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EARLY NEONATAL DEATHS IN VERY AND EXTREMELY LOW BIRTH WEIGHT PRETERM INFANTS – PERINATAL RISK FACTORS AND CAUSES

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ABSTRACT

Background: Neonatal mortality has become increasingly the most important component of infant mortality. Of all neonatal deaths, three quarters occur in the first week of life and 28% of these early deaths that are not related to congenital malformations result from prematurity. Therefore, the aim of this study was to assess the perinatal risk factors associated with early neonatal death and determine the categorical cause of death in very and extremely low birth weight (VLBW_ELBW) preterm infants. **Materials and Methods:** Prospective cohort study of preterm infants with gestational age < 32 weeks and birthweight 500_1499 g who admitted to neonatal intensive care unit at Tishreen University Hospital in Lattakia in the period between October 2019 and October 2021. **Results:** The study included 114 consecutive preterm infants admitted to our neonatal intensive care unit (NICU) at Tishreen university hospital with a gestational age of < 32 weeks and birthweight 500 - 1499 g between October 2019 and October 2021, of whom 48 (42%) died within 0–7 days after birth. Early neonatal death was associated with: gestational age <28 weeks (RR 3.5; p value 0.006), birthweight <1000 g (RR =3.6; P value 0.003), absence of antenatal steroids (RR 2.2; p value 0.005), 5th minute Apgar <7 (RR 6.1; p value 0.0001), Delivery room resuscitation (RR 5.9; p value 0.0001). The most common cause of early neonatal death in the study was cardiorespiratory problems (52%), followed by neurologic problems (16.7 %), infections (6.25%), Gastrointestinal problems (6.25%) and unknown cause (18.75%). **Conclusion:** The risk of early neonatal death was significantly higher in the cases of neonatal birth weight < 1000 g, gestational age < 28 weeks, absence of antenatal steroids, 5th minute Apgar <7, Delivery room resuscitation. Cardiorespiratory problems were the most common causes of early neonatal death in Very and extremely Low Birth Weight VLBW- ELBW preterm Infants.

KEYWORDS: Perinatal, preterm infants, very low birth weight, extremely low birth weight, Neonatal mortality, Early neonatal mortality, Neonatal ICU.

1. INTRODUCTION

Prematurity is a major public health problem, and a significant factor in increasing neonatal mortality and morbidity rates, as well as the financial effects on health caresystems.[1]

The World Health Organization (WHO) estimated that every year 15 million babies are born preterm (before 37 completed weeks of gestation) and about one million of them die after birth as a result of complications of prematurity.[2] On average, 5- 7% of babies are born preterm in developed countries compared to 18% in many ofdeveloping countries.[3]

Neonatal mortality has become increasingly the most important component of infant mortality. The slow reduction of neonatal mortality rate in poor or developing countries is worthy of attention. Of all neonatal deaths, three quarters occur in the first week of life and 28% of these early deaths that are not related to congenital malformations result from prematurity.[4]

Birthweight is a major determinant of neonatal mortality with deaths of very low birth weight VLBW accounting for about 50% of neonatal deaths in general, 30 % of early neonatal deaths.[5]

Studies investigating the health outcomes of those

neonates from the Arab countries are scarce.[6_8] Given this, the aim of this study was to assess the perinatal risk factors associated with early neonatal death and determine the categorical cause of death in very and extremely low birth weight (VLBW_ELBW) preterm infants born at Tishreen University Hospital in Lattakia.

2. MATERIALS AND METHODS

2.1 Study population and data collection

After approval by the Ethics Committee of Tishreen University, a monocentric prospective cohort study was conducted in all preterm infants who admitted to Neonatal Intensive Care Unit (NICU) at Tishreen university hospital over the study period and fulfilled the criteria.

Inclusion Criteria were as follows

All preterm infants born with a gestational age of < 32 weeks and birthweight 500 -1499 g who were admitted (inborn and outborn) to our neonatal intensive care unit (NICU) at Tishreen University Hospital in Lattakia, Syria, over a period of two years between October 2019 and October of 2021.

Exclusion Criteria

1- Major congenital malformations.
2- Birthweight less than 500 g 3- Death in the delivery room. 4- Transfer from another hospital in case of incomplete information.

Detailed information was collected from the time of admission until discharge or death about all the preterm infants enrolled in the study.

Data collection included neonatal characteristics (birth weight, gestational age, sex, Multiple or singleton, SGA), maternal characteristics and complications during pregnancy (Maternal age, Peripartum hemorrhage, Peripartum infection, Hypertension in gestation, Diabetes during gestation, PROM, Antenatal steroids), delivery history (Cesarean section, resuscitation in the delivery room, 5th minute Apgar <7).

The outcome variable was death in the first 0–7days after birth. We analyzed and compared maternal and neonatal risk factors divided into two groups:

1- The early neonatal death group (Preterm infants who died in the first seven days after birth).
2- The survival group (who survived for more than 7 days).

A clinical follow-up was performed on all preterm infants during the study period from admission to discharge or death to determine the immediate cause of death in the early neonatal death group, The following tests were performed in all preterm infants: Chest radiograph and/or Echocardiography, Abdominal radiograph and/or abdominal ultrasound, Complete blood count with differential, Blood culture, Arterial blood gas, Cranial ultrasound.

The cause of death was categorized based on the International Classification of Diseases (10th revision, Clinical Modification)] 9 [as]:

1- Cardiorespiratory causes: including respiratory distress syndrome (RDS), air leak syndromes, pulmonary hypertension, pulmonary hemorrhage, pulmonary hypoplasia, heart failure and other cardiorespiratory causes.
2- Neurological causes: including severe intraventricular hemorrhage (IVH) and its sequelae, hypoxic-ischemic encephalopathy or asphyxia and other neurological diseases.
3- Gastrointestinal, including necrotizing enterocolitis (NEC), spontaneous intestinal perforation, and other gastrointestinal diseases.
4- Infection: congenital or acquired infection, septic shock.
5- Other causes: including trauma, accidents, inborn errors of metabolism, multisystemic failures of unknown etiology or any other cause that may be responsible and was not classified in the previous groups.

In this study, Cases in which death occurred without a specific cause because of the presence of more than one probable cause of death, intervening pathogenesis, or death before completing the investigations necessary to confirm the diagnosis were categorized in a separate group.

2.2 Statistical Study

Statistical analysis was performed by using IBM SPSS (version 20). Basic Descriptive statistics included means, standard deviations (SD), median, Frequency and percentages. Chi-square test or Fisher exact was used to study the relation between categorical variables and Independent T student test to compare the mean differences between two independent groups.

A univariate analysis was performed to find the correlation between variables and the outcome (early neonatal death). The variables that were statistically significant in the univariate analysis were included in the multivariate model (multiple logistic regression). The associations are presented as relative risk (RR), with a correspondent 95% confidence interval (95% CI).
P-value ≤0.05 was considered statistically significant.

Definitions

Gestational age was determined by last menstrual period and antenatal ultrasound and new Ballard scoring[10] was used to confirm gestational age in case no antenatal care was provided.

Early neonatal deaths defined as death of a newborn infant within the first week or first seven days of life. Late neonatal death was defined as death of a newborn infant between 8-28 days of life.[28]

Preterm were categorized based on gestational age as

extremely preterm (less than 28 weeks), very preterm (28–32 weeks), moderate-to-late preterm (33–37 weeks).[2]

Neonates were classified based on birth weight as normal birth weight (≥ 2500 g), low birth weight (1500-2499 g), very low birth weight (1000-1499 g) and extremely low birth weight (less than 1000 g).[28]

Small for gestational age (SGA) was defined as birth weight below the 10th percentile.[11]

Maternal hypertension was defined if there is any maternal diagnosis of pregnancy induced hypertension or chronic hypertension. Prolonged rupture of membranes (PROM) was defined as rupture of membranes more than 18 hours before delivery.[28]

Intraventricular hemorrhage (IVH) was determined by cranial ultrasound, with grades from 1-4 defined according to Papile classification.[36] Necrotizing enterocolitis (NEC) was classified and recorded according to Bell's classification.[12] Delivery room (DR) resuscitation was defined when Positive-pressure ventilation (PPV), cardiac compression was done or medication was administered in the DR.

Immediate cause of death: The disease, injury or complication that directly preceded death.[16]

Antenatal steroids were defined as administration of a single course of antenatal corticosteroids 24 hours to 7 days before birth.

RESULTS

The study included 114 consecutive preterm infants admitted to our neonatal intensive care unit at Tishreen university hospital with a gestational age of < 32 weeks and birthweight 500 - 1499 g between October 2019 and October 2021, comprising 10.7% of total admissions; after 8 preterm infants were excluded: 1 with congenital malformations, 5 deaths in the delivery room, 2 with birthweight < 500g. Gestational ages ranging from 24 weeks + 6 days to 31 weeks + 6 days, with birthweight between 600 - 1495 g. The gestational age mean ± SD was 29+6 (± 2.1). The birth weight mean ± SD was 1188.37 (± 250 g). Boys were 53.5% (n=61) and 46.5% (n=53) were girls of all enrolled births. The antenatal steroids rate was 51.7%.

Among the 114 preterm infants in the study. Of these 48 (42.1%) died within the first 0–7 days of life, and 66 (57.9%) survived. The first day mortality was (10.5%), comprising one quarter of the early neonatal mortality. The study included 19 neonates < 28 weeks, of whom 13 (68%) died within 0–7 days after birth; 95 neonates were born between 28–32 weeks, of whom 35 (37%) died within 0–7 daysafter birth.

An analysis of the neonatal factors in the two groups) early neonatal death and survival) showed that there were differences in gestational age and birthweight (p=0.01, 0.003 respectively). Mean gestational age ± SD was 30.4 week ± 1.5 and 29.19 week ± 2.6 in survival and death group respectively, with a P value = 0.01. Mean birth weight ± SD were 1254.7 ± 223 g and 1097 ± 258.6 g in survival and death group respectively, with a P-value =0.003.

On univariate RR analysis, birth weight < 1000 g (RR 3.8; P 0.003), gestational age < 28 weeks (RR 3.7; P 0.01), absence of antenatal steroids (RR 2.4 ; p 0.001), Peripartum infection (RR 3.6; P 0.001), Apgar score <7 in the fifth min(RR 7; P 0.001), delivery room resuscitation (RR 6.7; P0.0001) were significant risk factorsof early neonatal death.

The distribution of maternal and neonatal characteristics and delivery history factors in relation to the presence of early neonatal death in VLBW-ELBW preterm infantscan be seen in **(Table 1).**

Table 1: Maternal, neonatal and delivery history characteristics according with the survival or early neonatal death in VLBW-ELBW preterm infants in NICU at Tishreen University Hospital.

Characteristics	Death <7 days (n =48)	Survival ≥7 days (n =66)	p
Male	28 (58.3%)	33(50%)	0.3
Gestational age < 28 weeks	13(27.1%)	6(9.1%)	0.01
Birth weight <1000 g	18(37.5%)	9(13.6%)	0.003
SGA	6(12.5%)	12(18.2%)	0.4
Multiple gestation	13(27.1%)	17(25.8%)	0.8
Maternal age <20 years	7(14.6%)	3(4.5%)	0.1
Peripartum hemorrhage	18(37.5%)	22(33.3%)	0.6
Peripartum infection	35(72.9%)	28(42.4%)	0.001
Hypertension in gestation	8(16.7%)	6(9.1%)	0.2
Diabetes during gestation	0(0%)	2(3%)	0.2
PROM	17(35.4%)	29(43.9%)	0.3
Absence of antenatal steroids	38 (79.2%)	40 (60.6%)	0.001
Cesarean section	34(70.8%)	53(80.3%)	0.2

Delivery room resuscitation	30(62.5%)	13(19.7%)	0.0001
5th minute Apgar	12(25%)	3(4.5%)	0.001

After factor adjustment (multiple logistic regression) 5 parameters were statistically significant: gestational age <28 weeks (RR 3.5; p value 0.006), birthweight <1000g (RR =3.6; P value 0.003), absence of antenatal steroids (RR 2.2 p value 0.005), 5th minute Apgar <7 (RR 6.1; p value 0.0001), Delivery room resuscitation (RR 5.9; p value 0.0001) **(Table 2).**

Table 2: Parameters associated with early neonatal death among VLBW-ELBW preterm infants in NICU at Tishreen University Hospital.

Risk factors	RR b [CI95%]	RR a [CI95%]	p-value
Gestational age <28 weeks	3.7[1.2-10.6]	3.5[1.6-8.9]	0.006
Birth weight <1000 g	3.8[1.5-9.4]	3.6[1.5-9.1]	0.003
5th minute Apgar <7	7[1.8-16.4]	6.1[2.2-11.9]	0.0001
Delivery room resuscitation	6.7[2.9-15.7]	5.9[2.9-14.9]	0.0001
Antenatal steroids	2.4 [1.1-7.6]	2.2 [1.2-6.09]	0.005

As shown in **table (3)**, early neonatal death occurred in 25 (52%) preterm infants due to a cardiorespiratory cause, 8 (16.7%) due to neurologic cause. Infectious and Gastrointestinal deaths were equal in number; 3 (6.25% for each category), and 9 (18.75%) unknown causes. The majority of cardiorespiratory death occurred in preterm infants ≥28 weeks and more than half of the unknown cause group was in preterm infants <28 weeks.

Table 3: Categorical causes of early neonatal death among VLBW-ELBWpreterm infants in NICU at Tishreen University Hospital.

Cause of death	gestational age		Birthweight		number	Percentage
	≥ 28	< 28	≤1000	>1000		
Cardiorespiratory	22	3	16	9	25	52%
Neurological	4	4	5	3	8	16.7%
Gastrointestinal	3	0	1	2	3	6.25%
Infectious	3	0	3	0	3	6.25%
Unknown	3	6	5	4	9	18.75%

In this study, Cardiorespiratory causes included respiratory distress syndrome(RDS), Air leak syndrome, Pulmonary hemorrhage, heart failure, hydrops fetalis. The only neurologic cause of early neonatal death was Intraventricular hemorrhage (IVH) and the only Gastrointestinal cause was spontaneous intestinal perforation (SIP). Septic shock was diagnosed in three preterm infants in the death group and was classified in the category of infections.

DISCUSSION

Of the enrolled neonates, early neonatal death in this study occurred in 42.1% (n=48) while survival in the first week of life was 57.9% (n=66). When compared to **Castro et al.** study in Brazil on 627 preterm infants with gestational age 23-32 weeks and birthweight 500-1499 g in 2014, we find higher rate in this study (42.1%vs 29%). Also, the early neonatal mortality in the present study was higher than the rates in reported data from **Al-lawama** in Jordan 2017, **Zile** in Latvia 2017 (16%, 18%) respectively. The variations may be attributed to difference in the level of health care between hospitals.[13,15,23]

Of the 114 preterm infants studied, 12 (10.5%) died within the first 24 hours. This percentage was comparable to the previous studies (9.4% -5%) in **Castro** study in Brazil and the cohort study of **Muhammad** in the United states respectively.[13,18,21]

Neonates are among the most vulnerable population groups to contract illnesses, especially extremely preterm and very preterm newborns due to physiological immaturity, metabolic changes associated with multiple diseases, as well as exposure to multiple medications.[29]

GA and birthweight have been found to be inversely associated with VLBW infant mortality.[17,23,24]

In this study, prematurity less than 28 weeks of gestation (Extremely preterm) as well as birthweight less than 1000 g (ELBW) were independent risk factors of early neonatal death in VLBW-ELBW preterm infants, (RR 3.5, P value 0.006) and (RR3.6, P Value 0.003), respectively. This is consistent with other studies.[13,17]

In the study of neonatal characteristics related to early neonatal mortality, gender was not significant, which is similar to some other studies.[15,17]

However, Male gender in many studies was a risk factor of early neonatal death.[13,16]

Bardin et al have studied outcomes of SGA preterm infants and showed nodifference in the risk of death[19] Our results were similar. In contrast, other authors have reported that SGA is one of the risk factors of death in preterm infants.[14,16,26]

In the study of maternal variables related to early neonatal death, we found statistically significant differences with regard to peripartum infection (RR 3.6 - P value 0.001) on univariate analysis, while these findings were not statistically significant in the multivariate analysis, this is consistent with the results of previous studies.[13,18]

In common with other studies[23,25], Maternal age was not statistically significant in our study while some authors indicated a higher risk of death in preterm infants born to young mothers.[13,24]

We also did not find a statistically significant relationship between early neonatal death and each of these factors: peripartum hemorrhage, hypertension during pregnancy, diabetes mellitus, PROM. This is consistent with **Castro et al.** study where none of these variables were risk factors of early death in preterm infants.[13] However, **Almeida** have demonstrated that hypertension during pregnancy was a protective factor in early mortality.[18]

In a clinical review of prematurity, **Tucker** and **McGuire** reported that outcomes in multiple pregnancies may be better than single pregnancies and this may be resulted from greater follow-up during pregnancy.[22] In contrast, Multiple gestation in **Castro et al.** study was a significant factor of early death in preterm infants.[13] In this study, we found no significant difference in this variable between the two groups.

Today, there is no controversy that women with preterm birth <34 weeks should be received antenatal corticosteroid.[32] It has long been established that administration of a single course of antenatal corticosteroids 24 hours to 7 days before birth to women in preterm labor at less than 34 weeks' gestation improves lung maturity and associated with reductions in adverse outcomes in premature infants including respiratory distress syndrome, necrotizing enterocolitis, severe intraventricular hemorrhage, and death.[33,34]

In line with other studies, Early neonatal death was associated to: absence of antenatal steroids.[13,14]

In relation to delivery history variables, studies have indicated an association between caesarean section and a lower rate of death and morbidity[23,24] probably due to the full preparation required when performing a c-sec rather than the direct effect of the delivery method itself.[27] However, our study could not find statistically significant results in caesarean section, this agrees with **Ntuli** study. The reason for this result remains unclear and needs further study.[17]

The Apgar score at 5 min, acts as a prognostic precursor for neonatal mortality. Several components of the Apgar score may be influenced by gestational age. Consequently, it has been argued that a low Apgar score in preterm infants may reflect biologic immaturity rather than fetal depression in an otherwise healthy infant.[30] Similar to other studies, we found that a low Apgar score (<7) is closely related with early neonatal death.[13,17,23]

In line with other studies, Preterm infants in this study who were resuscitated during delivery had a higher mortality.[14,17]

In the present study, we found that the predominant causes of early neonatal death in VLBW-ELBW preterm infants were cardiorespiratory problems (52%) followed by neurological problems (16.7%), infections (6.25%), gastrointestinal problems (6.25%), unknown cause (18.75%). These findings are consistent with previous studies which found that the cardiorespiratory morbidity is the most common cause of death in preterm infants.[14,37] **Schindler et al.** also reported that the acute respiratory illnesses [ARI] and Major IVH were the most common causes of hospital mortality in this extremely to very preterm population, with the highest incidence in the first days of life.[16]

In this study, Cardiorespiratory causes included RDS, Air leak syndrome, Pulmonary hemorrhage, heart failure, hydrops fetalis. The only neurologic cause of early neonatal death in our study was Intraventricular hemorrhage IVH. The Gastrointestinal causes in this study were spontaneous intestinal perforation, with no NEC was reported in the first week. Infants who die from NEC and miscellaneous causes are more likely to die later (median age at death 25.2) and there are very few early deaths attributable to NEC.[16]

Many authors[14,31] discussed prematurity or unexplained immaturity as a cause of neonatal death. However, Research on the categorical causes of death in preterm infants is extremely rare.

Unknown causes of death were described in many studies.[14,35] Similarly, we could not determine a specific cause of early neonatal death in VLBW-ELBW preterm infants because of the presence of more than one probable cause of death, intervening pathogenesis, or death before completing the investigations necessary to confirm the diagnosis. Most of these cases were extremely preterm (< 28 w).

Conclusions and Recommendations

We conclude that, birth weight < 1000 g, gestational age < 32 weeks, absence of antenatal steroids, 5th minute Apgar <7, Delivery room resuscitation were associated with an increase in early neonatal mortality in VLBW-ELBW preterm infants . Identification of risk factors and

causes is a first step in formulating a national strategy for prevention and control of early neonatal mortality.

Important perinatal factors that are associated with early neonatal deaths in very low birth weight preterm infants can be modified by interventions such as improving fetal vitality at birth and reducing the incidence and severity of respiratory distress syndrome. Further profound analyses should be conducted in the future.

Declarations Competing of Interests
All the authors do not have any possible conflicts of interest.

Ethical consideration
After discussing the study with the parents, all of them gave a complete and clear informed consent to participate in the study.

Availability of data and materials
Most of the data was in the article, and other data can be asked from thecorresponding author.

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Author contributions
Both authors performed the measurements and wrote the article. Literature review was done by Dr. Heba AL-Shaaban, and both authors performed analytic calculations and performed the numerical simulations.

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