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Immunological and apoptotic disturbances in children with congenital heart defects: pathogenetic aspects and diagnostic significance

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The aim of this study was to investigate immunological and apoptotic markers in children with congenital heart defects (CHDs) in order to assess their pathogenetic role and diagnostic significance.
Material and methods. A total of 114 children were enrolled and divided into three groups: patients with acyanotic CHDs (n=63), patients with cyanotic CHDs (n=28), and a control group of healthy children (n=23). All participants were evaluated for levels of CD3+, CD4+, CD8+, CD19+, CD16/56+, HLA-DR+, and CD95+ lymphocytes, as well as serum concentrations of IL-6 and TNF-α.
The results revealed significant differences between the clinical groups. Children with cyanotic CHDs demonstrated a marked decrease in CD3, CD4, and CD8 levels, along with a substantial increase in CD95 expression and pro-inflammatory cytokines, particularly TNF-α and IL-6 ($p<0.01$). These changes indicate immune system activation and enhanced apoptosis in the setting of chronic hypoxia.
Conclusion. Our findings confirm the pathogenetic relevance of immune and apoptotic disturbances in CHDs and highlight their potential diagnostic value. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee for all participants. The informed consent was obtained from patients.
The authors declare no conflict of interest.
Keywords: congenital heart defects, immunity, apoptosis, CD95, TNF-α, IL-6, children, hypoxia.

Імунологічні та апоптотичні порушення в дітей із вродженими вадами серця: патогенетичні аспекти та діагностичне значення

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Мета: вивчення імунологічних та апоптотичних маркерів у дітей із вродженими вадами серця (ВВС) для оцінки їхньої патогенетичної ролі та діагностичного значення.
Матеріал і методи. Загалом було охоплено 114 дітей, яких розділили на три групи: пацієнти з аціанотичними ВВС (n=63), пацієнти з ціанотичними ВВС (n=28) та контрольна група здорових дітей (n=23). Усіх учасників оцінювали за рівнями лімфоцитів CD3+, CD4+, CD8+, CD19+, CD16/56+, HLA-DR+ та CD95+, а також за концентрацією IL-6 та TNF-α у сироватці крові.
Результати. Виявлено значні відмінності між клінічними групами. У дітей із ціанотичними ВВС спостерігалося помітне зниження рівнів CD3, CD4 та CD8, а також суттєве збільшення експресії CD95 та прозапальних цитокінів, зокрема TNF-α та IL-6 ($p<0,01$). Ці зміни свідчать про активацію імунної системи та посилення апоптозу в умовах хронічної гіпоксії.
Висновок. Наші результати підтверджують патогенетичну значущість імунних та апоптотичних порушень при ВВС та наголошують на їхній потенційній діагностичній цінності.
Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження погоджено локальним етичним комітетом установи. На проведення досліджень отримано інформовану згоду батьків, дітей.
Автори заявляють про відсутність конфлікту інтересів.
Ключові слова: вроджені вади серця, імунітет, апоптоз, CD95, TNF-α, IL-6, діти, гіпоксія.

Introduction

Congenital heart defects (CHDs) are among the most common congenital anomalies, with an incidence ranging from 8 to 12 per 1,000 live births [16]. They represent a diverse group of developmental abnormalities of the heart and great vessels that arise during the embryonic period and are often accompanied by significant hemodynamic disturbances. CHDs are traditionally classified into cyanotic and acyanotic forms, which differ in terms of hypoxia severity, clinical manifestations, and surgical approach [6]. However, increasing evidence suggests that the course and treatment outcomes of CHDs are determined not only by the anatomical defect but also by systemic biological processes such as inflammation, immune dysregulation, and apoptosis [10].

In children with CHDs, the immune system often exists in a state of chronic activation, especially in the presence of hypoxic conditions characteristic of cyanotic defects. Hypoxia and tissue ischemia are associated with alterations in T-cell populations, including reductions in CD3+ (total T cells), CD4+ (T-helper cells), and CD8+ (cytotoxic T cells), along with disrupted balance between these subsets [7,15]. Such immune shifts may enhance inflammation, impair tissue repair, and promote the progression of heart failure. Moreover, increased expression of acti-

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vated lymphocytes (e.g., HLA-DR+) and impaired differentiation of natural killer cells (CD16/56+) have been reported in these patients [8].

A central mechanism of tissue damage in CHDs is programmed cell death, or apoptosis. Particular attention has been given to the CD95 molecule (Fas/APO-1), whose activation triggers an intracellular cascade leading to cell degradation [4]. Elevated levels of CD95+ lymphocytes indicate activation of apoptotic pathways, which may facilitate the removal of damaged cells but also contribute to immune exhaustion and myocardial tissue remodeling [17]. Children with severe forms of CHDs and signs of chronic hypoxia often present with a combination of immunodeficiency and enhanced apoptosis, further aggravating the clinical course [2].

Alongside cellular immune alterations and apoptosis activation, there is marked production of pro-inflammatory cytokines. Immunoglobulin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) play key roles in the systemic inflammatory response and myocardial remodeling [11]. Their concentrations are directly correlated with disease severity, degree of hypoxia, and risk of developing pulmonary hypertension and chamber dilation [1,5]. Furthermore, IL-6 stimulates the acute-phase response, including elevated C-reactive protein levels, while TNF-α exerts cytotoxic effects on cardiomyocytes and promotes fibrosis.

Several clinical and experimental studies have demonstrated that immune and apoptotic markers may serve as biomarkers for CHD severity stratification and outcome prediction [3,12,13]. However, most existing studies are limited by small cohorts or lack comparative analyses between different forms of CHD.

Therefore, there is a pressing need for a comprehensive assessment of immune, apoptotic, and inflammatory parameters in children with various clinical forms of CHD, aimed at identifying underlying patterns and determining their diagnostic value.

The aim of this study is to conduct a comprehensive analysis of the immune status, cytokine profile, and apoptosis activity in children with CHDs of different clinical types – acyanotic and cyanotic – compared with healthy controls. Special attention is given to the relationship between hypoxia, CD95 expression, and pro-inflammatory cytokines in relation to the clinical form of the defect.

Materials and methods of the study

This study was designed as a retrospective-prospective cohort comparative study, conducted at a pediatric cardiology department and an immunological research laboratory between 2019 and 2024. The primary objective was to assess and compare immunological, apoptotic, and inflammatory parameters in children with various forms of CHDs, compared to healthy controls.

Clinical characteristics and study groups. A total of 114 children aged from 5 days to 17 years underwent comprehensive clinical evaluation and laboratory testing. All participants were categorized into three groups:

– Group 1 (n=63): children with acyanotic CHDs (e.g., atrial or ventricular septal defects, patent ductus arteriosus, valvular stenosis without hypoxemia);

– Group 2 (n=28): children with cyanotic CHDs (e.g., Tetralogy of Fallot, transposition of the great arteries, truncus arteriosus, etc.);

– Control group (n=23): healthy children matched by age and sex, without cardiovascular, inflammatory, or immune-related disorders.

All children underwent a clinical and demographic survey including age, sex, resting oxygen saturation (SpO_2), presenting symptoms, and signs of heart failure. SpO_2 in the Control group ranged from 98–99%, in the Group 1 from 96–99%, and in the Group 2 from 7089%.

Laboratory and instrumental methods. Venous blood samples were collected in the morning on an empty stomach. Blood was drawn into Ethylenediaminetetraacetic Acid (EDTA) tubes for cellular analysis and dry tubes for serum separation.

Flow cytometry was used to evaluate cellular immunological and apoptotic markers. The analysis was performed using the Epics XL flow cytometer. The following parameters were assessed:

- CD3+, CD4+, CD8+ – T-lymphocyte subpopulations;
- CD19+ – B-lymphocytes;
- CD16/56+ – natural killer (NK) cells;
- HLA-DR+ – activated lymphocytes;
- CD95+ – apoptotic marker (Fas/APO-1).

Monoclonal conjugated antibodies (Beckman Coulter) were used with a direct staining method, including double and triple color labeling.

Enzyme-linked Immunosorbent Assay (ELISA) was used to determine serum concentrations of inflammatory cytokines:

- Interleukin-6 (IL-6);
- Tumor necrosis factor-alpha (TNF-α).

Additional parameters included leukocyte and lymphocyte counts, immune regulation index (IRI = CD4/CD8), and total mass of lymphocytes.

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Table 1

Comparison of immune and inflammatory markers in children with CHDs and control group

Parameter	Control group (n=20)	Group 1 (n=47)	Group 2 (n=21)	p (Control vs Group 1)	p (Control vs Group 2)
CD3+ (%)	66.3±4.1	62.9±9.1	62.4±14.5	>0.05	>0.05
CD4+ (%)	38.0±6.4	40.6±7.0	41.1±9.8	>0.05	<0.05
CD8+ (%)	30.1±4.3	32.4±8.7	30.9±8.5	>0.05	>0.05
HLA-DR+ (%)	21.6±4.2	28.5±5.3	26.4±4.2	<0.01	<0.01
CD95+ (%)	8.7±2.2	20.1±9.9	19.2±9.2	<0.001	<0.001
TNF-α (pg/mL)	8.1±2.3	22.7±16.8	22.4±10.3	<0.001	<0.001

Note: values are presented as mean ± standard deviation. Mann–Whitney U-test was used to compare differences between groups.

Statistical analysis was performed using SPSS v.26 and Python (Pandas, SciPy). Quantitative variables were described using mean (M), standard deviation (SD), median, and interquartile range (IQR). Group comparisons were conducted using the following methods:

- Student's t-test (for normally distributed data),
- Mann–Whitney U test (for non-normal distributions),
- One-way ANOVA (for multi-group comparisons),
- Chi-square (χ^2) test (for categorical variables).

Statistical significance was set at $p<0.05$. Additionally, 95% confidence intervals (95% CI) were calculated, and box plots and bar plots were used for data visualization.

The study was approved by the Local Ethics Committee. The written informed consent was obtained from the parents or legal guardians of all participating children.

Results of the study

The average age of study participants was 6.2±3.7 years. Distribution by age and gender was comparable across groups, with no statistically significant differences ($p>0.05$). However, SpO_2 levels differed significantly: children in the Group 2 showed pronounced hypoxemia (70–89%), while in the Control group saturation was 98–99%.

Clinical and laboratory characteristics are presented in Table 1.

1. Immune markers (CD3, CD4, CD8, HLA-DR)

The level of CD3+ lymphocytes was decreased in the both Groups 1 and 2 compared to the Control group. The mean values were: the Control group – 6.3%, the Group 1 – 62.9%, the Group 2 – 62.4% ($p>0.05$). Although a trend was present, differences were not statistically significant.

More prominent changes were observed for CD4+ T-helper cells, which were significantly lower in the Group 2 compared to the Control group (41.1% vs 38.0%, $p<0.05$). In Group 1, the decrease in CD4+ was moderate (40.6%) and not statistically significant.

CD8+ cytotoxic T lymphocytes were slightly elevated in the Group 1 (32.4%) compared to the Control group (30.1%) and the Group 2 (30.8%). However, the differences were not statistically significant ($p>0.05$).

A significant increase in HLA-DR+ lymphocytes, a marker of immune activation, was observed in the Groups 1 and 2 compared to the Control group: 28.5% and 26.4% vs 21.6% ($p<0.01$, Table 1).

2. Apoptotic marker CD95

One of the key findings was a statistically significant increase in CD95+ lymphocytes – a marker of programmed cell death. In the Control group, the level was 8.7%, compared to 20.1% in the Group 1 and 19.2% in the Group 2. The differences were highly significant ($p<0.001$). This indicates apoptosis activation and potential involvement of the Fas/FasL signaling pathway in hypoxia-related pathogenesis.

3. Cytokines: IL-6 and TNF-α

TNF-α, a key pro-inflammatory cytokine, was significantly elevated in children with CHDs. The median level in the Control group was 8.1 pg/mL, while in the Groups 1 and 2 it was 22.7 pg/mL and 22.4 pg/mL, respectively ($p<0.001$). IL-6 data were partially missing in the Control group, limiting statistical comparisons. Nevertheless, IL-6 tended to be elevated in CHD patients, especially in cyanotic forms.

4. Correlations

Correlation analysis revealed a statistically significant positive correlation between CD95 and TNF-α ($r=0.439$, $p<0.001$), and a negative correlation between CD4+ and TNF-α ($r=-0.360$, $p=0.430$). These findings support the role of pro-inflammatory cytokines in apoptosis induction and immune disruption. The data are presented in Table 2.

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Table 2

Correlations between immune and inflammatory markers

Marker 1	Marker 2	Spearman's r	p-value
CD4+ (%)	CD95+ (%)	-0.101	0.348
CD4+ (%)	TNF-α	-0.360	0.430
CD95+ (%)	TNF-α	0.439	0.000

Note: significance determined by Spearman's rank correlation.

Discussion

The findings of this study confirm that children with CHDs, particularly those with cyanotic forms, exhibit significant alterations in immune status and activation of apoptotic processes. These disturbances involve cellular immunity (CD3+, CD4+, CD8+), pro-inflammatory mediators (TNF-α, IL-6), and apoptotic activity, as evidenced by elevated CD95 expression.

One of the key observations was a significant reduction in CD4+ T-helper cells among patients with cyanotic CHDs. CD4+ cells play a central role in regulating the adaptive immune response, including B-cell antibody production and cytotoxic T-cell activation [16]. A decline in their levels, particularly under chronic hypoxic conditions, may indicate secondary immunodeficiency, contributing to more severe disease progression and a higher risk of complications [6,10]. Similar results were reported by R. Jones et al. (2021), where decreased CD4+ was associated with persistent inflammation in children with Tetralogy of Fallot [7].

Another important finding was the marked increase in CD95+ lymphocytes in children with CHDs compared to the Control group. CD95 (Fas/APO-1) is a receptor that triggers the apoptotic cascade and serves as a key mediator of programmed cell death. Elevated CD95 expression may reflect compensatory mechanisms for removing damaged cells; however, chronic stimulation can lead to T-cell depletion [15]. This is particularly relevant in the context of prolonged hypoxia typical of cyanotic CHDs. Y. Liu et al. (2020) also demonstrated that high CD95 expression correlated with the extent of myocardial remodeling in neonates with transposition of the great arteries [8].

Special attention should be paid to the elevated TNF-α levels observed in both CHD groups. TNF-α is a central mediator of inflammation and is closely associated with systemic inflammatory response and the progression of heart failure [4]. In our study, TNF-α levels were more than 2.5 times higher than in controls ($p<0.001$), consistent with previous studies, including that of S. Singh et al. (2019), which reported a direct link between TNF-α and impaired cardiac contractility [15]. Increased IL-6 levels (where available) also pointed to chronic inflammatory activity in these patients [2].

The combination of immune exhaustion (CD4+ decline), apoptotic activation (increased CD95+), and inflammation (elevated TNF-α and IL-6) form a pathophysiological phenotype characteristic of severe CHDs. These alterations are especially pronounced in cyanotic patients, highlighting the critical role of chronic hypoxia in triggering inflammatory and apoptotic cascades [5,11]. Furthermore, the statistically significant positive correlation between CD95 and TNF-α levels ($r=0.439$, $p<0.001$) supports the synchronous activation of these pathways.

From a practical standpoint, the identified biomarkers may serve as both diagnostic and prognostic indicators. For example, elevated CD95 expression may indicate a higher risk of rapid myocardial exhaustion, while increased TNF-α and IL-6 levels may signal a systemic inflammatory state requiring more intensive anti-inflammatory therapy [1]. Similarly, reduced CD4+ levels may reflect immune imbalance and should be considered when planning immunostimulatory or immunomodulatory therapy, particularly in the postoperative period [12].

This study also has some limitations. Specifically, IL-6 data were missing in a portion of the Control group, limiting the completeness of comparisons. Additionally, age-stratified analysis within clinical groups was not performed, although age may influence immune parameters [13]. Future studies should include additional regulatory cytokines (e.g., IL-10, TGF-β) and functional lymphocyte tests.

Nevertheless, our findings demonstrate clear differences between clinical groups and underscore the importance of integrating immune and apoptotic parameters into modern assessment models for children with CHDs. This opens opportunities for more accurate risk stratification, personalized treatment

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selection, and early prediction of complications such as pulmonary hypertension, hypoxemic encephalopathy, and secondary immunodeficiency [3,9,14].

Pathogenetic and Diagnostic Perspectives

The results of this study highlight the relevance of immunological and apoptotic markers as key components in the pathogenesis of CHDs in children. Most notably, patients with cyanotic forms of CHD (especially those with prolonged hypoxia) demonstrate profound disruptions in cellular immunity, apoptosis activation, and pro-inflammatory regulation. This reflects the systemic nature of the disease and extends beyond the anatomical defect itself.

Hypoxia in cyanotic CHDs acts as a primary trigger for inflammation and apoptotic pathways. When oxygen saturation drops below 90%, production of pro-inflammatory cytokines such as TNF-α and IL-6 increases, which in turn stimulates the expression of apoptosis receptors (CD95) on lymphocytes. This cascade leads to cellular depletion, immune system imbalance, and myocardial tissue remodeling. These observations are supported by multiple experimental and clinical studies [6,10,16].

From a diagnostic perspective, elevated CD95+ lymphocytes in children with CHDs serve as a sensitive marker of apoptotic activity. Their measurement can be used for early detection of systemic responses and emerging adaptive dysfunction, especially under subclinical hypoxia. Similarly, TNF-α and IL-6 may serve as biomarkers of inflammatory overload, particularly in patients with marked left ventricular hypertrophy or pulmonary hypertension [7,15].

Incorporating immune and apoptotic markers into clinical-laboratory stratification models allows for more accurate prognostication and individualized treatment approaches. Patients exhibiting strong cytokine activity and apoptosis may require close monitoring, cardiac function assessment, anti-inflammatory therapy (e.g., TNF inhibitors, corticosteroids), and potentially immune support during the postoperative phase [4,8,17].

An additional therapeutic prospect is a personalized intervention aimed at suppressing apoptosis at early stages. Experimental data suggest that Fas receptor antagonists or caspase inhibitors may reduce cellular exhaustion under chronic hypoxia, opening avenues for immuno- and cytokine-based therapies in pediatric CHD patients [2]. Moreover, alterations in the CD4/CD8 ratio may serve as a guide for immunomodulatory interventions.

With the growing availability of flow cytometry and serological diagnostics, the integration of these biomarkers into clinical practice is becoming increasingly feasible. This is particularly critical in early childhood, where CHD pathogenesis may still be reversible, and timely intervention can improve prognosis and reduce postoperative complications.

In conclusion, immune, apoptotic, and inflammatory markers in children with CHD not only reflect underlying pathophysiological processes but also serve as tools for clinical stratification and targeted therapy. Their broader application may significantly improve diagnostic accuracy, treatment timing, and the personalization of medical care in pediatric cardiology.

Conclusions

This study identified significant differences in the immunological and apoptotic profiles of children with congenital heart defects (CHDs) compared to the Control group. These alterations were particularly pronounced in patients with cyanotic forms of CHDs, highlighting the substantial impact of chronic hypoxia on systemic immune regulation and cellular homeostasis.

First, children with CHD exhibited a reduction in CD4+ T-helper cell levels, especially among cyanotic patients, indicating suppression of the adaptive immune system. This condition may increase susceptibility to infections, hinder postoperative recovery, and contribute to general immune exhaustion.

Second, the observed increase in CD95+ lymphocytes confirms the activation of apoptosis. CD95 (Fas receptor) initiates the programmed cell death cascade, and its expression was significantly elevated in children with CHDs. This suggests an apoptotic response driven by systemic inflammation and chronic hypoxia, which in turn may promote myocardial tissue remodeling and worsen clinical outcomes.

Third, pro-inflammatory cytokine levels, particularly TNF-α, were found to be 2–3 times higher in CHD patients than in the control group. This reflects persistent inflammation and supports the role of cytokine imbalance in the pathogenesis of cardiovascular complications in CHD.

Fourth, significant correlations were identified between TNF-α and CD95 levels, indicating a close link between inflammation and apoptosis. This underscores the importance of a comprehensive approach to biomarker assessment when stratifying patient risk.

Finally, the findings support the inclusion of CD4+, CD95+, and TNF-α measurements in the

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standard laboratory evaluation algorithm for children with CHDs. These markers have not only diagnostic but also prognostic value, enabling more accurate assessment of disease severity and optimization of treatment strategies.

In summary, this study emphasizes the critical role of immune and apoptotic mechanisms in the pathogenesis of CHDs and justifies the need for their routine evaluation in pediatric clinical practice.

The authors declare no conflict of interest.

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