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Association of Heme Oxygenase-1 Promoter Polymorphisms and Plasma Heme Oxygenase-1 Levels with Atrial Septal Defect–Associated Pulmonary Arterial Hypertension

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ABSTRACT

Pulmonary arterial hypertension is a serious complication of atrial septal defect driven by oxidative stress and vascular remodelling. Heme oxygenase-1 (HO-1), encoded by the HMOX1 gene, exerts antioxidant and cytoprotective effects, and its expression is influenced by promoter polymorphisms. This study investigated the association of $(GT)_n$ repeats, rs2071746, and plasma HO-1 levels with atrial septal defect-pulmonary arterial hypertension (ASD-PAH) in the Javanese population. A total of 101 participants from Dr. Sardjito Hospital, Indonesia, were enrolled, including 51 ASD-PAH and 50 ASD patients non-PAH. Hemodynamic parameters were assessed by echocardiography and right heart catheterization. Plasma HO-1 and endothelin-1 levels were measured using ELISA. HMOX1 polymorphisms were analyzed using PCR-based methods, and associations were evaluated by logistic regression. ASD-PAH patients showed significantly higher pulmonary vascular resistance (8.15 ± 6.36 vs. 4.41 ± 6.72 Wood units; p = 0.0014), mean pulmonary arterial pressure (48.57 ± 16.67 vs. 37.55 ± 19.00 mmHg; p = 0.01), and endothelin-1 levels (p = 0.04). Plasma HO-1 levels did not differ significantly. The L allele of (GT)n repeats increased ASD-PAH risk (OR = 2.04; p = 0.015), while the rs2071746 T allele showed a strong association (OR = 4.61; p < 0.001), with AT+TT genotypes conferring >10-fold risk. Multivariate analysis confirmed that the S allele and higher HO-1 levels reduced ASD-PAH risk. HMOX1 polymorphisms and HO-1 expression influenced ASD-PAH susceptibility. The S allele and elevated HO-1 are protective, while the L and T alleles increase disease risk, supporting their potential as complementary biomarkers.

Keywords: Atrial Septal Defect, Heme Oxygenase-1, Polymorphism, Pulmonary Arterial Hypertension

Introduction

Pulmonary arterial hypertension (PAH) is a condition assessed by three hemodynamic criteria assessed through right heart catheterization (RHC) examination: -i.e. mean pulmonary arterial pressure (mPAP) > 20 mmHg, pulmonary arterial wedges pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) ≥ 2 Wood units (WU).[1,2] Symptoms of early stage of PAH were not specifics, but can be observed for symptoms that point to right heart failure include shortness of breath, weakness, fainting, dry cough, nausea and vomiting associated with physical activity.[3] PAH is part of pre capillary pulmonary hypertension (group I) and can be classified into: -idiopathic PAH (IPAH), heritable PAH (HPAH), drug and toxin induced, PAH long-term responders to calcium channel blockers, PAH associated connective tissue diseases, HIV, and congenital heart disease (Eisenmenger syndrome, PAH associated with prevalent systemic-to-pulmonary shunts, PAH with small/coincidental defects). [4]

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The estimated prevalence of PAH is around 15 cases per million adults, [5] but estimated prevalence in some countries in Asia including Indonesia is still unknown. [6,7] PAH including congenital heart disease is associated with a number of ailment according to Shah and one of them is atrial septal defect (ASD), [4] with 6-35% of PAH shown to be associated with congenital heart disease mostly with uncorrected secundum ASD. [8] The pathogenesis of PAH probably entails multiple mechanisms. The imbalance between vasoconstriction and vasodilation in the pulmonary arteries results in the formation of neointima. The pathophysiology of PAH involved an imbalance of endothelin-1 (ET-1) as a vasoconstrictor and cell proliferation, meanwhile prostacyclin and nitrite oxide function as vasodilators. ET-1 stimulates cell proliferation, neointima formation and thickening of tunica media. In uncorrected secundum type ASD, shunts from left to right often occur and will stimulate inflammation. [4,9–12]

Heme oxygenase-1 (HO-1) is an intracellular enzyme responsible for catalyzing the degradation of heme into three byproducts ;i.e. carbon monoxide (CO), biliverdin, and ferrous iron (Fe^{2+}). These substances have anti-inflammatory, antioxidant, anti-apoptotic, and anti-proliferative effect.[13] HMOX1 gene also known as heat shock protein 32(HSP32) contains 4 introns and 5 exons. The gene encoding HO-1 in humans is located on chromosome 22q12, with a length of 6.8 kb HO-1 expressed in several organs including endothelial cells, smooth muscle cells and blood vessels.[14] HO-1 is an important regulator of smooth muscle cell function. HMOX1 overexpression suppresses smooth muscle cells proliferation by multiple mechanism including the upregulation of p21 expression and induction of cell cycle arrest at the

G0/G1 phase. The HMOX1 gene also blocks migration of vascular smooth muscle cells (VSMC) induced by platelet derivate growth factor (PDGF) through growth factor receptors inactive vascular endothelium-2/PDGF receptor β heterodimer that inhibits PDGF signal. [15]

Bile pigments;i.e. biliverdin and bilirubin function as scavengers of reactive oxygen species (ROS) and reactive nitrogen species (RNS) with a recycling mechanism, and bilirubin can suppress inflammatory responses and reduce cellular toxicity.[16] Biliverdin/bilirubin can inhibit proliferation of smooth muscle cell (SMC) in the cell cycle pathway. Inhibition of SMC growth by this pigment appears to involve suppression of the rapidly accelerated fibrosarcoma /Extracellular Signal-Regulated Kinase /Mitogen-Activated Protein Kinase (Raf/ERK/MAPK) signalling, acceleration of the expression of P53, hypophosphorylation of retinoblastoma protein, and lysis of protein yin yang 1(YY1).[15] CO can modulate the MAPK and p38β pathways to elicit antiapoptotic, antiproliferative, and anti-inflammatory properties. CO stabilizes hypoxia induction factor-1α(HIF-1α), a key regulator in macrophage function and angiogenesis. [16,17] CO also plays a role in inhibiting respiratory chain cytochromes and nicotinamide adenine dinucleotide phosphate oxidase (NOX), so it is associated with a decrease in ROS.[16] Heme elicits an inflammatory response through toll like receptor4 (TLR4). Specifically, iron released as a result from HO-1 activity facilitates catalysis of membrane lipid peroxidation and Fenton catalysis. Iron will be regulated by ferritin, which then converts the iron into an inactive form.[18,19] There are several studies that link HO-1 expression with the occurrence of PAH. Van Loon et al. 2015 in their study showed that in experimental PAH, erythropoietin treatment restored the number of circulating endothelial progenitor cells (EPCs) increasing pulmonary vascular remodelling, and showed an interaction with HO activity. Inhibition of HO activity in PAH *mice* increased pulmonary vascular remodelling.[20]

Polymorphism in promoter of HMOX1 gene can affect the expression of HO-1, we found that microsatellite $(GT)_n$ and rs2071746 (A>T) are responsible for some outcomes in lung function, fatty liver, pre-eclampsia and malaria especially for long allele (>24 repeat).[21–23] To date, no study has examined the combined role of HMOX1 $(GT)_n$ promoter polymorphisms, rs2071746 variants, and circulating HO-1 levels in congenital heart disease–related PAH within the Indonesian or broader Asian population. This study aimed to fill this knowledge gap, to examine the association of $(GT)_n$ repeat and rs2071746 in patient with ASD-PAH.

Materials and Methods

Study population

This was an observational study with a case–control design. Fifty-one patients with ASD-PAH were enrolled as the case group, while 50 patients with ASD with non-PAH served as the control group at the Integrated Heart Center, Dr. Sardjito Hospital, Yogyakarta, Indonesia (GPS: -7.768403684847436, 110.37340982163165). All patients were subjected to anamnesis and examination for ASD-PAH and ASD non-PAH diagnosis by anamnesis, physical examination, ECG, transoesophageal echocardiography (TOE), transthoracic echocardiography (TTE), right heart catheterization (RHC) by a consultant cardiologist from October 2023 to July 2024. All subjects were Javanese and ≥ 18 years old. Patients who had ventricle septal defect (VSD) and multiple heart defects were excluded. All the patients signed an informed consent form prior to the study i.e. after they received information on the, aim, and risk associated of the study. All methods were carried out in accordance with the ethical principle outlined in the international and national guidelines on ethical standards and procedures for researchers in human beings and approved by the ethical committee of the Faculty of Medicine, Nursing and Public Health Universitas Gadjah Mada approval number KE/FK/0922/EC/2023.

Data Collection

For demographic data, at the time of hospital visit, we collected age, gender, data related to PAH diagnosis (i.e. PAWP, PVR, mPAP, urea serum and creatinine) of each patient.

Laboratory investigation

Approximately 5 mL of peripheral venous blood was collected from each patient into EDTA-containing vacutainer tubes. For DNA analysis, 200 µL of whole blood was obtained, and centrifuge for HO-1 and ET-1 plasma examination. The DNA of each subject was isolated with DNA isolation kit (Favorgen® FABGK-001-2 Taiwan). The concentrations of HO-1 and ET-1 in plasma were quantified using commercial ELISA kits from Elabscience® (Elabscience® Human HO-1 ELISA kit E-EL-H2172.US and Human ET-1 ELISA Kit E-EL-H0064), following the manufacturer's instructions.

DNA Genotyping

The $(GT)_n$ repeat length in the promoter region of the HMOX1 gene was determined by polymerase chain reaction (PCR) amplification using a FAM-labelled primer forward: 5'-AGA GCC TGC AGC TTC T-3' and reverse: 5'-ACA AAG TCT GGC CAT AGG AC-3'.[22] The resulting PCR product were analyzed using an automated DNA sequencer (Applied Biosystems, USA). The length of $(GT)_n$ repeat was calculated by GeneScan Analysis software (Applied Biosystems GeneMapper5). For rs2071746 we used primer forward: 5'-GTT CCT GAT GTT GCC CAC CAA GC-3' and reverse: 5'-CTG CAG GCT CTG GGT GTG ATT TTG-3, PCR condition: 95°C 5 min, 35 cycles: (95°C 1 min, 60°C 1 min, 72°C 1 min), 72° C 7 min. The PCR product was then analyzed with 2% agarose gel. Restricted fragment length polymorphism was done with *HindIII* enzyme and then visualized via 3% agarose gel. [24]

Statistical Analysis

Data was expressed as mean±SD. Comparisons of continuous variables between groups were assessed using the Mann–Whitney test as appropriate. Categorical variables were compared by Chi-square test and for genotype distribution frequency we also calculated the Hardy-Weinberg Equilibrium. Multivariate binary logistic regression analysis was used to test independent predictors. $P<0.05$ or a 95% confidence interval (CI) for odds ratio (OR) $\geqslant 1.0$ was defined as statistically significant.

Results and Discussion

A total of 101 participants were enrolled, consisting of 51 ASD-PAH patients and 50 ASD non-PAH (control group). Baseline demographic (Table 1.) characteristics were comparable between groups, with no significant differences in age, or renal functional markers (urea and creatinine). The proportion of males and females in the ASD-PAH group was 15.6% and 84.4%, respectively, while in the control group 24% and 76% respectively. Hemodynamic assessment (Table 1.) revealed significantly higher PVR (8.15 ± 6.36 vs 4.41 ± 6.72 WU; $p = 0.0014$) and mPAP (48.57 ± 16.67 vs 37.55 ± 19.00 mmHg; $p = 0.01$) in the ASD-PAH group compared to the controls, while PAWP values did not differ significantly. Plasma ET-1 levels were significantly elevated in the ASD-PAH group (3.09 ± 2.90 vs 2.80 ± 2.44 pg/mL; $p = 0.04$), in contrary plasma HO-1 concentration did not differ significantly between group.

Genetic analysis demonstrated distinct differences in HMOX1 $(GT)_n$ polymorphisms (Table 2). The L allele was more frequent among ASD-PAH patients (49.1% vs 32% in controls), whereas the S allele was enriched in the controls (68%). Logistic regression (Table 3.) confirmed that the L allele was significantly associated with ASD-PAH risk (OR = 2.04; 95% CI: 1.15–3.62; $p = 0.015$). Genotype-based model showed a trend towards increased risk with the presence ≥1 L allele (OR = 2.17; 95% CI: 0.97–4.84) or homozygous LL (OR = 2.40; 95% CI: 0.92–6.27) although these did not reach statistical significance.

For rs2071746, obvious differences were observed. The T allele was substantially overrepresented in the ASD-PAH group (52% vs 19% in controls), conferring marked increased risk (OR = 4.61; 95% CI: 2.45–8.68; $p < 0.001$). The dominant model (AT+TT vs AA) showed a >10-fold higher risk (OR=10.35; 95% CI: 4.13-25.95; $p< 0.001$) indicating that T carriers are particularly at high risk of developing ASD-PAH.

The distribution of $(GT)_n$ microsatellite polymorphisms in the HMOX1 gene promoter were analyzed. The SL genotype was the most prevalent in ASD-PAH group (35%), while in control group, was S allele (52%).

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Table 1: Characteristic of respondent

Variable	ASD-PAH n=51	ASD non-PAH n=50	P*
Age (30>/≤30 years old):	40.0	36.0	0.09
Mean	13.1	11.3	
SD			
Gender:			
Male(%):	8 (15.6)	12(24)	-
Female(%)	43(84.4)	38(76)	
PVR (Wood Unit):			
Mean	8.15	4.41	0.0014
SD	6.36	6.72	
mPAP (mmHg):			
Mean	48.57	37.55	0.01
SD	16.67	19.00	
PAWP (mmHg):			
Mean	10.81	11.97	0.52
SD	4.94	6.05	
Urea (mg/dL):			
Mean			
SD	10.84	10.37	0.99
	4.84	3.44	
Creatinine (mg/dL):			
Mean	0.77	0.75	0.82
SD	0.20	0.15	
ET-1 (pg/mL):			
Mean			
SD	3.09	2.80	0.04
	2.90	2.44	
HO-1 (ng/mL):			
Mean			
SD	0.31	0.35	0.47
	0.22	0.35	

*Mann Whitney test; PVR: pulmonary vascular resistance; mPAP: mean pulmonary arterial pressure; PAWP: Pulmonary artery wedge pressure; ET-1: endothelin-1; HO-1: heme oxygenase-1

Table 2: Genotype distribution in groups

Genotype	ASD-PAH n (%)	P*	HWE	ASD non-PAH n (%)	P*	HWE
SS	17(33.3)			26(52)		
SL	18(35.2)			16(32)		
LL	16(31.5)	4.404	0.035	8(16)	3.503	0.061
Allele						
S	52(50.9)			68(68)		
L	50(49.1)			32(32)		
rs2071746						
AA	11(21.6)			37 (74)		
AT	27(52.9)			7 (14)		
TT	13(25.5)	0.186	0.665	6 (12)	14.86	0.001
Allele						
A	49(48.0)			81(81)		
T	53(52.0)			19(19)		

*χ^2 test significant if p<0.05 ; HWE: Hardy Weinberg Equilibrium; AT: adenine-thymine; TT: thymine-thymine; AA: adenine-adenine;

Figure 1a. shows that the majority of distribution in the control group were GT repeats between 12 until 16, the longest allele in control group was 28 repeats. In Figure 1b. majority repeat in case group was around 19 until 24 repeats, while the longest allele was 32 GT repeats. We divided the groups into short and long allele with cut off at 17 repeats because the proportion of allele frequencies below or above 17 GT repeats was around 50%. The results of genotyping the HMOX1 gene using PCR were shown in a 151 bp product (Figure 2.). RFLP analysis then found the genotypes AA, AT, and TT at bands 20 bp, 94 bp, and 131 bp, respectively. Pulmonary arterial hypertension remains one of the most challenging complications of congenital heart disease, particularly atrial septal defect.[1] The present study provides new insights by demonstrating that genetic polymorphisms of the HMOX1 promoter region and circulating HO-1 levels independently influence the risk of ASD-PAH in the Javanese population. Specifically, the L allele of $(GT)_n$ repeats and the T allele of rs2071746 significantly increased susceptibility to PAH, while the S allele and higher HO-1 concentration conferred a protective effect. This dual role of molecular and genetic determinants underscores the complex pathophysiology of PAH in the setting of congenital shunts, where mechanical, inflammatory and oxidative stress-related factors converge. It represents the most common form of atrial shunt disorder, and unless it is closed in period time it will cause hemodynamics imbalance. [25] Patients with PAH associated with congenital heart disease are 6-35% of patients with uncorrected secundum ASD. The strategy for proper closure of the defect remains controversial.[1,8,26,27] PAH caused by ASD could be reversible but as the pathology progresses it become irreversible. Criteria for closure depend on diameter of defect, saturation, comorbidities, type of shunt, and PVR (<4 WU x m^2 or 4-8 WU x m^2).[28–30]

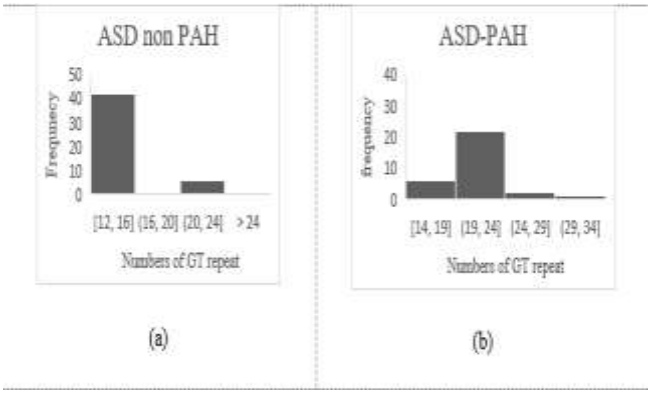

Figure 1: (a) numbers of GT repeat in control group; (b): numbers of GT repeat in case group

Table 3: Logistic regression of risk factors in ASD-PAH

Model	OR	95% CI	P
$(GT)_n$			
SL+LL vs SS	2.17	0.97 – 4.84	0.071
LL vs SS+SL	2.40	0.92 – 6.27	0.101
L vs S	2.04	1.15 – 3.62	0.015
rs2071746			
AT+TT vs AA	10.35	4.13 – 25.95	<0.001
TT vs AA+AT	2.51	0.87 – 7.24	0.126
T vs A	4.61	2.45 – 8.68	<0.001

$(GT)_n$: guanine-thymine repeat; SS: short-short; SL: short-long; LL: long-long;
S: short; L: long; AT: adenine-thymine; TT: thymine-thymine; AA: adenine-adenine;

Our findings confirmed that ASD-PAH patients had significantly higher pulmonary vascular resistance (PVR), and mean pulmonary arterial pressure (mPAP) compared to control group patients. Elevated PVR is widely recognized as a marker of advanced pulmonary vascular remodeling, characterized by neointima proliferation, medial hypertrophy and adventitial fibrosis. In the context of a chronic left-to-

right shunt, persistent pulmonary overcirculation accelerates endothelial dysfunction, smooth cell proliferation and vascular rarefaction. The molecular counterpart of this hemodynamics stress is oxidative injury, wherein reactive oxygen species disrupt endothelial homeostasis. Elevated endothelin-1 (ET-1) levels observed in our ASD-PAH patient support this paradigm, consistent with prior reports that link ET-1 upregulation with vasoconstriction, vascular remodeling, and poor clinical outcomes. [4,31–34]

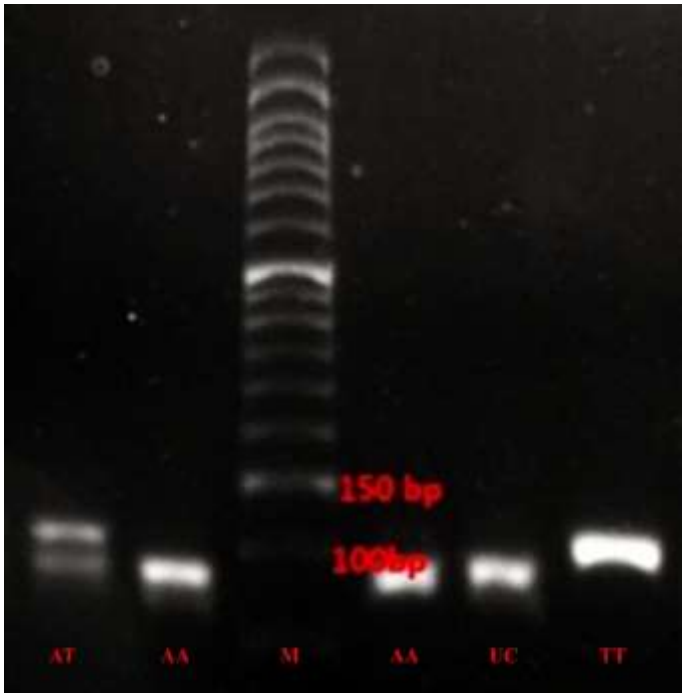

Figure 2: Genotyping of rs2071746;M:marker;UC: uncut; bp: base pair; AT: adenine-thymine; TT: thymine-thymine; AA: adenine-adenine

The promoter region of the HMOX1 gene contains a variable $(GT)_n$ microsatellite repeat. Long repeat adopted Z-DNA conformation which hinder transcription factor binding and reduce promoter activity. Conversely, short repeat facilitating robust HO-1 transcription.

In our study the L allele was significantly enriched in ASD-PAH patients (49.1% vs 32% in controls), and logistic regression confirmed its role as a risk factors. This finding corroborates studies in coronary artery disease and metabolic disorders, where long GT repeats are associated with heightened oxidative stress and endothelial dysfunction. Importantly in our Javanese subjects, the S allele was relatively frequent, suggesting population specific allele distributions that may partly explain divergent results across ethnic studies.

The rs2071746 polymorphism further amplified genetic susceptibility. Carriers of the T allele had over a four-fold increased risk of ASD-PAH, with heterozygous and homozygous variant (AT/TT) conferring a>10-fold risk compared to AA homozygotes. Mechanistically, rs2071746 is located in the proximal promoter region, influencing transcription factor binding and mRNA splicing efficiency. Reduced transcriptional activity associated with the T allele likely diminishes HO-1 induction under oxidative stress. [25,35–38] Incorporating biomarkers such as HO-1 into risk assessment may refine current algorithms by complementing hemodynamic thresholds. Moreover, environmental and lifestyle factors such as smoking, diet, and exposure to oxidative stress may further modulate HO-1 expression, representing potential confounders that were not fully captured in the present cross-sectional design.

According to this study, Javanese individuals are more likely to have short allele compared to other studies that show more variety of long allele.[36] This theory supports our study regarding the ASD-PAH group which had more individuals with higher frequencies of L allele or SL and LL genotypes, this is in contrast with study by Sandrim et al. that $(GT)_n$ is not associated with preeclampsia women.[39] This context-dependent distribution highlights the necessity of population-specific genetic studies, as findings from one ethnic group may not be generalized to another. Such genetic variability has clinical implications for screening strategies. [40]

The integration of genetic and molecular markers into clinical practice offers transformative potential. Traditionally, the decision to close an ASD relies on hemodynamic thresholds, particularly PVR values. However, these criteria are not always sufficient to capture individual susceptibility to irreversible pulmonary vascular remodelling. Our study suggested that HMOX1 polymorphisms and plasma HO-1 levels could complement current risk stratification tools such as,. high risk genotype (L or T carriers) may benefit from earlier defect closure or closer hemodynamic surveillance. Low HO-1 plasma levels could flag individual who require adjunctive therapies aimed at enhancing antioxidant defence. Pharmacological inducers of HO-1 such as statins, curcumin, and resveratrol[41–43] hold promise as potential adjunctive intervention, though further clinical trials are needed. [14,44]

Conclusion

The present study demonstrates that the HMOX1 $(GT)_n$ polymorphism and rs2071746 variants, together with plasma HO-1 levels, independently shape susceptibility to ASD-PAH in the Javanese population. Carriers of the S allele and those with higher HO-1 expression appear protected. While carriers of the T and L alleles are predisposed to disease development. These results reinforce the critical role of oxidative stress regulation in congenital heart disease-related PAH and suggest that HO-1 based genetic and molecular profiling may refine current clinical algorithms. Ultimately, integrating hemodynamic, genetic, and biochemical data may enable personalized, precision based management of ASD patient at risk of pulmonary vascular complications. This study has limitations, i.e. environmental or lifestyle factors that may influence HO-1 expression (e.g., smoking, inflammation, diet, onset of disease, defect diameter, defect closure treatment) were not controlled. Patients are advised that unhealthy lifestyle factors worsen disease progression despite favourable genetic profiles. Smoking cessation, proper nutrition, inflammation control, and adherence to medical or interventional therapy are critical components of long-term management. The cross-sectional design preludes any causal inference. Future research with longitudinal follow-up is warranted to confirm these results and elucidate the underlying mechanisms. Ultimately, combining molecular, hemodynamic, and imaging data may enable personalized approaches to congenital heart disease management.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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