SANAMED
2024; 19(3): 267–274
ISSN-1452-662X

DOI: 10.5937/sanamed0-54887
UDK: 616.9:615.33.015.8
ID: 160132361
Original article

PERINATAL PREDICTORS OF NEURODEVELOPMENTAL OUTCOMES IN HIGH-RISK NEONATES

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Primljen/Received: 05. 11. 2024. Prihvaćen/Accepted: 04. 12. 2024. Published online first: 12. 12. 2024.

Abstract: **Background:** Thanks to advancements in neonatal medicine, perinatal morbidity has been significantly reduced, but the number of high-risk neonates continues to rise. Efforts to predict neurodevelopmental outcomes at an early age remain limited. The aim of this study was to analyze perinatal predictors of neurodevelopmental outcomes in high-risk neonates.

Methods: A prospective, longitudinal two-year study was conducted at the Pediatric Clinic of the University Clinical Center in Tuzla. The study included 151 neonates, with 99 in the test group (with known perinatal risk factors) and 52 in the control group (without risk factors). Early neurodevelopment was assessed using the Alberta Infant Motor Scale (AIMS). Standard statistical methods were applied for data processing. The study was approved by the Institutional Ethics Committee.

Results: Of the 151 neonates observed, 108 (71.5%) had normal neurodevelopment at 18 months, 29 (19.2%) had mild disorders, and 14 (9.3%) had developmental delays. In the group with suboptimal neurodevelopment, significantly more twin pregnancies, health problems during pregnancy, unnatural births, artificial fertilization, and pregnancy complications were recorded. In neonates, there were significantly more premature births, hypoxic-ischemic encephalopathy, and intracranial hemorrhages. Significant correlations were found between the mother's age and parity and delayed neurodevelopment. Additionally, correlations were found between birth weight, gestational age, Apgar score, length of hospitalization, and NICU stay with neurodevelopmental delay. Gestational age and the Apgar score at 1 minute showed significant negative predictive value for neurodevelopmental delay.

Conclusion: Prematurity and perinatal asphyxia remain the greatest risks for adverse neurodevelopmental outcomes in neonates. These factors should be the focus of continued medical research and clinical practice. Neonates at the highest risk of developmental delay and their families should be prioritized for early identification, long-term follow-up, and timely interventions.

Keywords: perinatal risk factors, high-risk neonates, neurodevelopmental outcomes, predictors.

INTRODUCTION

Thanks to advancements in neonatal medicine, perinatal morbidity has been significantly reduced, but the number of high-risk neonates continues to rise (1). However, efforts to predict neurodevelopmental outcomes at the earliest stages remain limited. During pregnancy, childbirth, and early infancy, various factors can affect the developing nervous system, potentially leading to permanent consequences. The term "baby at risk" was first introduced in the United Kingdom around 1960 (2). In 1978, the World Health Organization defined a high-risk child as one who presents certain risk factors prenatally, perinatally, and postnatally. In developed countries, the incidence of such children is approximately 10% (3).

High-risk neonates need to be identified immediately after birth, using anamnestic data, clinical risk factors, and early neonatal neuroimaging of the brain. These neonates are highly dependent on their environment and are vulnerable, but they also have great potential for positive adaptation and overcoming difficulties if provided with a favorable environment (4, 5). Neurodevelopmental deviations can be expected in approximately 50% of high-risk children. Today, it is estimated that 70-80% of children with developmental disabilities belong to the group of high-risk children (6).

The registry and long-term follow-up of high-risk children, along with the strategy of early detection of neurodevelopmental deviations, were introduced by Victoria Sheridan in the United Kingdom in 1964 and

have been applied for the longest time (7). New research may enhance our ability to identify infants at high risk of developmental delays as early as possible, in line with evidence that early intervention can improve outcomes for these infants (8, 9, 10). Therefore, the timely identification of associated perinatal factors and focused work on their prevention can improve outcomes for high-risk neonates later in life (11).

The aim of this study was to analyze perinatal predictors of neurodevelopmental outcomes in high-risk neonates up to 18 months of age.

PATIENTS AND METHODS

The research was conducted prospectively and longitudinally over a two-year period (from August 1, 2017, to August 1, 2019) at the Pediatric Clinic of the University Clinical Center in Tuzla. Following the inclusion and exclusion criteria, 151 neonates were selected consecutively to participate in the study. The test group consisted of 99 neonates with known risk factors associated with pregnancy, childbirth, and the early neonatal period. This group included 49 term neonates with a gestational age (GA) of ≥ 37 weeks (GW) and 50 preterm neonates with a GA of < 37 GW. The control group included 52 neonates aged 37-42 weeks, without known risk factors.

Data collected from the mothers in the first phase of the study included their age, body weight, number of prenatal visits, any diseases during pregnancy, medication use, lifestyle and habits, and socioeconomic status. This information was obtained from medical records and an additional questionnaire.

Perinatal and postnatal data were collected for the neonates, which included gestational age, birth weight, birth length, head circumference, Apgar score, resuscitation procedures, morbidity, therapeutic treatments during the perinatal and postnatal periods, diet, examination records, health monitoring, growth and development observations, developmental deviations, and any diagnostic or therapeutic procedures performed, including physical treatment. These data were obtained from medical records and an additional questionnaire.

All neonates were monitored with brain ultrasound during the first 6 months of life, and for some, further examinations were conducted up to a year, or up to 18 months, when necessary. Magnetic resonance imaging (MRI) of the brain was performed on selected cases where indicated.

Early neurodevelopment was assessed using the Alberta Infant Motor Scale (AIMS) protocol (12, 13, 14) at 4, 8, 12, and 18 months of age.

Standard descriptive statistics were used for data processing. Categorical variables were analyzed using the $\chi 2$ test and Fisher's exact test. Spearman's non-parametric correlation was employed to assess significant relationships between variables. A difference between samples was considered significant if $p < 0.05$. All statistical tests were conducted with a 95% confidence level ($p < 0.05$).

All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committees, following the 1964 Helsinki declaration and its later amendments or comparable ethical standards (15). The study was approved by the Institutional Ethics Committee.

RESULTS

During the study follow-up, it was found that, out of 151 observed infants, 108 (71.5%) exhibited normal neurodevelopment at 18 months of age. A mild disorder was recorded in 29 infants (19.2%), while 14 infants (9.3%) experienced a delay in neurodevelopment. Additionally, 15 infants (9.9%) were diagnosed with a muscle tone disorder, and 6 infants (4.0%) had a significant movement disorder.

Infants in the high-risk group had statistically significantly lower scores on the Alberta Infant Motor Scale compared to the control group at all age assessments ($p < 0.001$).

The prevalence of perinatal risk factors was analyzed in relation to early neurodevelopmental outcomes, with the results presented in the following tables. Table 1 shows the prevalence of maternal-related perinatal risk factors in the two groups of infants, categorized by their neurodevelopmental outcomes.

In the group with neurodevelopmental delay, there were significantly more cases of twin pregnancies, health problems during pregnancy, infections, treated infertility, drug use during pregnancy, and more frequent use of antibiotics. Additionally, there was a significantly higher prevalence of smoking, alcohol use, and psychological trauma. A statistically significant correlation between these factors and delayed neurodevelopment was observed (Table 1). Table 2 shows the prevalence of obstetric risk factors in the two groups of subjects with different neurodevelopmental outcomes.

In the group with neurodevelopmental delay, there were significantly more unnatural births, artificial fertilization, and pregnancy complications. A statistically significant correlation was found between these factors and delayed neurodevelopment (Table 2).

Table 3 shows the prevalence of child-related perinatal risk factors in the two groups of subjects with different neurodevelopmental outcomes.

Table 1. *Prevalence of maternal-related risk factors in neurodevelopmental outcome groups*

Mother-related specifications	Neurodevelopment				χ^2	p	φ	p
	Normal		Delayed					
	n	%	n	%				
Pregnancy					7.748	**0.006**	0.235	**0.003**
Single	95	88.0	29	67.4				
Twins	13	12.0	14	32.6				
Health problems in pregnancy	28	25.9	20	46.5	5.099	**0.024**	0.196	**0.014**
Infections	14	13.0	13	30.2	5.126	**0.024**	0.199	**0.012**
Treated Sterility	2	1.9	5	11.9	4.728	**0.019***	0.209	**0.009**
Medicines in pregnancy	28	25.9	19	44.2	3.970	**0.046**	0.175	**0.029**
Antibiotics	14	13.0	13	30.2	5.126	**0.024**	0.199	**0.012**
Smoking	20	18.5	16	37.2	4.933	**0.026**	0.194	**0.015**
Alcohol	0	0.0	3	11.5	5.767	**0.013***	0.287	**0.002**
Mental trauma	13	12.0	19	44.2	17.157	**< 0.001**	0.335	**< 0.001**

* Fisher's exact test; χ^2 - chi-squared test; φ - phi coefficient (mean square contingency coefficient; p - probability value

Table 2. *Prevalence of obstetric risk factors in neurodevelopmental outcome groups*

Obstetric specifications	Neurodevelopment				χ^2	p	CC	p
	Normal		Delayed					
	n	%	n	%				
Type of delivery					9.57	**0.009***	0.257	**0.013**
Natural	80	74.1	22	51.2				
Induced	3	2.8	2	4.7				
Section	25	23.1	17	39.5				
Vacuum extraction	0	0.0	2	4.7				
Fertilization method					6.259	**0.020***	0.210	**0.030**
Natural	105	97.2	38	88.4				
Assisted	1	0.9	0	0.0				
Artificial	2	1.9	5	11.6				
Pregnancy complications					13.251	**0.002***	0.305	**0.001**
No complications	101	93.5	34	79.1				
Bleeding	5	4.6	1	2.3				
Cervical cerclage	2	1.9	4	9.3				
Premature uterine contractions	0	0.0	4	9.3				

* Fisher's exact test; χ^2 - chi-squared test; CC - correlation coefficient; p - probability value

Table 3. *Prevalence of the child-related perinatal risk factors in neurodevelopmental outcome groups*

Child-related specifications	Neurodevelopment				χ^2	p	φ	p
	Normal		Delayed					
	n	%	n	%				
Gestational age					15.459	< 0.001	-0.336	**< 0.001**
Preterm	25	23.1	25	58.1				
Term neonates	83	76.9	18	41.9				
Twins	18	19.4	14	41.2	5.186	0.023	0.223	**0.012**
Oxygen therapy	28	25.9	29	67.4	20.826	< 0.001	0.387	**< 0.001**
HIE	19	17.6	25	58.1	22.563	< 0.001	0.403	**< 0.001**
Sepsis	7	6,5	17	39.5	22.724	< 0.001	0.408	**< 0.001**
Ordered MRI of the brain	0	0.0	5	11.6	9.610	0.002	0.293	**< 0.001**

* Fisher's exact test; χ^2 - chi-squared test; φ - phi coefficient (mean square contingency coefficient; p - probability value; HIE: Hypoxic ischemic encephalopathy; MRI: magnetic resonance imaging

Table 4. *Prevalence of postnatal risk factors in neurodevelopmental outcome groups*

Postnatal specifications	Neurodevelopment				χ^2	p	CC	p
	Normal		Delayed					
	n	%	n	%				
Intracranial hemorrhage					15.628	0.001*	0.321	0.002
No	74	68.5	19	44.2				
first degree	22	20.4	8	18.6				
second degree	12	11.1	13	30.2				
Third/fourth degree	0	0.0	3	7.0				
Ultrasound follow-up					38.223	< 0.001	0.449	< 0.001
Up to 12 months	41	38.0	26	60.5				
Up to 18 months	6	5.6	14	32.6				
Speech development					115.021	< 0.001	0.650	< 0.001
Normal	76	70.4	1	2.3				
Mild speech delay	31	28.7	8	18.6				
Significant delay	1	0.9	21	48.8				

* Fisher's exact test; χ^2 - chi-squared test; CC - correlation coefficient; p - probability value

Table 5. *Correlation of perinatal risk factors with neurodevelopmental delay*

Perinatal risk factors	Neurodevelopmental delay	
	r	p
Mother's age	0.226	**0.005**
Parity	0.356	**< 0.001**
History of abortion	0.172	**0.034**
Birth weight	-0,228	**0,005**
Gestational age	-0,372	**< 0,001**
Apgar score in the 1st minute	-0,468	**< 0,001**
Apgar score in the 5th minute	-0,480	**< 0,001**
Length of hospitalization	0,490	**< 0,001**
NICU stay (days)	0,490	**< 0,001**
Antibiotic therapy	0,426	**< 0,001**
Duration of antibiotic therapy	0,507	**< 0,001**
AIMS score, percentiles	-0,640	**< 0,001**
AIMS score for age 8 months, percentiles	-0,791	**< 0,001**
AIMS score for age 12 months, percentiles	-0,775	**< 0,001**
AIMS score for age 18 months, percentiles	-0,704	**< 0,001**

r - Pearson correlation coefficient; p - probability value; NICU – neonatal intensive care unit; AIMS – Alberta Infant Motor Scale;

Table 6. *Predictive value of perinatal risk factors for neurodevelopmental delay*

Perinatal risk factors	B	S.E.	Wald	p	OR	95% C.I.	
						Lower	Upper
Mother's age	0.048	0.046	1.120	0.290	1.049	0.960	1.148
Parity	0.554	0.246	5.090	**0.024**	1.741	1.075	2.818
Abortion	0.542	0.373	2.114	0.146	1.720	0.828	3.573
Health problems in pregnancy	0.487	0.639	0.582	0.445	0.614	0.176	2.148
Birth weight	0.000	0.000	0.025	0.873	1.000	0.999	1.001
Gestational age	-0.447	0.179	6.259	**0.012**	0.640	0.451	0.908
Apgar score in th e 1st min.	-0.614	0.297	4.287	**0.038**	0.541	0.302	0.968
Apgar score in the 5th min.	0.105	0.477	0.049	0.826	1.111	0.436	2.827
Length of hospitalization	0.062	0.176	0.125	0.724	1.064	0.753	1.504
Days of NICU stay	0.114	0.083	1.848	0.1 74	1.120	0.951	1.319
Antibiotic therapy	-0.079	0.226	0.121	0.728	0.924	0.594	1.440

B – unstandardized regression weight; S.E. - possibilities of varying the unstandardized regression weight; Wald - test statistic for the individual predictor variable; p - probability value; OR – odds ratio; C.I. - confidence interval; Statistical model: $R^2 = 0,386$ (Cox & Snell), $R^2 = 0,555$ (Nagelkerke); $\chi^2 = 71,115$; d f= 9; $p < 0,001$; overal = 82,2

In the group with neurodevelopmental delay, there were significantly more premature births, more twins, more instances of oxygen therapy, hypoxic-ischemic encephalopathy, sepsis, and a higher number of ordered brain magnetic resonance imaging (MRI) exams. A statistically significant correlation was found between these factors and delayed neurodevelopment (Table 3).

Table 4 shows the prevalence of postnatal risk factors in the two groups of subjects with different neurodevelopmental outcomes.

In the group with delayed neurodevelopment, there were significantly more intracranial hemorrhages ($p = 0.002$), more brain ultrasound follow-ups, and more cases of delayed speech development ($p < 0.001$) (Table 4).

The correlation between perinatal risk factors and early neurodevelopmental outcomes, as well as the sequence of neurodevelopmental delay, was analyzed. The results are presented in the following table (Table 5).

A statistically significant positive correlation was found between the mother's age, parity, number of abortions, and delayed neurodevelopment. Additionally, a statistically significant negative correlation was observed between birth weight ($p = 0.005$), gestational age, Apgar score, AIMS score, and delayed neurodevelopment. Furthermore, a statistically significant positive correlation was found between the length of hospitalization, number of days in the NICU, antibiotic therapy, and the duration of therapy with delayed neurodevelopment ($p < 0.001$) (Table 5).

These indicators were tested as predictors of neurodevelopmental delay using a logistic regression statistical model, as presented in Table 6.

Parity showed a significant positive predictive value for neurodevelopmental delay. The model was statistically significant, explaining between 20.5% and 29.5% of the variance, and correctly classified 75.2% of the cases. The other maternal-related risk factors did not show a significant predictive value. Among child-related risk factors, gestational age and the Apgar score at the 1st minute showed a significant negative predictive value for neurodevelopmental delay. The model was statistically significant, explaining between 38.6% and 55.5% of the variance, and correctly classified 82.2% of the cases. The other indicators did not show a significant predictive value (Table 6).

DISCUSSION

High-risk neonates are attracting attention due to numerous still unresolved dilemmas related to their assessment, monitoring, and treatment. The age for their selection is getting lower and lower, in the perinatal period, and earlier, because their neurodevelopmental outcome is dubious, and largely depends on both biomedical and environmental factors. The analysis of perinatal risk factors is important, in an attempt to select the most significant, those that can have the greatest impact on the long-term outcome of the affected children. The aim of this study was to analyze perinatal predictors of neurodevelopmental outcomes for high-risk neonates up to 18 months of age.

In our research, AIMS was used to monitor the early neurodevelopment of the examined neonates. During the 18-month follow-up of early neurodevelopment, children from the high-risk group showed statistically significantly lower scores on the Alberta Infant Motor Scale at all age assessments, with $p < 0.001$. AIMS can be used as a screening tool to detect and monitor early developmental delay. In our study, AIMS correlated well with early neurodevelopmental outcomes. The latest recommendations for dealing with high-risk children dictate that imaging tests such as brain ultrasound or brain magnetic resonance imaging (MRI) should be performed in children with an abnormal examination (1). The common clinical practice is to perform brain MRI before discharge (16), which was the case in our study as well. In our study, 108 infants (71.5%) had normal neurodevelopment at the age of 18 months. A mild disorder was recorded in 29 subjects (19.2%), while 14 (9.3%) had neurodevelopment delay. Additionally, 15 subjects (9.9%) had a confirmed diagnosis of muscle tone disorder, while 6 (4.0%) had a significant movement disorder. These results are generally in agreement with studies by others (3, 4, 6).

Functional outcomes should be assessed with a follow-up of at least 2 years (1, 10). Some studies observed that cognitive performance at 6 months in neuro-risk neonates was not a reliable predictor of cognitive status at 24 months and found that early intervention could improve their functional outcomes (17). On the other hand, the longitudinal study of high-risk infants (18), observed that cognitive performance at the age of 12 months, serves only as a general predictor for cognition at the age of 12 months and preschool age. Therefore, supervision of early development and early interventions should be implemented until at least 2 years of age.

In our study, significantly more mother-related, obstetrical, and child-related risk factors were found in the group with suboptimal neurodevelopment compared to healthy subjects which is consistent with previous reports. Many studies have analyzed perinatal and postnatal risk factors, their significance, and correlation with early neurodevelopment (19, 20). A study by Tskimanauri et al. (11) on the correlation between perinatal risk factors and neurodevelopmental outcomes in children at 24 months of age reports that gestational age and neonatal sepsis were strongly correlated with

adverse neurological disorders, and a less significant correlation was with hypoxic-ischemic encephalopathy and intracranial hemorrhage. Risk factors for neonatal sepsis partly overlap with risk factors for neurodevelopmental delay (21). The most significant single risk factor for abnormal neurodevelopmental outcomes in this study was gestational age, maternal age, and pregnancy pathology. Also, an Indian study (22) reports a higher prevalence of neurodevelopmental delay in neonates from the low birth weight, preterm, and twin groups. Neonatal sepsis, convulsions, and perinatal asphyxia also showed significant association with adverse neurodevelopmental outcomes. Critically ill neonates who require treatment in the NICU deserve special attention. In our study, in the group with delayed neurodevelopment, there were significantly more premature births, oxygen therapy, hypoxic-ischemic encephalopathy, sepsis, and intracranial hemorrhages. Most previous studies conclude that higher gestational age at birth and higher birth weight are associated with a lower risk of developmental delay. Cohort studies focused on motor development showed that the degree of impairment decreased over time (23). A significant number of studies analyze perinatal brain injuries and their neurodevelopmental outcome. Research on the outcome of neonatal encephalopathy suggests that a mild form of encephalopathy does not affect later development, while a severe form of encephalopathy results in marked delay. Great variability occurs in children who have moderate encephalopathy (19). Severe intraventricular hemorrhage is also associated with severe cognitive impairment and paraventricular leukomalacia. The development of motor, cognitive, and speech functions is directly related to the degree of intracranial hemorrhage (20).

Gestational age and Apgar score in the 1st minute showed a significant negative predictive value for neurodevelopmental delay. Many perinatal risk factors are intertwined with prematurity, however, the incidence of neurodevelopmental disorders among these infants remained high and was inversely related to gestational age (23).

Prematurity and perinatal asphyxia remain the greatest risks for neurodevelopmental adverse outcomes in neonates and should be the focus of medical science and practice. This study has its limitations, given that it is a single-center study with a small sample. A multicenter study on a larger sample is needed, based on which we can obtain more reliable guidelines for further action in this area.

CONCLUSION

In our study, a mild neurodevelopmental disorder was observed in one-fifth of the participants, while 9.3% had delayed neurodevelopment. The Alberta Infant Motor Scale demonstrated a strong correlation with early neurodevelopmental outcomes. A significantly higher number of perinatal risk factors were found in the group with suboptimal neurodevelopment compared to the healthy group. A significant correlation was identified between the mother's age, parity, number of abortions, and delayed neurodevelopment. Additionally, a correlation was found between birth weight, gestational age, Apgar score, AIMS score, length of hospitalization, days of NICU stay, and antibiotic therapy with delayed neurodevelopment. Gestational age and the 1st-minute Apgar score showed significant negative predictive values for neurodevelopmental delay. Children at the highest risk of developmental disabilities, along with their families, should be prioritized for timely identification, monitoring, and early intervention. Early supervision, development monitoring, and rehabilitation of high-risk neonates should continue until at least 2 years of age."

List of abbreviations

AIMS - Alberta Infant Motor Scale
GA - Gestational age
GW- Gestational week
MRI - Magnetic resonance imaging
HIE - Hypoxic ischemic encephalopathy
NICU – Neonatal intensive care unit
χ^2 - chi-squared test
φ - phi coefficient (mean square contingency coefficient)
CC - correlation coefficient
r - Pearson correlation coefficient
B – unstandardized regression weight;
S.E. - possibilities of varying the unstandardized regression weight;
Wald-test statistic for the individual predictor variable;
OR – odds ratio;
C.I. - confidence interval

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No

Author contributions: Conception and design: DH, ZH, FS; Acquisition, analysis, and interpretation of data: DH and FS; Drafting the article: ZH and DH; Revising the article critically for intellectual content: DH and FS; Approved the final version of the manuscript: ZH, DH, FS.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

PERINATALNI PREDIKTORI NEURORAZVOJNIH ISHODA KOD VISOKORIZIČNIH NOVOROĐENČADI

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Uvod: Zahvaljujući napretku neonatalne medicine, perinatalni morbiditet je značajno smanjen, ali se povećava broj visokorizične novorođenčadi. Međutim, napori da se predvidi neurorazvojni ishod u najranijoj dobi su ograničeni. **Cilj** ovog istraživanja bio je analizirati perinatalne prediktore neurorazvojnog ishoda kod visokorizičnih novorođenčadi. **Metode:** Prospektivno, longitudinalno dvogodišnje istraživanje sprovedeno na Klinici za dečije bolesti, Univerzitetskog kliničkog centra u Tuzli, obuhvatilo je 151 novorođenče, 99 u grupi sa poznatim perinatalnim faktorima rizika i 52 u kontrolnoj grupi bez rizika. Rani neurorazvoj je procenjen AIMS (Alberta Infant Motor Scale) skalom. U statističkoj obradi korištene su standardne metode. Studiju je odobrio Etički komitet ustanove. **Rezultati:** Od 151 posmatrane novorođenčadi, u dobi od 18 meseci, njih 108 (71,5%) imalo je normalan neurorazvoj, blagi poremećaj je zabeležen kod 29 ispitanika (19,2%), dok je 14 (9,3%) imalo zastoj u neurorazvoju. U grupi sa suboptimalnim neurorazvojem bilo je značajno više blizanačkih trudnoća, zdravstvenih problema tokom trudnoće, više artificijalnih porođaja, veštačkih oplodnji i komplikacija u trudnoći. Kod novorođenčadi je bilo značajno više prevremenih porođaja, hipoksične ishemijske encefalopatije, intrakranijalnih krvarenja. Pronađena je značajna korelacija između starosti majke i pariteta sa zaostajanjem u neurorazvoju. Utvrđena je korelacija između porođajne težine novorođenčeta, gestacijske dobi, Apgar skora, dužine hospitalizacije, dana boravka u neonatalnoj intenzivnoj nezi, sa odgođenim neurorazvojom. Gestacijska dob i Apgar skor u 1. minuti pokazali su značajnu negativnu prediktivnu vrednost za predviđanje zaostajanja u neurorazvoju. **Zaključak:** Prevremeno rođenje i perinatalna asfiksija ostaju najveći rizici za neurorazvojne neželjene ishode kod novorođenčadi i trebali bi biti u fokusu medicinske nauke i prakse. Novorođenčad koja su u najvećem riziku od kašnjenja u razvoju i njihove porodice treba da imaju prioritet za pravovremenu identifikaciju, dugoročno praćenje i ranu intervenciju.

Ključne reči: perinatalni faktori rizika, visokorizična novorođenčad, neurorazvojni ishod, prediktori.

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***How to cite this article**:* Hajric Z, Hadzic D, Skokic F. Perinatal Predictors of Neurodevelopmental Outcomes in High-Risk Neonates. Sanamed. 2024; 19(3): 267-274. doi: 10.5937/sanamed0-54887.