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PROGNOSTIC BIOMARKERS IN CONGENITAL HEART DISEASE

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This study aimed to assess the diagnostic significance of N-terminal pro-B-type natriuretic peptide in detecting and evaluating disease severity in infants less than one year of age with congenital heart disease. Results showed, that N-terminal pro-B-type natriuretic peptide levels in critically ill infants with congenital heart anomalies were approximately 10 times higher than in healthy infants (p<0.001). However, the difference in N-terminal pro-B-type natriuretic peptide levels between survivors and non-survivors were not statistically significant, though there was a notable high deviation in the non-survivors group. We observed a statistically significant increase in lactate levels in the deceased group compared to survivors, with a positive correlation between lactate and N-terminal pro-B-type natriuretic peptide levels (rho=0.333; p=0.003). These findings highlight the importance of monitoring both N-terminal pro-B-type natriuretic peptide and lactate levels as key biomarkers for predicting outcomes in critically ill infants.

Key words: congenital heart anomalies, NT-proBNP, lactate, mortality risk indicator, infants.

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ПРОГНОСТИЧНІ БІОМАРКЕРИ ПРИ ВРОДЖЕНИХ ВАДАХ СЕРЦЯ

Метою даного дослідження була оцінка діагностичної значущості N-кінцевого пропептиду мозкового натрійуретичного пептиду у виявленні та оцінці тяжкості захворювання у немовлят віком до одного року з вродженими вадами серця. Результати показали, що рівні N-кінцевого пропептиду мозкового натрійуретичного пептиду у тяжкохворих немовлят із вродженими аномаліями серця були приблизно в 10 разів вищими, ніж у здорових немовлят (p<0,001). Однак різниця в рівнях N-кінцевого пропептиду мозкового натрійуретичного пептиду між тими, хто вижив, і тими, хто не вижив, не була статистично значущою, хоча в групі тих, хто не вижив, спостерігалося помітне високе відхилення. Ми спостерігали статистично значуще підвищення рівнів лактату в групі померлих, порівняно з тими, хто вижив, із позитивною кореляцією між рівнями лактату і N-кінцевого пропептиду мозкового натрійуретичного пептиду (rho=0,333; p=0,003). Ці результати підкреслюють важливість моніторингу рівнів N-кінцевого пропептиду мозкового натрійуретичного пептиду і лактату як ключових біомаркерів для прогнозування результатів у тяжкохворих немовлят.

Ключові слова: вроджені аномалії серця, NT-proBNP, лактат, індикатор ризику смертності, немовлята.

Congenital heart disease (CHD) is defined as a structural abnormality of the heart and/or great vessels resulting from intrauterine development [10]. The detection of congenital defects during the prenatal period or immediately after birth remains a significant challenge in modern medicine. Despite advancements in diagnostic techniques, a significant number of children with CHD remain undiagnosed until severe complications develop. These undiagnosed cases often lead to increased morbidity and mortality, highlighting the need for improved early detection strategies. Furthermore, delays in CHD diagnosis can significantly impact the long-term quality of life of these children, making early intervention critical [13].

CHD is one of the most common congenital anomalies worldwide, affecting approximately 9.5 per 1000 live births (0.8 %–1.2 %) [10]. However, the incidence and mortality rates of CHD exhibit substantial variability across different geographical regions and countries. Research indicates that CHD incidence varies by location, with reported rates ranging from 1.2 to 17 per 1000 live births. Although significant advancements in cardiology and cardiovascular surgery have led to a remarkable reduction in mortality, enabling most patients to reach adulthood, congenital heart anomalies still remain a leading cause of infant mortality and significantly impact quality of life. CHD accounts for approximately 3 % of infant deaths. Studies have demonstrated that timely detection and early intervention can reduce neonatal mortality rates from 2.0–3.0 per 1000 to 0.6–0.8 per 1000 live births [5].

Various diagnostic methods are being evaluated to increase early detection of cardiovascular diseases and reduce mortality rates. One such method is pulse oximetry screening, which aids in identifying critical CHD by facilitating early diagnosis in infants who were not prenatally diagnosed. Meta-analyses have shown that this screening test has a specificity of 99.9 %, a sensitivity of approximately 76 %, and a false-positive rate of 0.14 % for critical CHD [11]. While screening has become mandatory in many high-income nations, its implementation in low- and middle-income countries (LMICs) continues to pose challenges [1].

The 2016 European Society of Cardiology (ESC) guidelines recommend the use of brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) as clinical biomarkers for diagnosing and assessing heart failure [12]. In CHD, NT-proBNP has emerged as a valuable marker due to its correlation with ventricular dysfunction and hemodynamic status. Compared to BNP, NT-proBNP is more stable, with a significantly longer serum half-life (60–120 minutes vs. 20 minutes for BNP).

Cantinotti et al. (2015) highlighted the significance of BNP/NT-proBNP as an additional biomarker for screening, diagnosing, and managing congenital heart disease. The authors emphasized the clinical value of these peptides, particularly NT-proBNP, as key biomarkers in CHD due to their association with specific hemodynamic parameters [3]. The plasma half-life of NT-proBNP is approximately 1–2 hours. Cardiomyocytes in the heart's ventricles secrete pro-BNP, an inactive precursor, which is subsequently cleaved into BNP (biologically active) and NT-proBNP (biologically inactive) in a 1:1 ratio. Due to its greater stability, NT-proBNP appears in higher plasma concentrations than BNP.

Serum NT-proBNP levels correlate with the severity of left ventricular dysfunction and functional status, aiding in the differentiation of dyspnea caused by respiratory disorders from that due to heart failure. The diagnostic and prognostic value of NT-proBNP in heart failure has been well established. Numerous studies have underscored the importance of natriuretic peptide testing in heart failure management, from initial diagnosis to ongoing monitoring, leading to strong recommendations for their use in clinical practice [12].

Lactate is a well-recognized biomarker in critically ill patients, with elevated levels indicating anaerobic metabolism, tissue hypoxia, and hemodynamic compromise – factors that are particularly relevant in CHD [2]. Hyperlactatemia is a key indicator in shock states, resulting from anaerobic metabolism and reflecting inadequate oxygen delivery. Combining NT-proBNP with lactate measurements could enhance our understanding of the metabolic and hemodynamic alterations in critically ill CHD infants, potentially improving clinical outcomes.

The purpose of the study was to evaluate the diagnostic significance of NT-proBNP and the potential correlation between NT-proBNP and lactate levels in critically ill infants less than one year of age with congenital heart disease.

Materials and methods. The study was conducted at the Scientific Research Institute of Pediatrics named after K.Y. Farajova (Intensive Care Unit), Azerbaijan Republic in the period of 2020–2023. A total of 101 infants were included in the study, divided into two groups: those diagnosed with CHD (n=81) and a control group of healthy infants (n=20). Blood samples were collected from central or peripheral vessels and analyzed for NT-proBNP levels using Cobas E601 and Cobas E602 analyzers. The measurement range for NT-proBNP was 10–35,000 pg/ml. The Limit of Blank, Limit of Detection, and Limit of Quantitation were established according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) EP17-A2. Blood lactate levels were measured concurrently to assess their relationship with NT-proBNP and their prognostic value in the patient cohort.

Infants with renal failure, sepsis, or those who remained in the intensive care unit for less than 24 hours were excluded from the study. Specific types of congenital heart defects were not categorized. This approach ensured that the study focused on patients with the most severe forms of CHD, thereby providing more relevant clinical data.

The study adhered to the ethical principles set forth in the Declaration of Helsinki throughout its course. Approval for the research was granted by the Ethics Committee of Azerbaijan Medical University, allowing for the collection of additional blood samples from infants diagnosed with congenital heart disease (Ethics Approval No: 18.10.2024/36). Informed consent, both written and verbal, was obtained from the parents or legal guardians of all participating infants.

Statistical analyses were performed using IBM SPSS Statistics 26 software. The data were assessed using various statistical methods, including t-tests (Student-Bonferroni), U-Mann-Whitney tests, H-Kruskal-Wallis tests, and discriminant analysis (Chi-square Pearson). Variance analysis was conducted using the F-test (Fisher), and correlation analysis was performed using Spearman's Rho. A p-value of less than 0.05 was considered statistically significant, leading to the rejection of the null hypothesis [4].

Results of the study and their discussion. NT-proBNP testing was conducted in 55 out of 81 infants (67.9 %) with critical congenital heart disease within the first 28 days of life, in 21 infants (25.9 %) between 1 and 6 months, and in 5 infants (6.2 %) between 7 and 12 months. Among the total cohort, 56 infants (69.1 %) were male, and 25 infants (30.9 %) were female.

When analyzing the patient group based on gestational age, 22 infants (27.2 %) were classified as preterm (<37 weeks of gestation), while 59 infants (72.8 %) were born at term (≥37 weeks of gestation). The mean gestational age was 37.3±0.2 weeks. The average postnatal age of these patients was 38.6±7.1 days, and the mean birth weight was 2933.1±61.9 grams. Regarding the mode of delivery, 29 infants

(35.8 %) were born via vaginal delivery, while 52 infants (64.2 %) were delivered by cesarean section. The mean Apgar score at 1 minute was 6.3±0.1, with 40 infants (49.4 %) having a score below 7. At 5 minutes, the mean Apgar score increased to 6.8±0.1, with 19 infants (23.5 %) still scoring below 7.

In the control group, 10 out of 20 infants (50 %) were tested within the first 28 days, 3 infants (15 %) between 1 and 6 months, and 7 infants (35 %) between 7 and 12 months. Additionally, 5 infants (25 %) in the control group were preterm, while 15 infants (75 %) were full-term. The control group consisted of 17 male infants (85 %) and 3 female infants (15 %). The mean birth weight of the control group was 2957.5±107.7 grams, with 9 infants (45 %) born via vaginal delivery and 11 infants (55 %) delivered by cesarean section. The mean Apgar score at 1 minute was 7.7±0.2, and the mean score at 5 minutes was 8±0.1.

Upon examining the reasons for intensive care unit (ICU) admission, it was found that 33 patients (40.7 %) had no associated anomalies, 32 patients (39.5 %) had confirmed anomalies, and 16 patients (19.8 %) were suspected of having an anomaly. In terms of the type of anomaly, 80 patients (98.8 %) had structural anomalies, while 1 patient (1.2 %) had both structural and functional anomalies. Among these patients, multiple anomalies were identified in 12 cases (14.8 %). Of these, 4 patients (4.9 %) had concurrent gastrointestinal anomalies, 2 patients (5 %) had nervous system anomalies, 1 patient (1.2 %) had metabolic disorders, and 8 patients (9.9 %) had other types of anomalies.

In terms of treatment, 47 patients (58 %) required mechanical ventilation support, with a mean duration of 4.5±0.6 days. The average duration of parenteral nutrition was 1.9±0.3 days. A total of 9 patients (11.1 %) underwent surgical intervention. The mean length of stay in the intensive care unit was 10.8±0.9 days. As a result, 16 patients (19.8 %) in this cohort died.

The mean NT-proBNP value in the 81 infants with critical congenital heart disease was 12,811.6±810.7 pg/ml (range 445–40,163 pg/ml). In contrast, the control group of 20 infants had a mean NT-proBNP level of 135.6±14.0 pg/ml (range 78–320 pg/ml), which was a statistically significant difference ($p<0.001$).

When analyzing NT-proBNP levels for specific congenital heart defects, it was observed that the highest NT-proBNP values were seen in cases of Ebstein anomaly (19,643.3±5,652.5 pg/ml), followed by Fallot's tetralogy (15,163.2±1,368.0 pg/ml). The analysis of NT-proBNP values in relation to congenital heart defects is presented in Table 1.

Table 1

Analysis of NT-proBNP values of congenital heart defect anomalies

Type of CHD	Number of patients	NT-proBNP, mean value, pg/ml	Pf	Pu
Coarctation of the aorta	7	11651.7±1705.1	<0.001	<0.001
Aortic stenosis	4	13295.0±1454.3	<0.001	0.002
Aortic hypoplasia	3	10233.3±2316.8	<0.001	0.006
Atrial septal defect (ASD)	48	12228.2±1056.7	<0.001	<0.001
Atrioventricular Septal Defect(AVSD)	14	15816.6±2952.4	<0.001	<0.001
Dextrocardia	2	12136.0±7624.0	<0.001	0.022
Ebstein anomaly	3	19643.3±5652.5	<0.001	0.006
Tetralogy of Fallot	10	15163.2±1368.0	<0.001	<0.001
Transposition of the Great Arteries (TGA)	8	11993.8±2147.8	<0.001	<0.001
Patent Ductus Arteriosus (PDA)	14	16413.4±2497.9	<0.001	<0.001
Pulmonary Stenosis	24	12799.8±1617.6	<0.001	<0.001
Single ventricle	4	15782.5±1485.5	<0.001	0.002
Ventricular septal defect (VSD)	42	11290.7±837.8	<0.001	<0.001

Note: Pf – coefficient of significance (according Fisher F–test), Pu – coefficient of significance (according Mann-Whitney U–test).

Lactate and NT-proBNP levels were analyzed across different age groups. The mean lactate levels did not show significant variation between the age groups: 1–28 days (6.0±0.2 mmol/L), 1–6 months (5.9±0.5 mmol/L), and 7–12 months (6.3±1.1 mmol/L) ($p=0.943$). Lactate levels were recorded as follows: an average of 6.0±0.2 mmol/L in the first 28 days, 5.9±0.5 mmol/L from 29 days to 6 months, and 6.3±1.1 mmol/L from 6 to 12 months. For NT-proBNP, the values were slightly higher in the 1–28-day group (13,398.2±1,095.5 pg/ml) compared to the 1–6-month (10,951.9±1,082.4 pg/ml) and 7–12-month (12,060.0±3,438.4 pg/ml) groups, though the difference was not statistically significant ($p=0.442$).

Using Spearman's rho method, we found a significant positive correlation between lactate and NT-proBNP levels (rho=0.333; $p=0.003$).

In the group of surviving infants (65 infants, 80.2 %), the mean lactate level was 5.6±0.2 mmol/L, and the NT-proBNP level was 12,894.9±853.3 pg/ml. In the group of deceased patients (16 infants, 19.8 %), a significantly elevated blood lactate level was observed (7.9±0.8 mmol/L) ($p<0.001$ for lactate, $p=0.017$ for NT-proBNP). The NT-proBNP level in the deceased group was 11,903.8±2,371.2 pg/ml ($p=0.603$). As seen from the figures, although the difference in blood lactate levels between the surviving and deceased groups was statistically significant, the difference in NT-proBNP levels between the two groups was not statistically significant.

The use of biomarkers to predict outcomes in critically ill patients has gained considerable attention in recent years, especially in clinical conditions such as congenital heart disease. With the increasing prevalence of CHD diagnoses and the growing complexity of its management, the need for reliable prognostic tools has become even more critical. The NT-proBNP test has emerged as an essential tool for diagnosing heart failure and assessing the severity of cardiac pathology, offering valuable insights into patient prognosis. While it is widely recognized that NT-proBNP levels in patients with severe cardiac pathology are indicative of heart failure severity, we explored the role of this biomarker in predicting complications and mortality in children admitted to ICU with CHD diagnoses. Additionally, we evaluated lactate levels, which reflect tissue hypoxemia, and analyzed their correlation with NT-proBNP levels in hypoxia caused by heart defects, thereby assessing their prognostic value. BNP levels may serve as a prognostic criterion in patients admitted to cardiac intensive care units, indicating the presence of left ventricular volume and pressure overload in the presence of shunts and helping to identify overt cardiac disease in acute care settings [8].

Harris et al. identified NT-proBNP as a key biomarker for predicting the development of hemodynamically significant patent ductus arteriosus (HsPDA). They found that ventilation, hypoxia, and hemoglobin levels did not significantly affect NT-proBNP, although creatinine levels showed a positive correlation with NT-proBNP [6].

High end-diastolic pressure and increased ventricular wall stress are primary triggers for BNP synthesis [7]. BNP, a peptide hormone, regulates circulating blood volume and arterial pressure by stimulating diuresis, natriuresis, inhibiting renin and aldosterone synthesis, and inducing vasodilation. NT-proBNP levels rise due to increased intraventricular pressure during heart failure, and these levels correlate positively with the severity of heart failure.

In neonates, NT-proBNP concentrations are highest at birth and decrease nearly twofold within the first week of life. Measuring NT-proBNP levels can be useful for identifying newborns at risk for CHD and heart failure during the neonatal period. NT-proBNP levels decrease over time, from approximately 400 ng/L in the first 3 months to 138 ng/L in girls and 65 ng/L in boys by the age of 18 [8]. In our study, NT-proBNP levels were higher in infants with CHD in the first 28 days compared to older age groups (1–6 months and 6–12 months).

Several factors can influence BNP/NT-proBNP plasma concentrations in pediatric patients. Studies have shown that elevated BNP/NT-proBNP levels are more common in infants with conditions like maternal type 1 diabetes, premature birth, intrauterine growth restriction, cesarean delivery, multiple births, and prenatal stress. Serum NT-proBNP levels are also used to differentiate dyspnea caused by respiratory failure from that caused by heart failure, with higher levels correlating with more severe left ventricular dysfunction. NT-proBNP concentrations are highest in the first few days of life and decline rapidly during the first week, continuing a slower decline during the first month of life. High NT-proBNP and BNP values are seen in infants with hemodynamically significant PDA, pulmonary hypertension, bronchopulmonary dysplasia, retinopathy, inflammation or sepsis, and in premature infants [3].

In our study, 22 (27.2 %) of the patients were preterm, with 17 tested in the first 28 days, 5 between 1 and 6 months, and 7 of them died. Among infants diagnosed with CHD, NT-proBNP levels were highest in those with Taussig-Bing anomaly, followed by Ebstein's anomaly and AVSD. In our study, patients with PDA also exhibited other defects such as transposition of the great arteries, coarctation of the aorta, ASD, and VSD. Twelve patients were born at term (≥37 weeks), two at 36 weeks gestation, and other heart defects were observed alongside PDA.

A 2025 study emphasized that serum lactate, NT-proBNP, and serum albumin are reliable biomarkers for predicting adverse outcomes in children with CHD during the postoperative period [15]. Sulu et al. highlighted that the benefit of NT-proBNP in diagnosing heart disease in children could not be demonstrated, contrasting with studies in adults. Thus, randomized prospective studies are recommended to establish NT-proBNP's diagnostic value in distinguishing cardiac disorders from non-cardiac diseases in children [14].

Several researchers found that preoperative NT-proBNP levels predicted the length of pediatric ICU stays, additionally, blood lactate and NT-proBNP were identified as suitable prognostic indicators for the need for ventilatory support [9]. In our study, NT-proBNP was measured in 47 (58 %) of patients receiving mechanical ventilation, with an average duration of 4.5±0.6 days. In our study, blood lactate levels were significantly elevated in patients who died (p<0.001), suggesting lactate monitoring as a cost-effective tool for prognosis in critically ill infants with congenital heart anomalies. A positive correlation between NT-proBNP and lactate levels was also identified.

In our practice, patients with monitored NT-proBNP levels had an average ICU stay of 10.8±0.9 days. While we found no statistically significant difference in NT-proBNP levels between the surviving and deceased groups, the significant variability in the latter raises questions about whether NT-proBNP could be a predictor of mortality. Further research with larger patient cohorts is needed to clarify the role of NT-proBNP in predicting mortality in critically ill patients with congenital anomalies. Notably, the statistical deviation index in the deceased group was 2.8 times higher than in the survivors, indicating that NT-proBNP levels in some deceased patients were slightly elevated due to limited compensatory capacity in critical conditions. Elevated BNP synthesis occurs due to increased pressure in the heart cavities, and many of the deceased patients in our study received inotropic support to normalize their blood pressure.

Conclusions

1. NT-proBNP levels in critically ill infants with congenital heart anomalies were approximately 10 times higher than in healthy infants (p<0.001). However, the difference in NT-proBNP levels between survivors and non-survivors was not statistically significant, though there was a notable high deviation in the non-survivors group. Larger-scale randomized studies are necessary to explore NT-proBNP as a potential mortality predictor in critically ill infants with heart defects.

2. Conversely, we observed a statistically significant increase in lactate levels in the deceased group compared to survivors, with a positive correlation between lactate and NT-proBNP levels (rho=0.333; p=0.003).

These findings highlight the importance of monitoring both NT-proBNP and lactate levels as key biomarkers for predicting outcomes in critically ill infants. Further research is required to determine their combined potential for improving clinical outcomes and guiding treatment decisions.

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