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Risk Factors for Mortality in Low Birth Weight Infants with Respiratory Distress Syndrome

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Abstract

Objective: To study the structure of concomitant pathologies in low birth weight premature newborns with respiratory distress syndrome (RDS). To identify mortality risk factors in these newborns.

Materials and methods: Data from 374 premature newborns weighing less than 1500 g and gestational age less than 32 weeks with RDS treated in the intensive care unit were analyzed.

Results: Several comorbidities were more common among children with RDS compared to children without RDS. Thus, disseminated intravascular coagulation syndrome (DIC) occurred 2 times, atelectasis 1.3 times, necrotizing enterocolitis (NEC) 2.4 times, and anemia 1.8 times more often among children with RDS compared to those without RDS.

In multivariate logistic regression, such factors as 1-3 points on the Apgar scale at 1 minute (OR - 2.478, 95% CI - 1.289-4.764, p = 0.007), 1-3 points on the Apgar scale at 5 minutes (OR - 3.754, 95% CI - 1.788-7.878, p<0.0001), DIC (OR -4.428, 95% CI -2.206-8.887, p<0.0001), NEC (OR - 4.508, 95% CI - 2.270-8.954, p<0.0001) showed a positive association with death in children with RDS.

When assessing the effect of the combination of DIC and NEC on death, it was found that the combination of these two pathologies in children with RDS increases the risk of death by more than 2 times. Thus, the area under the curve (AUC) for DIC was 0.283, for NEC the AUC was 0.335, and for the combination ICE+NEC it was 0.782).

Conclusions: The structure of comorbidities in low birth weight infants with RDS differs from that of infants without RDS. Premature infants with RDS were more likely to develop anemia, DIC, atelectasis, and NEC. The presence of comorbidities increases the risk of death in low birth weight infants with RDS. Low Apgar score, DIC syndrome, and NEC can increase the risk of death in low birth weight premature infants with RDS. It is anticipated that the collected data will enhance personalized care for low birth weight, premature infants with multiple health conditions, ultimately reducing mortality rates in this vulnerable patient group.

Keywords: respiratory distress syndrome, premature newborns, risk factors, mortality.

Introduction

Neonatal respiratory distress syndrome (RDS) is a serious breathing problem that primarily affects premature babies. This condition occurs when the lungs lack sufficient surfactant, a substance essential for proper lung function. RDS was first identified in 1959 and continues to be a significant cause of illness and death in newborns [1].

Approximately 1% of all live births are affected by RDS, but the risk is significantly higher for premature babies. The earlier a baby is born, the greater the risk and severity of RDS. For example, around 80% of infants born at 28 weeks gestational age develop RDS, while this figure rises to nearly 90% for those born at 24 weeks [2].

Although modern treatment and prevention methods, including antenatal corticosteroids, use, postnatal exogenous surfactant administration, early use of spontaneous continuous positive airway pressure in the newborn, have improved the prognosis for

neonates with RDS [3], this pathology continues to be one of the main causes of neonatal morbidity and mortality, primarily among low birth weight preterm infants [4].

Key risk factors for premature infant mortality can be both maternal and premature infant factors. Maternal factors include maternal age, bad habits, preeclampsia, parity, mode of delivery, and maternal complications. Child factors include gestational age, congenital anomalies, neonatal infections, and perinatal asphyxia [5].

There are several other pathologies also associated with the incomplete formation of organs and a decrease in their adaptive capabilities to new conditions required at birth. These primarily include diseases such as bronchopulmonary dysplasia (BPD), diseases of the central nervous system such as intraventricular hemorrhage (IVH), periventricular hemorrhagic infarction (PVHI), and periventricular leukomalacia (PL), as well as retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and others [6, 7]. It should be noted that some of these diseases, in turn, could also cause death in premature newborns.

Currently, the significance of such biomarkers as low birth weight, severe prematurity, Apgar values, and some others in neonatal mortality has been well studied [8, 9, 10]. However, the extent to which the combination of pathologies associated with prematurity increases the risk of death in low birth weight newborns has not been sufficiently studied.

Objective of the study: to study the structure of concomitant pathologies in low birth weight premature newborns with respiratory distress syndrome (RDS); to identify mortality risk factors in these newborns.

Materials and method

The study design is an observational retrospective case-control study. The medical records of 374 premature babies weighing less than 1500 grams and born before 32 weeks who had respiratory distress syndrome (RDS) in the neonatal intensive care unit at the Center for Perinatology and Pediatric Cardiac Surgery in Almaty between 2021 and 2023 were studied. Clinical data, including Apgar scores, birth weight, gender and gestational age were obtained from medical records. The presence of complications such as intraventricular hemorrhage, atelectasis, DIC syndrome, necrotizing enterocolitis were determined based on neonatal intensive care unit (NICU) records. Inclusion criteria: premature infants weighing less than 1500 g, gestational age less than 32 weeks with RDS. Exclusion criteria: full-term babies, preterm babies born at 33 weeks or later and weighing over 1500 grams without RDS.

Data analysis

Statistical data processing was carried out using IBM SPSS Statistics 23.0. Continuous data was presented as mean ± standard deviation, while categorical data was presented as percentages and counts. The following variables were examined: gender, Apgar score at 1 and 5 minutes, presence of intraventricular hemorrhage, disseminated intravascular coagulation, atelectasis, necrotizing enterocolitis, anemia, and pneumonia. The method of contingency tables with $\chi 2$ assessment was used to compare qualitative variables. A univariate logistic regression was used to identify factors associated with death in preterm infants. The statistically significant parameters were further analyzed using multivariate logistic regression. ROC analysis was carried out to assess the prognostic significance of the totality of identified factors in the development of death. Differences were considered statistically significant at $p \leq 0.05$.

Ethical approval

The study was approved by the Ethics Committee of the Asfendiyarov Kazakh National Medical University (Min. No. 8 (144), November 3, 2023). The clinic administration was informed of the study, and clinic employees participated in this study. The data can be published publicly without any objections.

Results

1. Descriptive characteristics of the study group

The main characteristics of the study group are shown in Table 1.

Table 1 Descriptive characteristics of the study group

№	Parameters	Total number of premature babies with RDS (n=374)
1	**Gender**	
	female	178 (48%)
	male	196 (52%)
2	**Weight, (M±m)**	1037,32±15,7
3	**Gestational age, (M±m)**	27,91±0,13
4	**Apgar scores at 1 minute**	
	1-3 scores	183 (49%)
	4 scores or more	191 (51%)
5	**Apgar scores at 5 minutes**	
	1-3 scores	64 (17%)
	4 scores or more	310 (83%)
6	**Intraventricular hemorrhage (IVH)**	
	yes	176 (47%)
	no	198 (53%)
7	**Disseminated intravascular coagulation syndrome (DIC syndrome)**	
	yes	215 (57%)
	no	159 (43%)
8	**Atelectasis**	
	yes	209 (56%)
	no	165 (44%)
9	**Pneumonia**	
	yes	323 (86%)
	no	51 (14%)
10	**Necrotizing enterocolitis (NEC)**	
	yes	65 (17%)
	no	309 (83%)
11	**Anemia**	
	yes	166 (44%)
	no	208 (56%)

In this study, the number of males and females was 196 (52%) and 178 (48%). The average weight of premature newborns was 1037.32 g. The mean gestational age was 27.91 weeks. 1-3 points on the Apgar score at 1 minute were noted in 49% of children. At the same time, at the 5th minute, 1-3 points on the Apgar score were recorded in 17% of premature infants. The presence of IVH and DIC was diagnosed in 47% and 57%, respectively. At the same time, in these premature infants, atelectasis and pneumonia were detected in 56% and 86%, respectively. NEC was detected in 17%, and anemia in 44% of children.

2. The structure of concomitant diseases in low birth weight premature neonates with RDS

Comparative data on the presence of concomitant diseases in premature infants with and without RDS is presented in Table 2.

Table 2 Comparative analysis of data from premature infants with and without RDS

№	Parameters	RDS presence (n=374)	RDS absence (n=85)	P
1	**IVH**			
	yes	176 (47%)	45 (53%)	0,328
	no	198 (53%)	40 (47%)	
2	**DIC syndrome**			
	yes	215 (58%)	24 (28%)	<0,0001
	no	159 (42%)	61 (72%)	
3	**Atelectasis**			
	yes	209 (56%)	36 (42%)	0,025
	no	165 (44%)	49 (58%)	
4	**NEC**			
	yes	65 (17%)	7 (8%)	0,037
	no	309 (83%)	78 (92%)	
5	**Anemia**			
	yes	166 (44%)	21 (25%)	<0,0001
	no	208 (56%)	64 (75%)	
6	**Pneumonia**			
	yes	323 (86%)	68 (80%)	0,137
	no	51 (14%)	17 (20%)	

Comparative analysis of premature infant data with and without RDS revealed several statistically significant differences between the indicators (Table 2). Among children with RDS, DIC was 2 times more common than in the group of children without RDS. There were 1.3 times more children with atelectasis in the group with RDS compared to the group without RDS. In the group of children with RDS, the presence of NEC was 17% of the total number of the study group, while in the group without RDS, there was only 7%. In children with RDS, anemia was 1.8 times more common compared to children without RDS. No differences were found for pneumonia and IVH.

3. Mortality risk factors in low birth weight premature infants with RDS

3.1 Comparative analysis of parameters of low birth weight newborns with fatal outcome

A comparative analysis of the parameters of low birth weight premature infants with fatal outcomes in the presence of RDS is presented in Table 3.

Table 3 Comparative analysis of deceased and surviving premature infants with RDS

№	Parameters	Dead premature babies (n=114)	Surviving premature babies (n=260)	P
1	**Gender**			
	female	49 (43%)	129 (50%)	0,238
	male	65 (57%)	131 (50%)	
2	**Apgar scores at 1 minute**			
	1-3 scores	91 (80%)	92 (35%)	<0,0001
	4 scores or more	23 (20%)	168 (65%)	
3	**Apgar scores at 5 minutes**			
	1-3 scores	45 (39%)	19 (7%)	<0,0001
	4 scores or more	69 (61%)	241 (93%)	
4	**IVH**			
	yes	71 (62%)	105 (40%)	<0,0001
	no	43 (38%)	155 (60%)	
5	**DIC syndrome**			
	yes	100 (88%)	115 (44%)	<0,0001
	no	14 (12%)	145 (56%)	
6	**Atelectasis**			
	yes	92 (91%)	117 (44%)	<0,0001
	no	22 (9%)	143 (56%)	
7	**NEC**			
	yes	46 (40%)	19 (7%)	<0,0001
	no	68 (60%)	241 (93%)	
8	**Anemia**			
	yes	55 (48%)	111 (43%)	0,320
	no	59 (52%)	149 (57%)	
9	**Pneumonia**			
	yes	93 (82%)	230 (88%)	0,074
	no	21 (18%)	30 (12%)	

The number of deceased premature infants, whose condition was assessed by the Apgar score at 1-3 points at the 1st minute, was 2.3 times higher compared to surviving infants (80% versus 35%, p<0.001). At the same time, 1-3 points on the Apgar score at the 5th minute were noted 5.6 times more often among deceased premature infants (39% versus 7%, p<0.0001). The presence of IVH and DIC was also more often recorded among deceased infants compared to surviving infants (62% versus 40%, p<0.0001) and (88% versus 44%, p<0.001), respectively. Of the other factors, in the group of deceased children compared to the group of surviving children, atelectasis (91% versus 44%, p<0.001) and NEC (40% versus 7%, p<0.001) were more common. Other parameters did not show significant differences.

3.2 Evaluation of the association of low birth weight preterm infants' characteristics with mortality

All the studied factors that showed significant differences in the comparative analysis (Table 3) were analyzed in the regression analysis to identify their association with the fatal outcome. The results are presented in Table 4.

Table 4 Evaluation results of the association of low birth weight preterm infants' characteristics with mortality

№	Parameters	Unadjusted odds ratio, 95% CI	p	Adjusted odds ratio, 95% CI	p
1	**Apgar scores at 1 minute**				
	4 scores or more	reference		reference	
	1-3 scores	7.225 (4.281-12.193)	**<0,0001**	2,478 (1,289-4,764)	**0,007**
2	**Apgar scores at 5 minutes**				
	4 scores or more	reference		reference	
	1-3 scores	8.272 (4.543-15.063)	**<0,0001**	3,754 (1,788-7,878)	**<0,0001**
3	**Atelectasis**				
	no	reference		reference	
	yes	5.111 (3.022- 8.644)	**<0,0001**	1,803 (0,941-3,455)	0,076
4	**DIC syndrome**				
	no	reference		reference	
	yes	9.006 (4.891-16.584)	**<0,0001**	4,428 (2,206-8,887)	**<0,0001**
5	**NEC**				
	no	reference		reference	
	yes	8.581 (4.716 - 15.610)	**<0,0001**	4,508 (2,270-8,954)	**<0,0001**
6	**IVH**				
	no	reference		reference	
	yes	2.437 (1.550-3.833)	**<0,0001**	1,648 (0,940-2,888)	0,081

In the univariate logistic regression model, all factors showed an association with death: 1-3 points on the Apgar score at the 1st minute (OR- 7.225, 95% CI- 4.281-12.193, p<0.0001), 1-3 points on the Apgar score at the 5th minute (OR- 8.272, 95% CI- 4.543-15.063, p<0.0001), atelectasis (OR- 5.111, 95% CI- 3.022-8.644, p<0.0001), DIC (OR- 9.006, 95% CI- 4.891-16.584, p<0.0001), NEC (OR- 8.581, 95% CI 4.716 - 15.610, p<0.0001) and IVH (OR – 2.437, 95% CI 1.550-3.833, p<0.0001).

However, when testing these factors in a multivariate logistic regression model, only 1-3 points on the Apgar score at the 1st minute (OR - 2.478, 95% CI - 1.289-4.764, p = 0.007), 1-3 points on the Apgar score at the 5th minute (OR - 3.754, 95% CI - 1.788-7.878, p < 0.0001), DIC syndrome (OR - 4.428, 95% CI - 2.206-8.887, p < 0.0001), NEC (OR - 4.508, 95% CI - 2.270-8.954, p < 0.0001) confirmed the association with a fatal outcome in children with RDS.

3.3 Evaluation of the prognostic significance of a set of factors for fatal outcome in low birth weight premature infants with RDS

A ROC analysis was conducted to identify which factors had the highest prognostic value. Acceptable and good area under the curve values should be greater than 0.7 [11].

The results are presented in Table 5 and Figure 1.

Table 5 ROC analysis results

№	Parameters	Area under the curve	Standard error	p
1	DIC syndrome	0,283	0,027	<0,0001
2	NEC	0,335	0.033	<0,0001
3	DIC syndrome+NEC (Predicted probability)	0,782	0.025	<0,0001

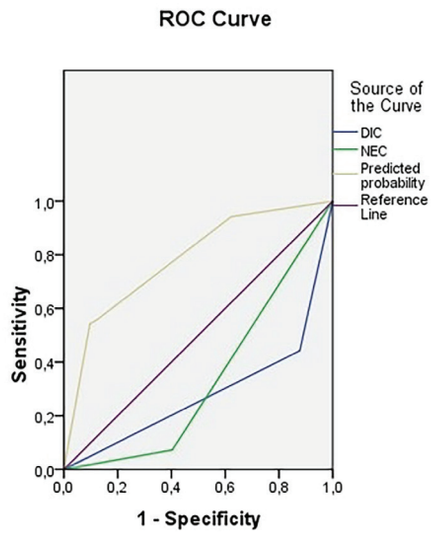

Figure 1 – ROC curves for DIC, NEC and their combination for predicting mortality in low birth weight preterm infants with RDS

ROC curves were created to assess how well DIC syndrome, NEC, and their combination predicted mortality in low birth weight preterm infants with RDS. The area under the curve for DIC syndrome was 0.283. At the same time, this indicator for NEC was 0.335. The area under the curve for the combination of DIC syndrome and NEC was 0.782 (Figure 1).

Discussion

This study was initiated due to the limited understanding of the interplay between respiratory distress syndrome (RDS) and other health conditions in premature, low-birth-weight infants, and the impact of these comorbidities on mortality rates.

Analysis of the concomitant pathologies structure in low birth weight premature newborns with respiratory distress syndrome

It has been found that low birth weight newborns with RDS, born at a low gestational age, are characterized by the presence of several concomitant diseases. In general, the data obtained are consistent with the studies of other authors [12-14].

Moreover, the main concomitant pathology in newborns both with and without RDS was pneumonia. These data indicate the predominant influence of prematurity on the risk of developing respiratory pathologies. A significant contributor to the high mortality rate among these infants is the requirement for mechanical ventilation and other forms of respiratory support. This can harm lung tissue [15], worsen RDS, and lead to ventilator-induced pneumonia [16]. Surprisingly, when newborns who survived were compared to those who didn't, no difference was found in the rate of pneumonia. It is believed that this is due to improved management and therapeutic strategies, which reduce the impact of pneumonia on mortality in this group of newborns.

It was also noticed that there were significant differences in the structure of concomitant diseases in low birth weight infants with and without RDS. Thus, infants with RDS were significantly more likely to have such diseases as anemia, DIC, atelectasis, and NEC. It is believed that the prevalence of these diseases in newborns with RDS is associated with the pathogenesis of these pathologies. Thus, the high frequency of anemia in RDS can be explained by bidirectional cause-and-effect relationships. On the one hand, neonatal anemia is also a consequence of prematurity and contributes to the development of hypoxia. In turn, hypoxia suppresses the development of epithelial cells and contributes to their death, simultaneously reducing the production of pulmonary surfactant, thus being a risk factor for RDS [17]. On the other hand, respiratory disorders can be a risk factor for hemorrhages, which increases the risk of anemia [18]. Atelectasis is also often associated with RDS. This is due to the similarity of the pathogenesis of these diseases. Both of these pathologies are associated with reduced surfactant production in premature infants. In addition, invasive respiratory support, often necessary for RDS, can contribute to the development of atelectasis [19].

An interesting feature of the study is the higher incidence of NEC in neonates with RDS. Although NEC is an independent disease, as is RDS, which is formed as a result of prematurity, our data confirm the presence of a multifactorial biological connection in critical illnesses, including cross-talk between the intestine and the lung, the so-called "lung-gut" axis [20]. As for the high incidence of DIC syndrome in RDS, it is hypothesized that this is due to the coagulation profile characteristic of RDS, which is manifested by hypocoagulation and high hyperfibrinolytic potential [21], as well as the birth of children with a low score on the Apgar score in the first and fifth minutes, which indicates hypoxia and its influence on the development of DIC.

Identification mortality risk factors in these newborns

Another objective of this study was to examine risk factors for mortality in the context of comorbidities. When analyzing risk factors for mortality in the study group, it was found that in

addition to the Apgar score, NEC and DIC are also risk factors for mortality. Well-studied risk factors for mortality are the Apgar score at the first and fifth minute and the use of advanced resuscitation after birth. The Apgar score at the first minute reflects how well the baby tolerated the birth process, and the Apgar score at the fifth minute reflects how well the baby feels after birth.

At the same time, it is considered that the identified association of NEC and DIC on mortality in neonates with RDS reflects their impact on mortality in preterm infants in general, and is not a feature of infants with RDS. In particular, NEC is the leading cause of death due to gastrointestinal diseases in preterm infants, affecting 5-12% of neonates born with very low birth weight. Moreover, mortality rates among newborns who require surgical intervention are estimated at 20–30% [22]. DIC is also a serious complication of the neonatal period in low birth weight infants and can either develop independently or be a manifestation of NEC in severe cases [23]. Considering that both DIC and NEC were more common in newborns with RDS and were identified as risk factors for death, the role of the synergistic effect of these two pathologies on mortality in such children was analyzed. It was found that the combination of these two pathologies increases the risk of death by two times.

This study differs from other similar studies in that it examines a specific population of extremely preterm infants born before 32 weeks, classified as extremely low birth weight (ELBW) and very low birth weight (VLBW) infants, without controlling for factors such as weight and gestational age, the effects of which have already been widely studied in previous studies. Moreover, the influence of concomitant pathologies, as well as their combination, on the lethal outcome in this category of newborns was studied.

Thus, in addition to previously studied factors such as low birth weight and gestational age, it was found that in the group of low birth weight premature infants with RDS, a combination of DIC syndrome and NEC made a significant contribution to the development of a fatal outcome.

A weakness of the study is the lack of analysis of the influence of social and maternal factors on the studied characteristics of newborns. In the future, we plan to conduct such an analysis. Also, the results of this study are specific to premature infants weighing less than 1500 g and with a gestational age of less than 32 weeks, and therefore cannot be applied to other categories of newborns.

The study's strength is its ability to assess how the interplay of different health conditions influences mortality rates in extremely premature infants with respiratory distress syndrome. It is thought that our findings will contribute to lower mortality rates in low-birth-weight premature infants with RDS. By understanding the structure of concomitant pathologies and identifying mortality risk factors in preterm infants with RDS has direct implications for clinical decision-making and patient care.

Conclusion

The structure of comorbidities in low birth weight infants with RDS differs from that of infants without RDS. Premature infants with RDS were more likely to develop anemia, DIC, atelectasis, and NEC.

The presence of comorbidities increases the risk of death in low birth weight infants with RDS. Low Apgar score, DIC syndrome, and NEC can increase the risk of death in low birth weight premature infants with RDS.

It is anticipated that the collected data will enhance personalized care for low birth weight, premature infants with multiple health conditions, ultimately reducing mortality rates in this vulnerable patient group.

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