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Original Article

Neonatal Mortality in an Iranian Referral Level III Neonatal Intensive Care Unit: A Cross-Sectional Study

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ABSTRACT

Background: Despite the significant improvement in neonatal intensive care, neonatal death is still one of the most important challenges worldwide. Understanding the causes of neonatal mortality is important for health policymakers. This study aimed to assess neonatal mortality in an Iranian referral level III Neonatal Intensive Care Unit (NICU).

Methods: This cross-sectional study was conducted on the neonates who were referred to a level III NICU between 2014 and 2019. Data collection was performed by the research assistants, using a pre-designed checklist from the neonatal medical records. All the neonatal records of the patients who died during the infancy period were collected. Data were analyzed using SPSS (version 23).

Results: In total, 388 (12%) out of 3,078 inpatient neonates died In this study. The mean gestational age of neonates who died was 34.9 weeks and 53% of them were males. In addition, 92 (23%) of them died when they aged between 0-7 days and hyponatremia was the most common (30.9%) abnormal laboratory finding among them. The main causes of mortality included sepsis (26%), congenital multiple anomalies (21%), prematurity (20%), surgical procedures (15%), congenital heart disease (8%), inborn metabolic disorder (6%), hypoxic-ischemic encephalopathy (2.8%), and some unknown reasons (1.2 %), respectively. Sepsis, as the most common disorder in neonatal mortality among the patients, was detected in 74 (58.27%) preterm infants, and Acinetobacter was the main microbial detected pathogen. The rate of sepsis was significantly different in different gestational ages (P<0.001).

Conclusion: Based on the obtained results, sepsis, prematurity, and congenital multiple anomalies are the most common causes of mortality among neonates. Causes of mortality during the first month of life were different indicating the need for evidence-based interventions and proper policymaking in the field of neonatal health.

Keywords: Congenital Anomalies, Infant, Iran, Mortality, Neonatal Intensive Care

Introduction

Neonatal mortality rate (NMR) is defined as mortality during the first month of life. The neonatal period is the most vulnerable time for the survival of infants and children (1). Based on the reports of the world health organization (WHO), newborn deaths account for 45% of deaths among children under the age of five globally. Despite the medical progress in recent decades, each year, more than 2.7 million infants die during the first month of life. In 2016, 2.6 million children died in the first month of life due to conditions and diseases associated with the lack of quality care at birth or skilled care and treatment immediately after birth (2).

It is worth mentioning that about two-thirds of neonatal deaths occur in ten countries which are mostly located in Asia. Moreover, 99% of NMR is occurring in developing countries in which the rate of mortality is twice that of the global rate due to the Human Immunodeficiency Virus (3, 4). The prevalence of NMR in the west Asian countries is 27 cases per 1000 live birth; however, based on a

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recent report, this rate is 10 per 1000 live birth in Iran. It is worth mentioning that this rate is 5 in 1000 live birth in the developed countries (5).

Globally, the most important causes of neonatal deaths include prematurity, asphyxia, sepsis, and pneumonia (6-8). Prematurity is the most frequent cause of neonatal mortality (9). The rate of preterm birth is 10.6% worldwide and based on the results of conducted study, the rate of mortality in the premature infant is 12%, which is much more than that in term neonates (10). Evaluation of the causes of neonatal mortality is one of the most important steps to improve the situation in high-risk populations (11). It should be noted that the causes of neonatal mortality are different in maternity hospitals. Identification of the cause of mortality in a particular setting is important for policymaking and designing interventions that aim to improve neonatal survival.

At Level 3 and 4 NICU that admit neonates with complicated medical and surgical problems, the underlying causes of neonatal mortality are different from those in nurseries. Therefore, determination of the most common cause of neonatal mortality can improve the process of care and implementation of interventions for neonatal survival. Mofid Children's Hospital in Tehran, Iran, is an educational medical hospital and a most well-known referral Iranian level 3 NICU that admits infants with surgical problems from all over the country. The present study aimed to thoroughly assess neonatal mortality in this Iranian referral level 3 NICU.

Methods

Study Area

This cross-sectional study was conducted during 5 years in Mofid Children's Hospital, affiliated with Shahid Beheshti University of Medical Sciences in Tehran, Iran. Mofid is an educational medical hospital in the capital city of Iran with level 3 referral surgical NICU and 31 NICU beds, which admits infants with medical, surgical, and neurosurgical problems (except cardiac surgery) from all over the country. There are facilities for peritoneal dialysis and other sophisticated procedures, such as imaging evaluation or consultation with other pediatrics subspecialties in the fields of metabolic disorders, congenital malformations, hypoxic-ischemic encephalopathy (HIE), and neonatal seizure as well. These are the most common causes for the referral of infants to this hospital.

Data collection

Data collection from the neonatal medical record was performed by a trained research assistant, who was a nurse at NICU. She collected all the neonatal records of the dead infants from April 2014 to April 2019 using a pre-designed checklist form. The checklist consisted of such items as the neonate's gender, age, birth weight, gestational age, congenital anomalies, cause of mortality, last laboratory tests, time of death. The underlying causes of mortality were determined by two neonatologists based on ICD-11 for Mortality and Morbidity Statistics (Version 04, 2019). All the neonatal records were reviewed and data were analyzed using SPSS software (Version 23). A p-value less than 0.05 was considered statistically significant.

Ethics Approval and Consent to Participate

The present study was extracted from a thesis in general medicine in Shahid Beheshti University of Medical Sciences, Tehran, Iran. All ethical considerations of the study were approved by the institutional review board and the Research Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR. SBMU. MSP.REC.1395.498).

Statistical Analysis

Data analysis was performed using SPSS software (Version 23; Chicago, IL) through descriptive statistics, Chi-Square Test, and Fisher's exact test. All data are presented as mean±SD unless stated otherwise.

Results

In total 3,078 neonates were admitted to the NICU of Mofid Children's Hospital between 2014 and 2019. However, 388 (12.6%) neonates died during this period. The majority of the neonates (n=205, 53%) were males. In addition, 187 (48.19%) and 201(51.80%) of neonates were full-term and premature, respectively. The mean gestational age and the birth weight of the patients were 34.9 weeks (24-41weeks) and 2235 grams (420-5100 grams), respectively (Table 1).
The most common underlying cause of death was sepsis (n=99, 26%), congenital anomalies (n=82, 21%), and prematurity (n=79, 20 %), respectively (Table 2). Totally, 161 (77%) out of 338 dead infants had undergone respiratory therapy, and there was a statistically significant relationship between respiratory therapy and motility (P-value=0.03). Moreover, 117 (30.9%) of dead infants had sodium less than 135mg/dl. Hyponatremia was the most frequent abnormal laboratory findings.

Table 1. Demographic Characteristics of the Patients

Variable		N (%)
Gender	Male	221 (57%)
	Female	167 (43%)
Delivery mode	C/S	278 (73%)
	NVD	101 (27%)
Gestational Age (weeks)	<28	47(12.11%)
	29-34	97(25%)
	35-36	57(14.69%)
	>37	187(48.19%)
Birth weight (Grams)	<1000	58(15%)
	1000-1499	88(24%)
	1500-1999	67(18%)
	>2000	155(42%)
Death age (Days)	0-7	92(23%)
	8-14	58(22%)
	15-28	80(20%)
	29-60	85(22%)
	<60	51(13%)
Time of death	Morning	120(31%)
	Evening	105(27%)
	Night	163(42%)
The site of referral hospital	Tehran province	272(70%)
	Other provinces	116(30%)

Table 2. The cause of mortality in 388 neonates (CHD: congenital heart disease, IEM: Inborn Errors of Metabolism, and HIE: Hypoxic ischemic encephalopathy)

Cause (ICD-11)	N (%)
Sepsis (ICD-11: KA60)	99 (26%)
Congenital anomalies (ICD-11: LD2Z)	82 (21%)
Prematurity (ICD-11: KA21.4)	79 (20%)
Post-surgical (ICD-11: QB6Y)	57 (15%)
CHD (ICD-11: LA8Z)	31 (8%)
IEM (ICD-11: 5C50)	24 (6%)
HIE (ICD-11: KB04)	11 (2.8%)
Unknown	5 (1.2%)

Sepsis

Blood culture is the gold standard for the diagnosis of sepsis (12). In this study, positive blood culture was the diagnostic method for sepsis and should be done in all cases before starting antibiotics. It is worth mentioning that, 1ml sample of blood is adequate for a blood-culture bottle containing 5-10 ml of culture media. Blood culture should be observed for 72 h before labeling it sterile. Although it is time-consuming, empirical antibiotics are administered during this period.

Sepsis as the most common underlying disorder for neonatal mortality in our patients was detected in 99 (26.5%) infants, of whom 46 (46.6%) were female and premature. Acinetobacter was the main microbial pathogen for septicemia. The rate of sepsis was significantly different in different gestational ages (P<0.001). The probability of sepsis, as the main cause of death, significantly increased with the reduction of gestational age. Sepsis was the most common cause of mortality in preterm infants (Table 3)., Neonatal sepsis was the first cause of mortality in our study. The diagnosis of sepsis was done by positive blood culture or clinical manifestations highly suggested this condition in patients.

Positive blood culture was detected in 64 (16.8%) of neonates who died due to sepsis. The abnormal laboratory markers of sepsis are shown in Figure 1.

Congenital Anomalies

Congenital anomalies were the most common

Table 3. Relationship between the cause of mortality and gestational age

Cause (N, %)	<28 47 (12.27%)	29-34 97 (25.32%)	35-36 55 (14.36%)	>37 184 (48.04%)	P-value
Sepsis (127, 32.73%)	12 (9.44%)	40 (31.49%)	22 (17.32%)	53 (41.73%)	<0.001
Congenital Anomalies (94, 24.22%)	11 (11.70%)	19(20.21%)	13 (13.82%)	51 (54.25%)	<0.001
Post-Surgical (86, 22.16%)	14 (16.27%)	23(26.74%)	10 (11.62%)	39 (45.34)	<0.001
CHD (38, 9.79%)	2 (5.26%)	8(21.05%)	4 (10.52%)	24 (63.15%)	0.007
IEM (27, 6.95%)	8 (29.62%)	5 (18.51%)	2 (7.40%)	12 (44.44%)	<0.001
HIE (11, 2.83%)	0	2(18.18%)	4 (36.36%)	5 (45.45%)	0.010

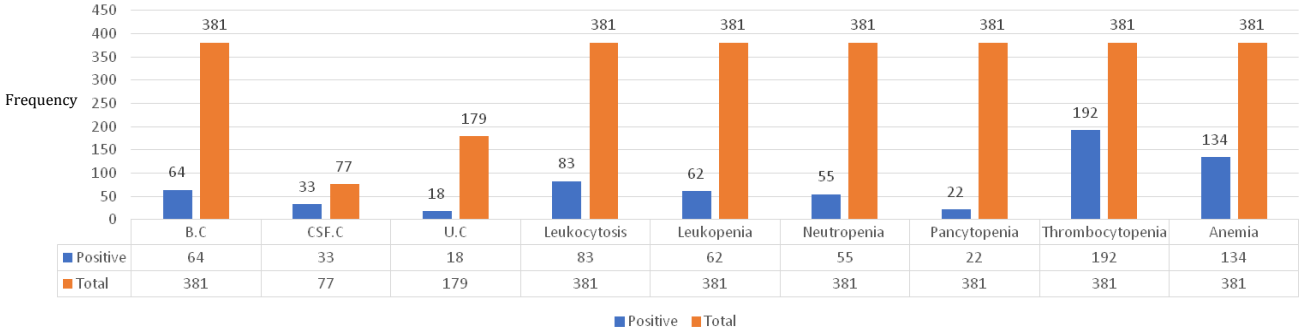

Figure 1. Laboratory finding confirming the infection in 99 infants with sepsis among dead patients

underlying disorder causing death in term and late preterm infants and the second cause of death in general (n=82; 21%). In total, 50 (60.97%) infants with congenital anomalies were male among term infants, and 43 (45.75%) infants were preterm. The most common congenital anomalies included cardiac, kidney, and brain diseases, respectively. The incidence of cardiac anomalies, as the cause of neonatal death, was 79.26 % (65 out of 82 neonates) and included such conditions as patent ductus arteriosus (PDA, 58%), atrial septal defect (ASD, 18%), ventricular septal defect (VSD) (14%), coarctation of the aorta (COA, 3%), tetralogy of fallout (TOF, 3%), tricuspid atresia (TA, 2%), and pulmonary atresia (PA, 2%).

The incidence of kidney anomalies as the cause of neonatal death was 24.39% (20 out of 82 neonates) and included conditions, such as hydronephrosis (55%), cyst (40%), and posterior urethral valves (PUV, 5%). Eventually, the incidence of brain anomalies as another cause of neonatal death was 10.97 % (9 out of 82 neonates) and included such conditions as intraventricular hemorrhage (IVH, 49%), hydrocephaly (40%), and periventricular leukomalacia (PVL, 11%).

Post-Surgery

The positive history of surgery was detected in 190 (48.9%) infants and 57(15%) neonates died directly due to surgical complications within 24 h after surgery. The rest of the patients succumbed to infection during the hospital stay. Moreover, 45 (78.94%) and 47 (82.45%) out of 57 dead infants, were male and preterm, respectively. The rate of surgical problems, as a cause of death, was significantly different in the different gestational ages (P=0.03; Table 3).

Inborn Errors of Metabolism (IEM)

The incidence of inborn errors of metabolism as the cause of neonatal death was 6% (24 out of 388 neonates) from whom 13 (54.16%) infants were female. Only 15 (62.5%) out of 24 infants were preterm. As listed in Table 3, the incidence of inborn errors of metabolism was significantly different in different gestational ages (P<0.01).

Hypoxic Ischemic Encephalopathy (HIE)

As an important cause of neonatal mortality and morbidity, HIE was reported in 11 (2.8%) infants. There was a statistically significant relationship between asphyxia and gestational age (P=0.01). The incidence of death due to HIE rose with an increase in gestational age (Table 3).

The incidence of hyponatremia in 44% of patients was the most frequent abnormal finding. The last laboratory findings of the infants near the death are presented in table 4.

Table 4. Last laboratory findings of patients near the death (BUN: Blood urea nitrogen, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase)

	Decreased N (%)	Normal Range N (%)	Increased N (%)	Total N (%)
BUN	7 (1.8)	319 (84.2)	53 (14)	379 (100)
Creatinine	3 (0.8)	311 (82.1)	65 (17.2)	379 (100)
Calcium	27 (7.1)	341 (90)	11 (2.9)	379 (100)
Phosphor	10 (2.6)	362 (955)	7 (1.8)	379 (100)
Magnesium	7 (1.8)	372 (98.2)	0 (0)	379 (100)
Sodium	117 (30.9)	250 (66)	12 (3.1)	379 (100)
Potassium	31 (8.2)	302 (79.7)	46 (12.1)	379 (100)
Blood sugar	21 (5.5)	311 (82.1)	47 (12.4)	379 (100)
SGOT	-	366(963)	14 (3.7)	380 (100)
SGPT	-	368 (96.8)	12 (3.2)	380 (100)
Ammoniac	-	3 (12)	22 (88)	25 (100)
Lactate	-	4 (16.7)	24(83)	28 (100)

Discussion

This cross-sectional study aimed to evaluate of causes of neonatal mortality in a referral level III NICU. Factors examined in the survival rate of the patients included infection, congenital anomalies, metabolic disorders, and the effect of the gestational age on neonatal mortality. The rate of neonatal mortality in the present study was 12.8 % (388 out of 3078 patients) during 5 years. A study conducted by Dandona et al. in India during 2011-2016 compared neonatal mortality rate among three postnatal age groups and reported a 23.3% decline in neonatal mortality rate between 2011 and 2016 and a 35.3% decline in neonatal death at the age of 0-2 days (13). The proportion of infantile deaths in the neonatal period increased in all regions of the world and has reached up to 41% globally. Although the rate of NMRs has been halved in some regions of the world, it has dropped to 27.8%, 6.4%, 6.9%, 4.6%, 7.2%, 17.6% in India, China, Pakistan, Congo, Nigeria, and Africa.

The main causes of mortality in this study were sepsis (26%), congenital anomalies (21%), and prematurity (20%). Sepsis is the most common cause of infantile mortality and in developing countries, it is responsible for about 30-50% of neonatal deaths (14). Sepsis is the most preventable cause of neonatal mortality. In a study carried out by Jacob et al. the most common underlying cause of neonatal death was prematurity, sepsis and, congenital multiple anomalies, respectively (15, 16).

Congenital anomalies (21%) and cardiac anomalies were the second and the most common causes of neonatal death in the present study. Based on the results of a study conducted by Ajao in Nigeria, the rate of congenital anomalies was 6.3% (67 out of 1,057 neonates) (17). Congenital anomalies are the main cause of infantile morbidity in developed countries (18, 19).

Cardiovascular system anomalies were the most common anomaly in the present study. Cardiac anomalies as the most frequently reported anomalies in many published articles were seen in 2.7-10 and up to 50 patients per 1000 live birth, based on some reports (20, 21). The top five common cardiac abnormalities according to Peng-Fei Sun et al. included ASD, VSD, PDA, PS, and TOF (20). In the present study, the top causes of cardiac abnormalities included PDA (58%), ASD (18%), VSD (14%), COA (3%), TA (2%), and PA (2%).

Prematurity is the leading cause of death in the neonatal period. The results of a study conducted by Brankovich et al. showed that nearly 1 out of 3 premature infants died due to respiratory distress syndrome (22). Birth asphyxia and preterm delivery were the main causes of death (16). In a study carried out by Mohamed et al. (21), it was indicated that the rate of mortality decreased by an increase in gestational age, which was consistent with the results of the present study in which the gestational age of the expired infants was significantly lower than that in the alive infants.

Gestational age is an important risk factor for neonatal outcome and is the leading cause of neonatal mortality. In the present study, prematurity is the third cause of neonate mortality; however, preterm birth is still among the first key causes of death (23). The global incidence of premature birth was 6.9%, of which 85% belonged to African and Asian countries (24). According to the WHO report, the incidence of premature birth was 11.69%, 9.13%, 7.35%, and 6.04% in 2000, 2005, 2010, and 2014, respectively (25).

The majority of infants' death occurred during the night shift (n=163, 42%). There are fewer nurses during the night shift, compared to the day shift. It should be noted that the ratio of nurse to patient was 1 to 7 during the night shift while it

was 1 to 3-4 during the morning and afternoon shifts. Given the fewer number of nurses during the night shifts compared to that in the morning and afternoon shifts, there is a concern that an increase in the incidence of death can be due to insufficient care provided to patients during the night shift. In another study performed by Babaee in Kermanshah, Iran, 274 out of 566 (49.9%) infant death happened during the night shifts (26).

Although neonatal death often occurs on the first day of life, the mean age of neonatal death in the NICU has been 26.5 days (1-90 days) in this study. The majority of neonates (n=226, 58%) at the time of admission aged less than 7 days. This discrepancy can be explained by the most critically ill patients on the first day of life who were dead before they were referred to the referral center in this study.

Sodium is one of the most common electrolyte disorders among hospitalized neonates. Hyponatremia in neonates is asymptomatic, it can be caused by various mechanisms, most of which could be avoided by optimized management (27). Hyponatremia is a frequent electrolyte disorder in the neonatal population, and the early diagnosis and management of this condition are crucial for the prevention of morbidity and mortality (28). Based on the laboratory evaluations of dead patients, hyponatremia (44%) was the most frequent abnormal finding. Some researchers including Yoon-Joo Kim have reported the influence of hyponatremia on the neonatal outcome and showed that there is an association between late-onset hyponatremia (aged more than two weeks), and the increased risk of moderate to severe bronchopulmonary dysplasia, extra-uterine growth retardation, periventricular leukomalacia, and retinopathy of prematurity (29). In the present study, hyponatremia was the main abnormal laboratory finding. Therefore, it is recommended that measures should be taken to control hyponatremia during the infancy period to prevent morbidity and mortality.

Acinetobacter was the main microbial pathogen for septicemia. Different pathogens causing sepsis have different effects on hematologic parameters and the severity of thrombocytopenia was directly associated with the rate of mortality (30).

There are many reports regarding the impact of delivery mode on neonatal outcomes and mortality. Although in the present study the rate of Caesarean section (C/S) was more than normal vaginal delivery (NVD) (73% Vs 27%), there was not a statistical difference between the two groups of patients in terms of delivery mode. Recently WHO reported on singleton preterm births with a gestational age of 22 to <37 weeks in 237 facilities centers from 21 countries (31). Based on the results of this report, C/S was associated with significantly increased odds of maternal and neonatal intensive care unit admission, maternal near-miss, and significantly decreased odds of a fresh stillbirth and perinatal death. Although the report concluded that the potential harms and benefits of C/S should be carefully considered when deciding about the mode of delivery in preterm births.

Based on the results of a study conducted by Archana Puri et al. on neonatal surgical mortality, 33.3% of operations lead to the loss of infants or prolonged ventilation (P=0.037, OR: 5.77), duration of surgery>120 min (P=0.007, odds ratio [OR]: 9.76), reoperations (P=0.031, OR: 7.16 (1.20–42.81), the requirement of high dose of vasopressors (P=0.003, OR: 25.65) as the predictors of neonatal surgical mortality (32). In the present study, the need for surgery was observed in 192 (48.9%) out of 388 patients and surgery as the main underlying cause of neonatal death was detected in 75(19.4%) infants. In the rest of the patients, other comorbidities, such as sepsis were the main causes of death. Most of the patients (n=183, 48.8%) in the surgery groups were term babies. This result can be explained by the lower referral rate of the preterm neonate to the hospital. The time interval between surgery and death was 0 to 150 days.

Regarding the limitation of the present study, one can refer to the retrospective pattern of research which might have been accompanied by incomplete records of patients. However, the evaluation of the causes of death in a referral NICU with complicated underlying disorders is the strength of the present study.

Conclusion

Sepsis was the most common cause of neonatal death and is related to prematurity. Considering the high prevalence of neonatal mortality and prematurity in Iran and other developing countries, careful nursing care along with the observation of hygiene requirements, identification of high-risk neonates, and targeting them for intensive care and therapy can be effective in the reduction of the rate of neonatal mortality. Moreover, it was revealed that hyponatremia is the most frequent abnormal laboratory finding. Therefore, it is recommended that hyponatremia should be considered more

seriously during the infancy period to prevent morbidity and mortality.

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Conflicts of interest

The authors declare that they have no competing interests regarding the publication of the present study.

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