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ORIGINAL RESEARCH

Early Clinical Markers of Developmental Vulnerability in Congenital Heart Disease: Pathobiological Implications for Adult Cardiovascular Emergencies

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ABSTRACT

Background: Congenital heart defects (CHDs) are the most prevalent birth anomalies and result from complex genetic and environmental factors. Beyond structural abnormalities, adverse intrauterine conditions may influence fetal development and contribute to long-term health outcomes. This study aimed to evaluate clinical and hematological markers of developmental vulnerability in a cohort of patients with CHD. **Materials and Methods:** A retrospective clinical analysis was conducted in 52 pediatric patients at the Institute of Cardiovascular Diseases (IBCV), Iași, Romania. Maternal clinical histories, hematological parameters (hemoglobin [Hb] and white blood cell [WBC] count), and neonatal parameters (birth weight, Apgar score, and birth Z-score) were analyzed. **Results:** Mean birth weight was 3,043.46 ± 642.34 g. Patients with cyanotic CHD had higher mean Hb concentrations than those with non-cyanotic CHD (13.82 vs. 12.82 g/dL), although the difference was not statistically significant ($p = 0.170$). Patients with identified genetic syndromes had significantly lower mean birth Z-scores than those without identified genetic syndromes (-1.26 vs. -0.57; $p = 0.028$). **Conclusions:** The lower birth Z-scores observed in patients with identified genetic syndromes suggest an association between genetic abnormalities and impaired fetal growth. The higher Hb concentrations observed in patients with cyanotic CHD, although not statistically significant, may reflect a compensatory response to chronic hypoxia. These readily available clinical parameters may provide additional information on developmental vulnerability in patients with CHD. Larger prospective studies are needed to clarify their potential role in long-term risk assessment and clinical follow-up.

Keywords: congenital heart defect, maternal environment, fetal programming, chronic hypoxia, genomic instability

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INTRODUCTION

Congenital heart defects (CHDs) are the most frequent major structural birth anomalies, affecting approximately 1% of live births globally.[1] Despite significant advancements in surgical interventions and neonatal intensive care, CHD remains a leading cause of infant mortality and long-term morbidity, necessitating a deeper understanding of the developmental trajectories initiated in early gestation. Human cardiogenesis is a highly regulated morphogenetic process that occurs within a narrow temporal window between the third and eighth weeks of development.[2] This complexity renders the embryonic heart exquisitely sensitive to disruptions in the delicate signaling pathways that govern cell fate, migration, and differentiation.

While traditional views centered primarily on monogenic causes, contemporary research has shifted toward a multifactorial model in which the maternal–fetal interface acts as a crucial modulator. The gestational environment is not merely a passive backdrop but a dynamic source of biochemical and physical signals that can modify or exacerbate genetic predispositions.[3] Disruptions in this environment, ranging from maternal metabolic disorders to environmental toxins, can lead to a cascade of developmental errors that extend beyond the anatomical boundaries of the heart.

A central pillar in understanding these long-term effects is the 'developmental origins of health and disease' (DOHaD) hypothesis, which suggests that environmental insults during critical windows of development can permanently 'program' an individual's physiology, increasing susceptibility to chronic diseases later in life.[4] In the context of CHD, this means that a malformation may not be an isolated event but a clinical manifestation of a broader systemic developmental shift.

Chronic tissue hypoxia, a hallmark of many cardiac defects, serves as an underlying factor for this reprogramming. When oxygen delivery is compromised in utero or in the early neonatal period, the fetus initiates compensatory mechanisms. These adaptations, while necessary for immediate survival, often involve epigenetic modifications that alter gene expression across multiple organ systems.[5] This biological 'memory' of early-life stress establishes a pathobiological foundation that may remain subclinical for decades before manifesting as complex adult-onset pathologies.

The objective of this study was to evaluate the clinical and hematological markers of fetal vulnerability in a cohort of patients with CHD. By examining the association between genomic syndrome status and fetal growth and comparing hematological parameters between cyanotic and non-cyanotic CHD, we aimed to explore whether routine clinical data may provide insight into developmental vulnerability in these patients.

MATERIALS AND METHODS

STUDY DESIGN AND SETTING

A retrospective, single-center cohort study was conducted to evaluate the clinical and pathobiological trajectories of pediatric patients diagnosed with CHD. The research was carried out at the Prof. Dr. George I.M. Georgescu Institute of Cardiovascular Diseases (IBCV) in Iași, Romania. The cohort comprised 52 pediatric patients who underwent comprehensive diagnostic evaluation and management at our institution between January 2015 and June 2025.

ELIGIBILITY CRITERIA AND STUDY POPULATION

Patient inclusion was governed by rigorous eligibility criteria to ensure data integrity and clinical relevance. The inclusion criteria were: 1) a confirmed diagnosis of CHD, 2) signed informed consent, and 3) a complete and accessible medical record including detailed family history, gestational course, and birth metrics.

Patients were excluded if they had incomplete demographic records, missing baseline anthropometric measurements at birth (including weight or Apgar scores), or missing admission laboratory profiles. Genetic syndromes were diagnosed based on karyotype analysis. Genetic evaluation was not routinely performed in the entire cohort but was selectively conducted in patients with clinical features suggestive of a syndromic condition.

DATA COLLECTION AND CLINICAL PARAMETERS

Clinical and pathobiological variables were extracted from the patients' observation charts and neonatal records. To construct a comprehensive profile of developmental vulnerability, the extracted data were stratified into three major domains:

1. Maternal and gestational environment: This domain included the presence of maternal chronic medical conditions, acute gestational infections, and associated genetic syndromes identified in the newborn.

TABLE 1. Summary of baseline neonatal anthropometric and clinical characteristics of the CHD cohort (n = 52).

Descriptive statistics	Valid	Missing	Mean (arithmetic)/ Frequency (%)	Std. deviation	Minimum	Maximum
Birth weight (g)	52	0	3,043.46	642.34	2,000	4,660
Environment (rural/urban)	52	0		37 (71.1%)/ 15 (28.9%)	N/A	N/A
Sex (female/male)	52	0	27 (51.9%)/ 25 (48.1%)	N/A	N/A	N/A
Apgar score	51	1	8.39	0.72	7	10

N/A, not applicable. Note: Apgar score valid data was available for n = 51 patients

2. Fetal anthropometric and developmental indices: Key measures of fetal growth and neonatal status included birth weight, birth Z-score (to quantify growth restriction), and the Apgar score as an immediate indicator of neonatal vitality.
3. Hematological biomarkers of systemic stress: Routine admission laboratory parameters, specifically hemoglobin (Hb) concentration and white blood cell (WBC) count, were collected to evaluate systemic physiological responses associated with the structural cardiac anomaly, including chronic hypoxia and inflammation. CHD severity was further classified into cyanotic and non-cyanotic phenotypes.

STATISTICAL ANALYSIS

All statistical analyses were performed using JASP v.96 (University of Amsterdam, The Netherlands). The analytical strategy was designed to link clinical observations with underlying pathobiological hypotheses.

Descriptive statistics were used to summarize the demographic and baseline clinical characteristics of the cohort, with means and standard deviations for continuous variables, and frequency distributions for categorical variables.

To investigate the associations of genetic factors and CHD severity with fetal development and hematological parameters, independent samples t-tests (incorporating Welch's correction where homogeneity of variances was not met) were used. Specifically, mean Z-scores were compared between patients with and without identified genetic syndromes, while hematological markers (Hb, WBC) were compared between CHD severity groups. Data normality and homogeneity of variances were assessed prior to conducting parametric tests. Statistical significance was established at $p < 0.05$.

RESULTS

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The study cohort comprised 52 pediatric patients diagnosed with CHD. The demographic distribution showed a slight female predominance (51.9% vs. 48.1%). A majority of the cohort (71.1%) were from rural areas, a factor that may reflect differences in access to prenatal care and potential exposure to unquantified environmental stressors.

Regarding fetal growth and neonatal status, the cohort had a mean birth weight of 3,043.46 ± 642.34 g. Neonatal status, assessed using the Apgar score, showed a mean value of 8.39 ± 0.72, indicating general hemodynamic stability at birth despite the underlying structural anomalies (Table 1). Retrospective assessment of maternal factors revealed a notably low prevalence of documented acute or chronic conditions, maternal infections and severe chronic diseases each being recorded in only 5.7% of the clinical charts.

HEMATOLOGICAL MARKERS AND COMPENSATORY RESPONSES TO HYPOXIA

To evaluate the systemic burden associated with the cardiac defects, routine admission hematological markers were analyzed as indicators of chronic hypoxia and systemic inflammation. The cohort was stratified by phenotypic severity into cyanotic and non-cyanotic groups.

The independent samples t-test assessing Hb concentrations revealed that patients with cyanotic CHD had a higher mean Hb level (13.82 g/dl) than those with non-cyanotic anomalies (12.82 g/dl), although the difference was not statistically significant ($p = 0.170$) (Figure 1).

In contrast, WBC counts, used as an indicator of systemic inflammation, were similar between the two groups (mean

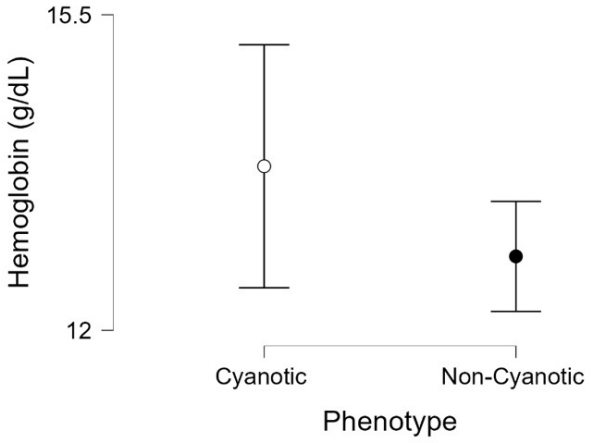

FIGURE 1. Boxplot distribution of admission Hb levels. The data illustrates a clinical compensatory polycythemic response in the cyanotic CHD group (mean, 13.82 g/dl) compared to the non-cyanotic group (mean, 12.82 g/dl).

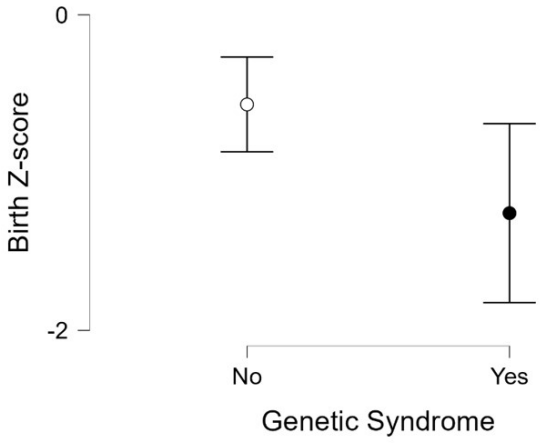

FIGURE 2. Distribution of birth Z-scores according to genomic status. The boxplot highlights the marked depression of fetal growth trajectories in patients with identified genetic disorders (mean Z-score, -1.26) versus the control group (mean Z-score, -0.57)

WBC, 9,697 cells/mm^3 in cyanotic vs. 9,507 cells/mm^3 in non-cyanotic patients; p = 0.825).

INTRINSIC GENOMIC VULNERABILITY AND FETAL GROWTH RESTRICTION

To assess fetal growth according to the presence of associated genetic abnormalities, the analysis focused on birth Z-scores. The cohort was stratified according to the presence or absence of an identified genetic syndrome.

An independent samples t-test showed a statistically significant difference in mean birth Z-scores between the two groups (p = 0.028; Table 2). Neonates with an identified genetic syndrome had a lower mean Z-score (-1.26) than those without an identified genetic syndrome (-0.57; Figure 2).

DISCUSSION

The present clinical analysis provides a pathobiological evaluation of the developmental vulnerabilities associated with CHD. By evaluating routine hematological biomarkers and measures of fetal growth, this study highlights two distinct but potentially intersecting aspects of CHD pathophysiology: physiological adaptation to chronic hypoxia and developmental vulnerability associated with underlying genetic abnormalities.

Our data revealed a trend toward higher Hb concentrations in cyanotic patients (13.82 g/dl) compared with their non-cyanotic counterparts (12.82 g/dl), although the difference did not reach statistical significance (p = 0.170). This trend is consistent with the well-documented erythropoietic response to chronic hypoxemia. Increased Hb concentration represents a compensatory mechanism that enhances the oxygen-carrying capacity of the blood and helps preserve tissue oxygenation.[8,9] However, when pronounced, secondary erythrocytosis may become maladaptive by increasing blood viscosity, impairing microcirculatory flow, and imposing an additional burden on the cardiovascular system.[10] Thus, Hb levels may provide an indirect indication of the chronic hypoxic burden experienced by patients with cyanotic CHD. In contrast, WBC counts were similar between the two groups, providing no evidence of differences in this marker of systemic inflammation according to cyanotic status. Nevertheless, the role of chronic low-grade inflammation in CHD is increasingly recognized. Hypoxia and hemodynamic instability may promote systemic inflammatory activity, oxidative stress, epigenetic reprogramming, and alterations in cellular signaling pathways.[11,12] In this context, the assessment of hematological markers may complement the anatomical characterization of CHD by providing insight into its systemic physiological conse-

TABLE 2. Welch's independent samples t-test analysis demonstrating the significant impact (p = 0.028) of identified genetic syndromes on fetal growth restriction (birth Z-score).

Independent samples t-test	t	df	p
Birth Z-score	2.502	11.65	0.028

df, degrees of freedom. Note: Welch's independent samples t-test was used to account for the unequal variances between the syndromic and non-syndromic groups. Statistical significance was established at p < 0.05.

quences. Over time, persistent hypoxic and inflammatory stimuli may contribute to adverse myocardial remodeling and increase susceptibility to ventricular dysfunction and arrythmias in adults with CHD.[13,14]

In this evolving epidemiological landscape,[15–17] the most significant finding of this cohort was the lower birth Z-score observed in patients with identified genetic syndromes ($p = 0.028$). This finding suggests a potential association between genetic abnormalities and impaired fetal growth.

The coexistence of CHD and an identified genetic syndrome adds another layer of developmental complexity. Genetic syndromes, including chromosomal abnormalities and pathogenic microdeletions, may act as intrinsic disruptors of cellular homeostasis, proliferation, and differentiation. These abnormalities may reduce the capacity of developing tissues to maintain normal growth trajectories, particularly in the presence of additional stressors such as hypoxia, inflammation, or altered placental function.[18–20] Therefore, whereas chronic hypoxia may be regarded as an environmental stressor to which the organism attempts to adapt, genetic abnormalities may directly interfere with the biological mechanisms governing fetal development and growth.

In clinical practice, the birth-weight Z-score provides a standardized measure of the extent to which fetal growth deviates from the expected value for gestational age. Consequently, a reduced Z-score in a patient with an identified genetic syndrome should not be regarded solely as an indication of lower birth weight. It may also reflect broader alterations in developmental pathways and an intrinsic susceptibility to additional pathobiological insults. Previous studies have linked fetal growth restriction to altered placental–fetal resource allocation, mitochondrial dysfunction, and disturbances in cellular energy metabolism during early development. Evidence derived from fetal programming studies further suggests that impaired early growth may contribute to subsequent endothelial dysfunction and vascular aging, potentially increasing long-term cardiovascular risk.[5]

Viewed through the lens of the DOHaD hypothesis, these findings suggest that intrauterine genetic and metabolic stressors may induce lasting biological changes, including alterations in pathways involved in the hypoxia response (HIF-1α), apoptosis, and cell proliferation. Such changes may involve pathways regulating the cellular response to hypoxia, including hypoxia-inducible factor 1α (HIF-1α), as well as apoptosis and cell proliferation.[21] Moreover, signaling pathways involved in cardiogenesis, including the Wnt, Notch, and Transforming Growth Factor β (TGF-β) pathways, also participate in fibrotic remodeling and adverse ventricular mechanics later in life. Therefore, disturbances in these pathways during fetal development may have implications extending beyond the formation of the structural cardiac defect.[3,22]

Thus, early clinical markers of vulnerability, such as a markedly reduced birth Z-score in patients with identified genetic syndromes, should be viewed not only as pediatric outcomes but also as potential indicators of long-term developmental vulnerability.[23] This framework extends the clinical perspective beyond the structural cardiac defect to the possibility of broader systemic consequences later in life, particularly progressive cardiovascular disease.[24]

While this study provides important pathobiological insights, several limitations must be acknowledged. First, the retrospective design relied on the accuracy and completeness of historical medical records, which may have resulted in the underreporting of subclinical maternal infections or mild gestational disorders (reflected in the 5.7% documentation rate). Second, the relatively small cohort ($n = 52$) from a single tertiary cardiovascular center may limit the generalizability of the findings. The study was also underpowered to detect modest differences in hematological markers, such as hemoglobin, where the observed trend ($p = 0.170$) warrants confirmation in larger cohorts. Finally, the subgroup of patients with confirmed genetic syndromes was small. Although the difference in birth Z-scores was reached statistical significance using Welch's t-test ($p = 0.028$), prospective studies with larger cohorts and precise molecular genetic screening are needed to validate these findings.

CONCLUSIONS

This study highlights the potential value of routine, accessible clinical parameters, including birth-weight indices and hematological markers, in assessing developmental vulnerability in patients with CHD. The lower birth Z-scores in patients with identified genetic syndromes suggest an association between genetic abnormalities and impaired fetal growth. The higher Hb concentrations observed in patients with cyanotic CHD, although not statistically significant, may reflect a compensatory response to chronic hypoxia. These readily available parameters may complement the anatomical assessment of CHD and provide additional information on its broader developmental and systemic effects. Larger prospective studies are needed to clarify their potential role in long-term risk assessment and clinical follow-up.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

The study was performed in strict adherence to the ethical principles outlined in the Declaration of Helsinki regarding medical research involving human subjects. The institutional research protocol was approved by the local Ethics Committee of the IBCV Iași (approval no. 167/01.07.2024).

CONSENT TO PARTICIPATE

Written informed consent was obtained from the parents or legal guardians of the pediatric patients prior to their inclusion in the study and subsequent data processing.

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AUTHOR CONTRIBUTIONS

P.C.M and C.F. conceived and designed the study. R.M. and O.E.F. collected the clinical data. R.O.C. curated the database and performed the statistical analysis. L.M. and S.M.D. interpreted the results. P.C.M. prepared the tables and figures and drafted the initial version of the manuscript. L.M. and R.O.C. critically reviewed the manuscript for important intellectual content. C.F. supervised the study and contributed to the final revision of the manuscript. All authors read and approved the final version of the manuscript and agreed to be accountable for the accuracy and integrity of the work.

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