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PREDICTION OF ADVERSE OUTCOMES IN HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN TERM NEWBORNS

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The purpose of the study was to identify and predict adverse outcomes in term neonates diagnosed with hypoxic-ischemic encephalopathy a total of 120 children, aged from birth to one year. The study cohort was divided into two groups: the main group (90 patients with hypoxic-ischemic encephalopathy), and the control group (30 healthy children without a history of asphyxia). To develop a predictive model, logistic regression analysis was employed, a robust statistical method designed to explore and quantify the relationships between dependent and independent variables. A total of 67 independent variables (predictors) were identified, encompassing anamnestic, clinical, and laboratory-instrumental parameters. Using multiple variable selection methods (Enter, Forward, Backward, and Wald-based approaches), we identified key predictors that contribute significantly to the prognosis of these neonates. The high classification accuracy achieved across all methods (ranging from 93.3 % to 96.7 %) demonstrates its potential in clinical settings for predicting neonatal outcomes.

Key words: neonates, hypoxic-ischemic encephalopathy, predictive model, logistic regression analysis, outcomes.

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ПРОГНОЗУВАННЯ НЕСПРИЯТЛИВИХ НАСЛІДКІВ ПРИ ГІПОКСИЧНО-ІШЕМІЧНІЙ ЕНЦЕФАЛОПАТІЇ У ДОНОШЕНИХ НОВОНАРОДЖЕНИХ

З метою дослідження з виявлення та прогнозування несприятливих наслідків у доношених новонароджених з діагнозом гіпоксично-ішемічна енцефалопатія, було обстежено 120 дітей віком від народження до одного року. Досліджувана когорта була розділена на дві групи: основну (90 пацієнтів з гіпоксично-ішемічною енцефалопатією) та контрольну (30 здорових дітей без асфіксії в анамнезі). Для розробки прогностичної моделі було використано логістичний регресійний аналіз – надійний статистичний метод, призначений для вивчення та кількісної оцінки взаємозв'язків між залежними та незалежними змінними. Усього було виявлено 67 незалежних змінних (предикторів), що охоплюють анамнестичні, клінічні та лабораторно-інструментальні параметри. Використовуючи методи множинного відбору змінних (Enter, Forward, Backward та Wald-based підходи), ми виявили ключові предиктори, які вносять значний внесок у прогноз цих новонароджених. Висока точність класифікації, досягнута всіма методами (від 93,3 до 96,7 %), демонструє її потенціал у клінічних умовах для прогнозування неонатальних результатів.

Ключові слова: новонароджені, гіпоксично-ішемічна енцефалопатія, прогностична модель, логістичний регресійний аналіз, результати.

Hypoxic-ischemic encephalopathy (HIE) is a leading contributor to neonatal mortality and long-term morbidity. Approximately 25 % of neonates diagnosed with HIE develop severe and irreversible neurodevelopmental impairments, such as intellectual disabilities, cerebral palsy, epilepsy, and sensorineural deficits. The primary etiology of neonatal HIE is perinatal asphyxia, often resulting from complications such as umbilical cord entanglement or abnormalities in amniotic fluid, which can lead to fetal distress, asphyxia, and hypoxia [2, 10].

The global incidence of hypoxic-ischemic encephalopathy is estimated to range from 1 to 3 per 1,000 live births in developed countries and from 2.3 to 30.6 per 1,000 live births in developing countries.

Other reports suggest an incidence of approximately 1.5 per 1,000 live births. However, significant discrepancies exist between figures reported in population-based and hospital-based studies, with estimates ranging from 1 to 8 per 1,000 live births. HIE represents a complex, multisystem pathological condition requiring intensive therapeutic management to monitor both cerebral function and dysfunction in non-central nervous system organs [1, 5, 7].

It is estimated that approximately 6,700 neonates die each day, accounting for 47 % of all deaths in children under five years of age—an increase from 40 % in 1990 [11]. Among neonates diagnosed with hypoxic-ischemic encephalopathy, 20 % to 30 % succumb during the neonatal period, while 33 % to 50 % of survivors experience lasting neurodevelopmental impairments, including cerebral palsy and intellectual disabilities [3, 4]. Mortality serves as a critical metric for assessing the performance of healthcare systems; however, accurately predicting it remains a complex challenge [9]. Reliable mortality prediction in the intensive care unit has the potential to significantly improve administrative, organizational, public health, and epidemiological planning, as well as therapeutic and diagnostic strategies.

The purpose of the study was to identify and predict adverse outcomes in term neonates diagnosed with hypoxic-ischemic encephalopathy.

Materials and methods. According to purpose, we determined risk factors: investigated clinical and demographic variables associated with increased mortality and morbidity in neonates with HIE; identified key predictors of long-term neurodevelopmental impairments (e.g., cerebral palsy, intellectual disability) and try to create the predictive model using logistic regression.

The work was performed on the basis of Azerbaijan Medical University. A total of 120 children, aged from birth to one year, were examined. The study cohort was divided into two groups: the main group included 90 patients with HIE of varying severity, all of whom had experienced perinatal asphyxia, while the control group consisted of 30 healthy children without a history of asphyxia or central nervous system (CNS) pathologies.

The main group was further stratified based on HIE severity into three subgroups: group I comprised 10 newborns (11.1 %) with mild HIE (grade I), group II – 46 newborns (51.1 %) with moderate HIE (grade II), and group III consisted of 34 newborns (37.8 %) with severe HIE (grade III).

To develop a predictive model, logistic regression analysis was employed, a robust statistical method designed to explore and quantify the relationships between dependent and independent variables. The core principle of logistic regression is the partitioning of the conditional space of the dependent variable into distinct classes by optimizing the likelihood of classification through maximum likelihood estimation. The analysis separates the data into categories in a manner that maximizes the probability of correctly assigning the initial value to a specific class.

Comparative analysis between surviving and deceased patients was performed using Student's t-test for independent samples. Predictive variables for outcomes in hypoxic-ischemic encephalopathy were identified by assessing statistically significant differences between surviving and deceased patients using Pearson's chi-square and Mann-Whitney U tests for independent samples. Only variables demonstrating statistically significant differences between these groups ($p<0.05$) were included in the predictive model for mortality. Model performance was assessed using a contingency table, receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) score. The construction of the logistic regression model involved a structured, stepwise process.

Results of the study and their discussion. Data analysis revealed that 77 patients achieved a favorable disease outcome, while 13 patients succumbed to the condition. To construct a logistic regression model, it was necessary to verify and satisfy a series of assumptions. This verification process was conducted in two stages: initially during data preparation prior to analysis, and subsequently during and after model construction. A total of 67 independent variables (predictors) were identified, encompassing anamnestic, clinical, and laboratory-instrumental parameters. These variables were subjected to comparative analytical assessments, focusing on statistically significant differences ($p<0.05$). Quantitative characterization of these parameters facilitated the identification of the most critical factors contributing to accurate diagnosis.

Predictive variables for outcomes in hypoxic-ischemic encephalopathy were summarized in Table 1.

Comparative analysis revealed significant differences between these groups across several parameters, including the number of deliveries, type of nutrition, clinical condition at admission, level of consciousness, the shape of eye slits and nasolabial folds, eyeball movement patterns, and pupil condition with photoreactive response ($P_{\chi 2}<0.05$, $P_U<0.05$).

Characteristics of outcome measures in HIE, were as following: sO_2 for survived children was 88.3±1.2; 95 %CI:85.9–90.7 (52–99.9); for died children was 77.2±3.5; 95 %CI:69.6–84.8 (50–94); $P_{\chi2}$=0.001; P_U=0.003. IR for survived children was 0.655±0.019; 95 %CI:0.616–0.693 (0.34–1) and for those who died was 0.552±0.043; 95 %CI:0.458–0.645 (0,42–1); $P_{\chi2}$=0.044; P_U=0.014. The liver right lobe for survived children was 62.3±1.1; 95 %CI:60.2–64.4 (44–86) and for died children was 55.8±2.0; 95 %CI:51.5–60.1 (45–69). The liver left lobe was 37.3±0.8; 95 %CI:35.7–38.8 (24–61) and 32.2±2.1; 95 %CI:27.6–36.8 (19–43); $P_{\chi2}$=0.0188; P_U=0.036, respectively. FTOE was 0.1±0.0; 95 %CI:0.1–0.2 (0.02–0.30) for survived children and 0.1±0.0; 95 %CI: 0.0–0.1 (0.02–0.10); $P_{\chi2}$<0.001; P_U<0.001.

Table 1

Characteristics of indicators predictors studied

		Result				$P_{\chi2}$	P_U Mann-Whitney test
		Survived		Died			
		Count	N %	Count	N %		
Childbirth	Primiparous	48	62.3 %	4	30.8 %	0.033	0.034
	Multiparous	29	37.7 %	9	69.2 %		
Feeding	Natural	26	33.8 %	1	7.7 %	0.01	0.002
	Mixed	23	29.9 %	1	7.7 %		
	Artificial	27	35.1 %	10	76.9 %		
	Parenteral	1	1.3 %	1	7.7 %		
	Existence	40	51.9 %	5	38.5 %		
Condition	Satisfactory	0	0.0 %	0	0.0 %	p<0.001	p<0.001
	Moderate	10	13.0 %	0	0.0 %		
	Serious	34	44.2 %	0	0.0 %		
	Extremely serious	33	42.9 %	0	0.0 %		
	Died	0	0.0 %	13	100.0 %		
Consciousness	Clear	0	0.0 %	0	0.0 %	0.001	p<0.001
	Medication sleep	10	13.0 %	0	0.0 %		
	Stupor	34	44.2 %	0	0.0 %		
	Coma	33	42.9 %	13	100.0 %		
Eye slits	Symmetric	71	92.2 %	8	61.5 %	0.002	0.002
	Asymmetric	6	7.8 %	5	38.5 %		
Eye movements	Full movement	5	6.5 %	1	7.7 %	0.003	0.013
	Floating	67	87.0 %	7	53.8 %		
	Paresis	5	6.5 %	5	38.5 %		
Pupils	Norm	41	53.2 %	2	15.4 %	0.022	0.006
	Miosis	28	36.4 %	7	53.8 %		
	Mydriasis	8	10.4 %	4	30.8 %		
Photoreaction of pupils	yes	26	33.8 %	4	30.8 %	0.001	0.106
	Weak	47	61.0 %	4	30.8 %		
	No	4	5.2 %	5	38.5 %		
Nasolabial folds	Symmetric	77	100.0 %	10	76.9 %	p<0.001	p<0.001
	Asymmetric	0	0.0 %	3	23.1 %		

Note: $P_{\chi2}$ – Pearson's criterion, P_U – Mann-Whitney test.

The results of the descriptive data analysis revealed statistically significant differences in several parameters among patients with a fatal outcome, including lower blood oxygen saturation, increased liver size, resistance index in the anterior cerebral artery, and FTOE values ($P\chi^2$<0.05, P_U<0.05).

The final predictive model included 14 variables. The next step involved constructing receiver operating characteristic (ROC) curves for the prognostically significant indicators. This approach was used to evaluate the clinical relevance of the predictors and to determine the optimal threshold values for the test, maximizing both sensitivity (the probability of correctly identifying deceased patients) and specificity (the probability of correctly identifying surviving patients).

Fig. 1 presents the ROC curve, illustrating the predictive accuracy of mortality at varying threshold levels for the following parameters: blood oxygen saturation, liver size, resistance index in the anterior cerebral artery, and FTOE value.

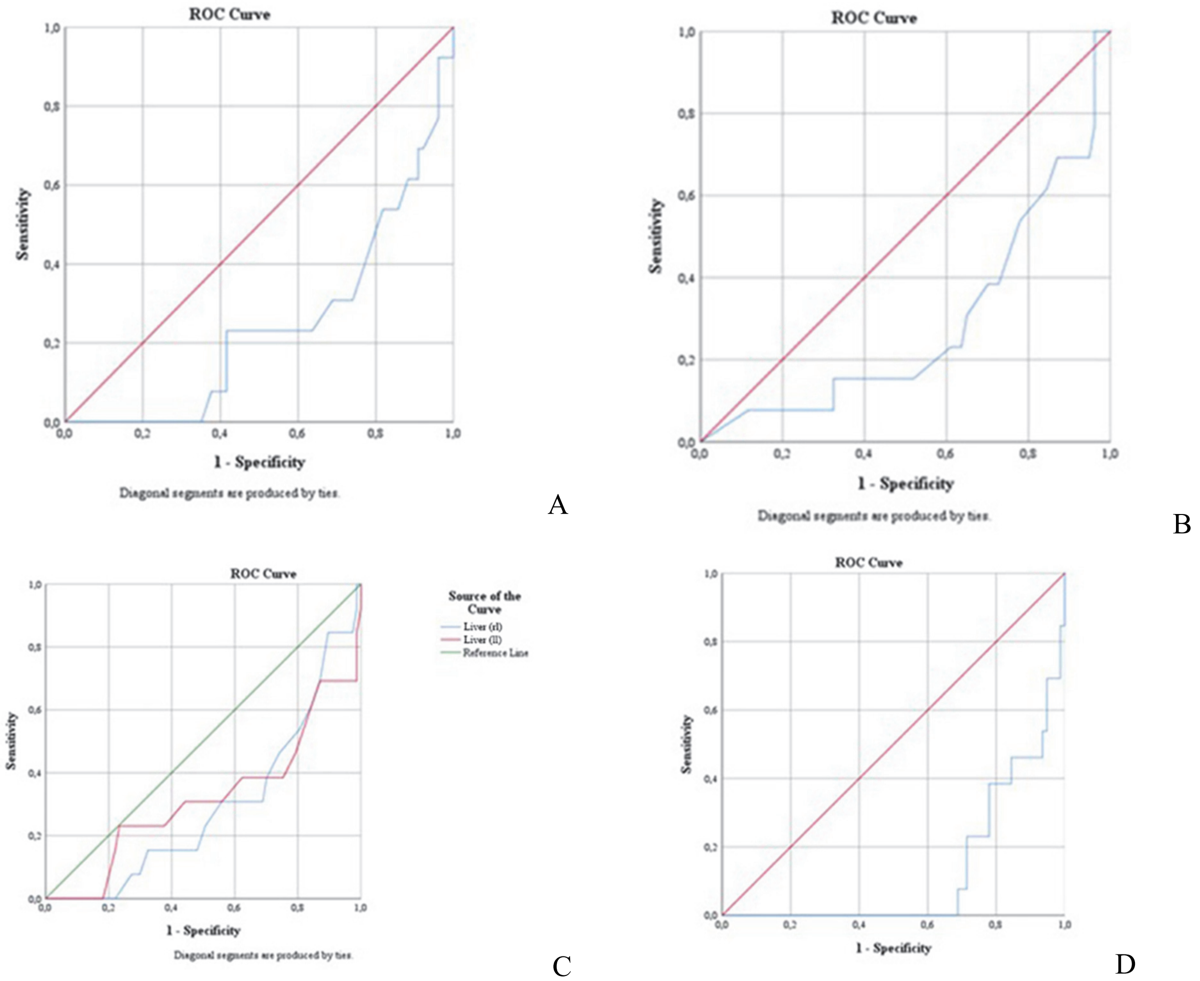

Fig. 1. Receiver operating characteristic (ROC) curve for the prognostic predictors. A) sO_2– blood oxygen saturation; B) IR– resistance index in the anterior cerebral artery; C) Liver size: rl–right lobe, ll–left lobe; D) FTOE–Fractional tissue oxygen extraction

The area under the curve (AUC) values were as follows: 0.243±0,067; 95 %CI: 0.111–0.375; p=0.003 for blood saturation (sO_2), 0.286±0.079; 95 %CI: 0.132–0.440; p=0.014 for the resistance index (RI), 0.293±0.072; 95 %CI:0.151–0.435; p=0.018 for the size of the right liver lobe, 0.318±0.089; 95 %CI:0.144–0.492; p=0.037 for the size of the left liver lobe, and 0.129±0.041; 95 %CI: 0.048–0.210; p<0.001 for FTOE. These findings highlight the high predictive accuracy of the model in estimating the likelihood of mortality in hypoxic-ischemic encephalopathy.

Consequently, these parameters may serve as reliable early-stage predictors of outcomes in HIE, enabling timely and targeted therapeutic interventions.

Cut-off points (threshold values) were calculated to establish levels that differentiate between positive and negative test results. These thresholds – sO_2 at 1.432, IR at 1.405, right liver lobe size at 1.38, left liver lobe size at 1.368, and FTOE at 1.688 – offer critical benchmarks for clinical decision-making and enhance the precision of early-stage prognostication in HIE management.

The analysis of the informativeness of significant indicators revealed that several variables, including the type and nature of nutrition, level of consciousness, liver size as assessed by ultrasound, anterior cerebral artery resistance index measured through neurosonography, and FTOE values determined by cerebral spectroscopy, demonstrate a notably high degree of diagnostic significance. Among these, consciousness and FTOE values exhibit the highest sensitivity at 100 %, while nutrition, IR, and liver size show sensitivity levels of 84.6 %, 76.9 %, and 69.2 %, respectively. However, the specificity of these indicators is relatively low, with values of 63.6 % for nutrition, 57.1 % for consciousness, 68.8 % for liver size, 63.6 % for IR, and 68.8 % for FTOE. The overall diagnostic value (ODV) for all indicators exceeds 60 %, indicating their utility in distinguishing between positive and negative outcomes.

The high negative predictive value (NPV) of these factors highlights the reliability of a negative test result in accurately ruling out the presence of the condition or factor of interest. While these indicators demonstrate good sensitivity, their specificity remains limited, reducing the diagnostic utility of positive test results. Consequently, these factors are most reliable for ruling out the presence of a condition when test results are negative, rather than confirming its presence with positive results.

To improve the accuracy of the model and avoid unnecessary complexity, we analyzed predictors for multicollinearity. The Spearman rank correlation coefficient (ρ) was calculated for this purpose. Predictors with ρ values exceeding 0.70 were excluded from the study. Table 4 provides a subset of the correlation analysis of predictors. A positive correlation was observed between lethality and nutritional types ($\rho=0.325$, $p<0.05$), as well as between lethality and consciousness level ($\rho=0.386$, $p<0.05$). Conversely, a negative correlation was identified between lethality and liver size ($\rho=-0.252$, $p<0.05$). Furthermore, blood oxygen saturation exhibited a negative correlation with both the PMA resistance index ($\rho=-0.261$, $p<0.05$) and FTOE (fractional tissue oxygen extraction) ($\rho=-0.452$, $p<0.05$). These findings provide a deeper understanding of the factors influencing outcomes in hypoxic-ischemic encephalopathy and highlight key variables to consider when developing a prognostic model.

Correlation analysis plays a pivotal role in identifying relationships between independent and dependent variables. This process is critical for understanding data structure and selecting the most significant predictors for inclusion in logistic regression models. To construct the predictive model, three variable selection methods – Enter, Forward, and Backward – were applied, each tailored to logistic regression.

The Enter method adds variables to the model in a single step based on their statistical significance. In this analysis, nine predictors were incorporated. The classification accuracy of the resulting model was 96.7 %, indicating that it correctly identified the status (survivor or deceased) of 96.7 % of all patients in the sample. This high value underscores the model's strong predictive capability. Classification accuracy, while a straightforward measure of model performance, provides an intuitive understanding of how well the model distinguishes outcomes within the data (Table 2).

Table 2

Logistic Regression, Forward

Variables not in the Equation					
			Score	df	P
Step 1	Variables	Childbirth	1.715	1	0.190
		Feeding	5.016	1	0.025
		Consciousness	5.900	1	0.015
		Eye movements	4.871	1	0.027
		Pupils	5.510	1	0.019
		Liver (rl)	5.749	1	0.016
		Liver (ll)	3.096	1	0.078
		sO_2	17.240	1	0.000
		IR	3.018	1	0.082
	Overall Statistics		27.052	9	0.001
Step 2	Variables	Childbirth	0.426	1	0.514
		Feeding	1.846	1	0.174
		Consciousness	1.829	1	0.176
		Eye movements	2.911	1	0.088
		Pupils	1.381	1	0.240
		Liver (rl)	6.344	1	0.012
		Liver (ll)	2.841	1	0.092
		IR	3.270	1	0.071
	Overall Statistics		12.615	8	0.126
Step 3	Variables	Childbirth	0.993	1	0.319
		Feeding	3.223	1	0.073
		Consciousness	0.459	1	0.498
		Eye movements	1.781	1	0.182
		Pupils	0.248	1	0.618
		Liver (ll)	0.705	1	0.401
		IR	2.843	1	0.092
	Overall Statistics		8.130	7	0.321

The Forward method, similar to the Enter method, evaluates variables for inclusion using additional criteria to optimize model performance. This method was conducted in three stages:

– Step 1 included nine predictors.

– Step 2 excluded one predictor.

– Step 3 retained seven predictors.

Despite the exclusion of two variables, the percentage of correct classifications remained high at 93.3 %. This retention of seven predictors suggests that the model prioritizes these variables as the most informative for classification, maintaining robust predictive accuracy.

The Forward Wald method, an extension of the Forward method, automates variable selection by evaluating the statistical significance of model coefficients using the Wald test. After three stages, this method yielded a model with six predictors and a classification accuracy of 93.3 %. This result confirms the efficacy of these predictors in explaining variability in the dependent variable and underscores their contribution to the model's predictive strength.

The Backward method begins with the inclusion of all variables in the model and sequentially removes the least significant ones based on a specified criterion, such as the p-value.

– In Step 1, the model started with nine predictors.

– Through an iterative process over five additional steps, the model excluded less informative variables, ultimately identifying five optimal predictors.

These five variables demonstrated sufficient explanatory power, resulting in a high classification accuracy of 96.7 %. This performance highlights their significance in predicting outcomes.

The Backward Wald method combines the backward elimination approach with the Wald test to refine variable selection further. Variables with the lowest statistical significance (highest p-value) are sequentially removed until an optimal set of predictors is identified. Over six steps, this method retained four predictors, which were deemed the most informative for classification and predictive modeling.

The model based on five variables demonstrates a high degree of predictive accuracy and may be valuable for further analysis or practical applications. The final logistic regression equation includes only the following parameters:

– Feeding (F): breastfeeding – 0, mixed – 1, artificial – 2, parenteral – 3;

– Liver size (right lobe RL);

– Blood saturation (sO_2);

– Resistance index (IR);

– Fractional tissue oxygen extraction (FTOE).

$Pp=40.836+1.008\times F - 0.207\times RL - 0.272\times sO2 - 6.074\times IR - 80.334\times FTOE$

The formula thus calculates the probability (P) of an unfavorable outcome for newborns with HIE who have experienced perinatal asphyxia.

In the other works the researchers found out that the outcomes in children with HIE might be related to motor and cognitive abilities [3].

Ramirez A, et al, studying 62 subjects with HIE to understand the features of development after neurological damages. But compered to our study they conducted the comparable evaluation with 35 subjects with congenital heart disease (CHD) to reveal the differences in the effects of HIE and CHD on the development of network topological parameters and functional outcomes. According to their findings, CHD newborns had worse 12–18month language ($p<0.01$) and 30month cognitive ($p<0.01$), language ($p=0.05$), motor outcomes ($p=0.01$). However, the other data such as global efficiency, a metric of brain integration, was lower in CHD ($p=0.03$) than in HIE, but transitivity, modularity and small-worldness were similar [8]. We assessed short-term outcomes, and long-term outcomes will be the objectives of our future studies.

With the purpose to build an evidence-based model to estimate case-specific risk of perinatal hypoxic ischemic encephalopathy Leith WM, et al (2023) performed a retrospective, cross-sectional study of all births in some USA, using linked maternal labor/delivery and neonatal birth records. They also used stepwise logistic regression and ROC-analysis to identify the most predictive ability of the parsimonious model. The authors revealed that the final model confirmed known risk factors (e.g., sentinel events and shoulder dystocia) and identified novel risk factors, such as maternal race and insurance status. That study showed the similar results with our work: the risk of perinatal hypoxic-ischemic encephalopathy can be estimated with a high degree of reliability [6].

Conclusion

The study successfully developed a predictive logistic regression model for adverse outcomes in term neonates diagnosed with hypoxic-ischemic encephalopathy and perinatal asphyxia. Using multiple variable selection methods, including Enter, Forward, Backward, and Wald-based approaches, we identified key predictors that contribute significantly to the prognosis of these neonates. The high classification accuracy achieved across all methods (ranging from 93.3 % to 96.7 %) indicates the robustness and reliability of the model, demonstrating its potential in clinical settings for predicting neonatal outcomes.

The variables identified as most informative, including clinical, anamnestic, and laboratory parameters, offer valuable insights into the factors influencing the prognosis of HIE. These predictors are crucial for guiding clinical decision-making, particularly in stratifying risk and determining the need for more aggressive interventions. Furthermore, the model's ability to accurately predict both mortality and long-term neurodevelopmental impairments emphasizes its relevance for both immediate and future care planning.

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