to 24% at 26 weeks (21). In a Swedish cohort between 1990 and 1992 on all

infants with a birth weight of 1000 grams or less, most of 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 (22). 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 (23). In another study in India, 14.8% of neonates under 1500 gr died before hospital discharge (24).

Various neonatal and maternal variables have been identified affecting in-hospital death in premature neonates completely matched with previous findings. Basu and his colleagues showed that mortality rate could be increased with decreased birth weight and gestational age, vaginal bleeding, failure to administer steroid antenatally, Apgar score equal to or less than 5 at one minute, apnea, gestational age, neonatal septicemia and shock (25). In another study by Dong et al., persistent pulmonary hypertension of newborn, pulmonary hemorrhage, birth weight < 1000 grams, gestational age < 33 weeks, feeding before 3 postnatal days and enteral feeding were predictors of in-hospital mortality (20). In another study, the most important high risk factors affecting mortality of neonates were low birth weight, need for resuscitation at birth, need for ventilator use

and intra-ventricular hemorrhage (26). Also in the study by Terzic et al. a significant difference was found between groups of survived and dead infants regarding gestational age, birth weight, Apgar score, Crib score, base excess, presence of respiratory distress syndrome and hemodynamic stability at birth (27). Indredavik et al. showed that lower birth weight, shorter gestation and intra-ventricular hemorrhage were risk factors for neurodevelopmental problems in very low birth weight group (28). Moreover, in 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 (29). In total, a combination of both neonatal and maternal underlying factors can predict in-hospital mortality in Iranian premature consistent with other communities worldwide. A retrospective, population-based analysis showed that high-volume neonatal care provided at birth may reduce neonatal mortality in very preterm infant (30). It seems that wide variations in mortality rate among premature neonates are due to the time definition of prematurity and presence of one or a set of triggering maternal and neonatal parameters. Therefore, identifying and management of these predictive factors can improve planning adopted programs for pregnancy, proper prevention of life-threatening complications in mother's and newborn's wards and raising personal attention to the care of mothers and infants.

In summary, approximately one quarter of premature neonates had early mortality, which can be predicted by low gestational age, low birth weight, low Apgar score, need to intensive supports, postpartum complications, multiple pregnancy and history of maternal illnesses.

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Authors' Contributions

Design and conduction of study: Behnaz Basiri, Management: Behnaz Basiri and Maryam Shokouhi, Analysis of data: Farzaneh Esna Ashari, Preparation, review and approval of the manuscript: Mohammad Kazem Sabzehei and Behnaz Basiri.

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References

1. Kliegman R. *Nelson Textbook of Pediatrics*. Elsevier/Saunders; 2011.
2. Luo ZC, Liu S, Wilkins R, Kramer MS, Infant Health Study Group of the Canadian Perinatal Surveillance S, Fetal. Risks of stillbirth and early neonatal death by day of week. *CMAJ*. 2004;**170**(3):337-41.

3. Martinez J, Paul VK, Bhutta ZA, Koblinsky M, Soucat A, Walker N, et al. Neonatal survival: a call for action. *Lancet*. 2005;**365**(9465):1189-97.
4. Sankaran K, Chien LY, Walker R, Seshia M, Ohlsson A, Canadian Neonatal N. Variations in mortality rates among Canadian neonatal intensive care units. *CMAJ*. 2002;**166**(2):173-8.
5. Moss W, Darmstadt GL, Marsh DR, Black RE, Santosham M. Research priorities for the reduction of perinatal and neonatal morbidity and mortality in developing country communities. *J Perinatol*. 2002;**22**(6):484-95.
6. Yasmin S, Osrin D, Paul E, Costello A. Neonatal mortality of low-birth-weight infants in Bangladesh. *Bull World Health Organ*. 2001;**79**(7):608-14.
7. Yu VY. Global, regional and national perinatal and neonatal mortality. *J Perinat Med*. 2003;**31**(5):376-9.
8. Copper RL, Goldenberg RL, Creasy RK, DuBard MB, Davis RO, Entman SS, et al. A multicenter study of preterm birth weight and gestational age-specific neonatal mortality. *Am J Obstet Gynecol*. 1993;**168**(1 Pt 1):78-84.
9. Tariq P, Kundi Z. Analysis of high-risk infant births and their mortality: ten years' data from chonnam national university hospital. *J Pakistan Med Assoc*. 1999;**49**:56-9.
10. de Castro MP, Rugolo LM, Margotto PR. [Survival and morbidity of premature babies with less than 32 weeks of gestation in the central region of Brazil]. *Rev Bras Ginecol Obstet*. 2012;**34**(5):235-42.
11. Choi YY, Song ES, Kim YH, Song TB. Analysis of high-risk infant births and their mortality: ten years' data from chonnam national university hospital. *Eas Med Sci*. 2011;**47**(1):31-8.
12. Draper ES, Manktelow B, Field DJ, James D. Prediction of survival for preterm births by weight and gestational age: retrospective population based study. *BMJ*. 1999;**319**(7217):1093-7.
13. WHO . France: 2006. Neonatal and prenatal WHO mortality, Country, Regional and Global Estimates.
14. Pignotti M, Donzelli G. Preterm babies at a glance. *J Clin Neonatol*. 2015;**4**(2):75.
15. Mandy GT. *Incidence and mortality of the premature infant. UpToDate*. 2015. Available from: www.uptodate.com.
16. Hadavi M, Alidalaki S, Abedinnejad M, Akhavan S. Etiologies and contributing factors of perinatal mortality: a report from south-east of Iran. *Taiwan J Obstet Gynecol*. 2011;**50**(2):145-8.
17. Brito AS, Matsuo T, Gonzalez MR, de Carvalho AB, Ferrari LS. [CRIB score, birth weight and gestational age in neonatal mortality risk evaluation]. *Rev Saude Publica*. 2003;**37**(5):597-602.
18. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, et al. Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. *Pediatrics*. 2001;**107**(1):E1.
19. Zardo MS, Procianoy RS. [Comparison between different mortality risk scores in a neonatal intensive care unit]. *Rev Saude Publica*. 2003;**37**(5):591-6.
20. Dong Y, Yue G, Yu JL. Changes in perinatal care and predictors of in-hospital mortality for very low birth weight preterm infants. *Iran J Pediatr*. 2012;**22**(3):326-32.
21. Express Group , Fellman V, Hellstrom-Westas L, Norman M, Westgren M, Kallen K, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA*. 2009;**301**(21):2225-33.
22. Finnstrom O, Olausson PO, Sedin G, Serenius F, Svenningsen N, Thiringer K, et al. The Swedish national prospective study on extremely low birthweight (ELBW) infants. Incidence, mortality, morbidity and survival in relation to level of care. *Acta Paediatr*. 1997;**86**(5):503-11.
23. Ancel PY, Goffinet F, Epipage- Writing Group , Kuhn P, Langer B, Matis J, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr*. 2015;**169**(3):230-8.
24. Vlbw Infant Survival in Hospitals of India Study Investigators , Murki S, Kumar N, Chawla D, Bansal A, Mehta A, et al. Variability in survival of very low birth weight neonates in hospitals of India. *Indian J Pediatr*. 2015;**82**(6):565-7.

25. Basu S, Rathore P, Bhatia BD. Predictors of mortality in very low birth weight neonates in India. *Singapore Med J*. 2008;**49**(7):556-60.
26. Nayeri F, Dalili H, Nili F, Amini E, Ardehali A, Khoshkrood Mansoori B, et al. Risk factors for neonatal mortality among very low birth weight neonates. *Acta Med Iran*. 2013;**51**(5):297-302.
27. Terzic S, Heljic S. Assessing mortality risk in very low birth weight infants. *Med Arh*. 2012;**66**(2):76-9.
28. Indredavik MS, Vik T, Evensen KA, Skranes J, Taraldsen G, Brubakk AM. Perinatal risk and psychiatric outcome in adolescents born preterm with very low birth weight or term small for gestational age. *J Dev Behav Pediatr*. 2010;**31**(4):286-94.
29. Almeida MF, Guinsburg R, Martinez FE, Procianny RS, Leone CR, Marba ST, et al. Perinatal factors associated with early deaths of preterm infants born in Brazilian Network on Neonatal Research centers. *J Pediatr (Rio J)*. 2008;**84**(4):300-7.
30. Watson SI, Arulampalam W, Petrou S, Marlow N, Morgan AS, Draper ES, et al. The effects of designation and volume of neonatal care on mortality and morbidity outcomes of very preterm infants in England: retrospective population-based cohort study. *BMJ Open*. 2014;**4**(7):e004856.