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Impact of Familial Congenital Heart Disease on the Clinical Phenotype of Ventricular Septal Defect in Iraqi Patients

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A B S T R A C T

Ventricular septal defect (VSD) is the most common type of cardiovascular malformation and a major risk factor for increased morbidity and mortality in newborns. Accumulating evidence and previous studies have pointed to genetic defects in its developmental mechanism. However, due to the genetic diversity of this defect, the genetic factors contributing to its clinical presentation in the majority of patients remain unknown. This pilot study will describe the impact of a family history of congenital heart disease on the clinical presentation of patients with VSD. Patients and Methodology: Data were proactively collected from 100 patients at the Najaf Heart Center, Najaf, Iraq, who underwent surgical closure of a VSD. These factors included age, weight, height, and the size and location of the VSD. The data were used to differentiate between two groups (patients with a family history versus patients without a family history). Results: 77% of patients had no family history of VSD, while 23% had a family history. Body mass index (BMI) was lower in patients without a family history compared to those with a family history (17.75 ± 7.4 vs. 21.59 ± 11.15). Patients without a family history underwent surgery at a younger age than those with a family history (7.13 ± 8.32 vs. 8.52 ± 11.14). Subaortic and muscular ventricular septal defects were more common in patients without a family history, while subpulmonary and surgical ventricular septal defects were more common in patients with a family history of ventricular septal defects. The results also showed that the group of patients without a family history of congenital heart disease had a higher percentage of small ventricular septal defects (27.27%) compared to the group of patients with a positive family history (30.43%). Furthermore, a higher incidence of large ventricular septal defects was observed in patients with a family history of the disease, although most p-values were not statistically significant ($p > 0.05$). In conclusion, based on these results, patients with a family history of ventricular septal defects may experience fewer symptoms, while patients without such a history may exhibit a more severe clinical course and require earlier surgical intervention, indicating no statistically significant differences in the outcomes obtained.

Keywords: *Ventricular septal defect (VSD), Body mass index (BMI), Echocardiography (Echo)*

1. Introduction

Congenital heart disease (CHD) comprises a heterogeneous group of structural and functional abnormalities of the heart and great vessels that arise during embryonic development and are present at birth. It represents one of the most frequent categories of congenital malformations and remains an important contributor to neonatal and childhood morbidity and mortality worldwide. Although considerable advances have been achieved in prenatal screening, neonatal echocardiography, pediatric cardiology, intensive care, catheter-based intervention, and cardiac surgery, CHD continues to impose substantial clinical and healthcare burdens, particularly in settings in which early diagnosis and specialized treatment are less readily available. Population-based studies have demonstrated considerable geographic variation in the reported prevalence of congenital heart defects, reflecting differences in genetic background, environmental exposures, case ascertainment, diagnostic technologies, and survival of affected infants (1, 2). Consequently, understanding both the developmental origins and the factors responsible for variation in the clinical expression of CHD remains a major objective in cardiovascular research.

Among congenital cardiac abnormalities, ventricular septal defect (VSD) is one of the most common structural lesions. A VSD is characterized by an abnormal opening in the interventricular septum that permits communication between the right and left ventricles. The hemodynamic consequences of the defect depend primarily on its size, anatomical location, pressure gradient between the ventricles, pulmonary vascular resistance, and the presence of additional cardiac abnormalities. Small defects may be physiologically restrictive and remain clinically silent, whereas larger defects can produce substantial left-to-right shunting, pulmonary overcirculation, congestive heart failure, failure to thrive, and progressive pulmonary vascular disease (3, 4). The clinical significance of VSD therefore ranges from an incidental echocardiographic finding with spontaneous closure to a serious congenital lesion requiring early surgical or transcatheter intervention.

The anatomical complexity of the ventricular septum contributes substantially to the diversity of VSD phenotypes. The interventricular septum contains muscular and membranous components that develop through coordinated interactions among multiple embryological structures. Defects can consequently occur in different anatomical regions, including perimembranous or subaortic, muscular, inlet, and outlet or subpulmonary regions. Classical cardiac pathological studies established the importance of precise morphological classification for understanding the relationship between defect anatomy, hemodynamics, associated lesions, and clinical management (5). In adults, persistent VSDs may also have important long-term consequences, including aortic regurgitation, infective endocarditis, arrhythmia, pulmonary hypertension, and, in severe untreated cases, Eisenmenger physiology (6, 7). Thus, the phenotype of VSD cannot be adequately characterized solely by the presence or absence of a septal opening; defect size, site, associated cardiovascular abnormalities, and patient characteristics must also be considered.

Contemporary understanding of VSD increasingly emphasizes its developmental and genetic basis. Normal cardiac morphogenesis requires highly coordinated specification, migration, proliferation, and differentiation of multiple populations of cardiac progenitor cells. Heart-field progenitor cells contribute to different cardiac chambers and structures, and disturbances in their developmental programs can produce a wide spectrum of congenital cardiovascular abnormalities (8). Cardiac septation is particularly dependent on the precisely timed interaction of myocardial, endocardial, neural crest, and second heart-field-derived tissues. Consequently, perturbations affecting developmental signaling pathways or transcriptional networks may alter septal formation and result in congenital defects that vary considerably in location and severity.

A number of transcription factors and regulatory genes have been identified as essential components of cardiac developmental programs. HAND transcription factors are involved in ventricular morphogenesis, chamber specification, and broader cardiac development, and disruption of their expression or regulatory pathways can contribute to abnormal heart formation (9). Similarly, members of the T-box transcription factor family regulate several stages of cardiac specification, chamber formation, conduction-system development, and septation (10). Experimental investigation of PITX2 expression has further demonstrated the complexity of spatial and temporal gene

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regulation during cardiac development and the potential consequences of altered developmental patterning (11). Collectively, these findings support the view that congenital septal abnormalities emerge from disturbances in highly integrated developmental networks rather than from a single uniform mechanism.

The genetic architecture of CHD is similarly heterogeneous. Familial clustering, recurrence among relatives, chromosomal abnormalities, copy-number variants, and pathogenic variants in individual genes all indicate an important inherited component, although the proportion attributable to identifiable genetic alterations varies considerably among phenotypes (12). Advances in genomic medicine have increasingly revealed that apparently isolated cardiac abnormalities can sometimes represent part of a broader genetic syndrome or developmental disorder. For example, severe congenital cardiac defects have recently been described in association with SSR4-related congenital disorders of glycosylation, illustrating how molecular diagnosis can clarify the etiology of complex neonatal cardiac presentations (13). Likewise, congenital cardiac abnormalities can occur within chromosomal syndromes with highly variable phenotypic expression, as demonstrated by reports of Cat Eye syndrome presenting with atypical combinations of congenital abnormalities (14). Such observations underscore the substantial genetic and phenotypic diversity underlying congenital cardiovascular disease.

The rapid development of genomic sequencing has also transformed the investigation of pediatric cardiac disease. Rapid exome sequencing can provide clinically meaningful molecular diagnoses in children presenting with cardiomyopathy or acute heart failure, potentially influencing diagnostic classification, prognosis, family counseling, and management (15). Reports of severe neonatal hypertrophic cardiomyopathy associated with compound heterozygous MYBPC3 variants further illustrate the potential for recessive or compound genetic mechanisms to produce life-threatening cardiovascular phenotypes early in life (16). Similarly, early-onset restrictive cardiomyopathy with malignant arrhythmias has been associated with homozygous DES mutations, demonstrating that inherited cardiac disorders can present with marked clinical severity during childhood (17). Although cardiomyopathies and septal defects are distinct disease entities, these genomic discoveries emphasize a broader principle relevant to CHD: inherited variation may substantially influence not only disease occurrence but also phenotype, severity, age at presentation, and clinical trajectory.

Family history therefore represents a clinically accessible surrogate indicator of inherited susceptibility when comprehensive molecular testing is unavailable. A positive family history of congenital heart disease may reflect shared genetic variants, chromosomal alterations, polygenic susceptibility, shared environmental exposures, or interactions between genetic and environmental factors. Importantly, inherited susceptibility need not produce identical phenotypes across relatives. The same family may exhibit different forms of congenital cardiovascular abnormality because developmental outcomes are influenced by penetrance, variable expressivity, modifier genes, epigenetic processes, and environmental conditions (12). Accordingly, examining family history in patients with VSD may provide information beyond recurrence risk and could potentially reveal differences in the clinical characteristics of patients who carry a stronger familial predisposition.

The clinical phenotype of VSD is particularly suitable for such investigation because the disorder exhibits marked variability in age at diagnosis, symptoms, defect size, anatomical site, associated abnormalities, and requirement for intervention. Neonatal VSDs may be detected prenatally, immediately after birth, or only after pulmonary vascular resistance declines and symptoms of left-to-right shunting become apparent. Echocardiography remains central to defining defect morphology and assessing hemodynamic significance, while clinical decisions integrate symptoms, growth, pulmonary pressure, shunt magnitude, valve involvement, and associated cardiac lesions (4). In some patients, small defects close spontaneously and require observation rather than intervention. In contrast, moderate or large lesions associated with substantial shunting may require closure to prevent irreversible pulmonary vascular disease and other complications (3, 18).

Several complications may modify both the timing and method of VSD treatment. Defects located near the aortic valve may be accompanied by aortic cusp prolapse and

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progressive aortic regurgitation, conditions that can create an indication for closure even when the magnitude of the ventricular shunt is not extreme. Transcatheter closure has been investigated in selected patients with VSD associated with aortic valve prolapse and regurgitation, illustrating the expanding range of interventional strategies available for carefully selected anatomical phenotypes (19). Acquired VSD may also rarely develop as a complication of infective endocarditis, further emphasizing that septal defects must be considered within a broad clinical and pathological context (20). Thus, anatomical location and associated complications may influence whether patients undergo observation, catheter-based treatment, or surgery.

Surgery nevertheless remains essential for many patients with hemodynamically significant VSD. Contemporary operative outcomes are generally favorable, but postoperative complexity and complications can be influenced by patient characteristics, defect morphology, associated anomalies, and preoperative clinical condition (21). Surgical techniques have also evolved to address complex anatomical patterns, including the use of single-patch approaches for multiple ventricular septal defects (22). At the same time, interventional pediatric cardiology has expanded the possibility of catheter-based treatment for selected congenital lesions, reducing the need for open surgery in appropriately chosen patients (23). These therapeutic advances have increased survival and improved quality of life, but they have also heightened the importance of identifying clinical variables that can help predict the natural history and optimal timing of treatment.

The importance of congenital cardiac disease also extends into adulthood and across generations. Improved survival has produced a growing population of adults with repaired or unrepaired congenital heart disease, including women of reproductive age. Pregnancy in women with congenital cardiac abnormalities requires careful risk stratification because maternal cardiovascular physiology may affect both maternal and fetal outcomes, while genetic susceptibility may influence the risk of congenital cardiac defects in offspring (24). The persistence of congenital heart disease across the life course therefore reinforces the clinical relevance of documenting family history and understanding familial patterns of disease.

Electrical and electrophysiological abnormalities provide another example of how genetic background may influence the phenotype of structural congenital heart disease. Investigations of atrial septal defects have demonstrated associations between structural abnormalities, electrical disturbances, and heritable developmental pathways (25). Although the anatomy and hemodynamics of atrial and ventricular septal defects differ, both conditions originate from disruptions of cardiac development, suggesting that genetic factors may influence multiple dimensions of congenital cardiac phenotype. Such evidence supports examining whether familial predisposition among patients with VSD is associated with variations in morphology or clinical presentation rather than considering family history exclusively as a binary risk factor for disease occurrence.

Clinical studies conducted in different populations have demonstrated substantial heterogeneity in VSD presentation. Experience from tertiary pediatric cardiac centers indicates that affected children may differ markedly in age at diagnosis, sex distribution, symptom severity, associated lesions, and treatment requirements (26). Population-based investigations likewise demonstrate geographic differences in congenital heart defect prevalence and associated risk factors (2). These variations may arise from demographic structure, environmental exposure, maternal factors, healthcare access, referral patterns, genetic background, and diagnostic practices. Consequently, data generated from one population cannot always be extrapolated directly to another, particularly where genetic ancestry and healthcare systems differ considerably.

Recent reports of rare congenital and cardiopulmonary anatomical combinations further illustrate the phenotypic complexity encountered in pediatric practice. Successful VSD closure in an infant with right lung agenesis and extreme cardiac dextroversion demonstrates how unusual anatomical configurations can substantially complicate operative planning and clinical management (27). Similarly, comprehensive analyses of pediatric pulmonary sequestration with uncommon systemic arterial supply demonstrate that congenital thoracic and cardiovascular anomalies may occur in anatomically diverse patterns requiring individualized evaluation (28). Although these disorders are uncommon, they reinforce the principle that congenital abnormalities frequently display substantial

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anatomical heterogeneity and that careful phenotypic characterization is necessary for understanding their developmental and clinical significance.

Cardiopulmonary interactions are especially relevant in children with significant congenital or acquired cardiac dysfunction. Altered pulmonary circulation is a central pathophysiological consequence of large VSDs, and strategies that modify pulmonary arterial flow can substantially affect ventricular loading conditions. The use of pulmonary artery banding in selected pediatric patients with dilated cardiomyopathy demonstrates the broader therapeutic significance of manipulating pulmonary and systemic hemodynamic relationships in childhood cardiac disease (29). In VSD, prolonged excessive pulmonary blood flow can similarly lead to vascular remodeling and pulmonary hypertension, highlighting the importance of appropriate surveillance and timely intervention before irreversible pulmonary vascular disease develops.

Despite the established genetic contribution to CHD, comparatively less attention has been given to whether a positive family history is associated with distinguishable clinical characteristics among patients who already have VSD. Most research has focused on the prevalence, embryology, diagnosis, natural history, complications, and management of VSD or on recurrence of congenital heart disease among relatives. Yet familial susceptibility could plausibly influence the anatomical location of the defect, its size, the severity or timing of symptoms, somatic growth, and age at surgical intervention. If such differences exist, family history could become a simple and inexpensive clinical variable for phenotypic stratification, especially in healthcare settings where routine genomic analysis is not readily available.

This question is particularly relevant in Iraq, where population-specific evidence concerning the relationship between familial congenital heart disease and VSD phenotype remains limited. Regional differences in genetic background, patterns of consanguinity, environmental exposures, access to specialized pediatric cardiology, timing of referral, and surgical resources may all influence the presentation of congenital cardiac disease. Characterizing Iraqi patients is therefore important both for generating locally relevant evidence and for determining whether observations from other populations are applicable in this setting. Furthermore, because clinical variables such as age at surgery, body size, VSD diameter, and anatomical location can be obtained routinely, their comparison according to family history offers a practical approach for exploring possible familial influences on disease expression before more extensive molecular investigations are undertaken.

Accordingly, integrating developmental biology, clinical morphology, inherited susceptibility, and contemporary cardiovascular management provides a strong rationale for evaluating family history as a potential determinant of VSD phenotype. Existing evidence confirms that VSD is developmentally complex, clinically heterogeneous, and influenced by genetic mechanisms, yet it remains uncertain whether patients with a family history of congenital heart disease exhibit a systematically different clinical presentation from apparently sporadic cases. Addressing this gap may improve understanding of the relationship between familial predisposition and phenotypic expression and may provide a foundation for future studies incorporating molecular genetic testing, larger multicenter samples, and long-term clinical follow-up.

Therefore, this study aimed to investigate the impact of a family history of congenital heart disease on the clinical phenotype of ventricular septal defect in Iraqi patients by comparing demographic characteristics, body mass index, age at surgical intervention, and the size and anatomical location of VSD between patients with and without a positive family history.

2. Methods and Materials

This prospective pilot study was conducted on Iraqi patients with ventricular septal defects (VSDs) who underwent corrective surgery at the Najaf Heart Center in Najaf, Iraq, between January 2024 and March 2026. Patients with atrial septal defects (ASDs) and Down syndrome were excluded from the study. This study was approved by the Research Ethics Committee of Tabriz University, Islamic Republic of Iran. Patients were divided into two groups: the first group consisted of patients with VSDs and no family history of congenital heart disease, while the second group consisted of patients with VSDs and a family history of the condition.

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Demographic and clinical data (age at admission, sex, weight, height, and family history) were collected through in-person interviews with the patients. Based on previously performed echocardiograms, the size and location of the ventricular septal defect (VSD), as well as any associated cardiac defects, were documented. VSDs were classified into three sizes (small, medium, and large) according to the diameter of the aorta. Their location was classified into four types: subaortic, subpulmonary, left ventricular inlet, and muscular VSD.

All numerical variables are presented as mean ± standard deviation. The unpaired Student's t-test was used to calculate p-values, and a p-value was considered statistically significant if p = 0.05 or less. GraphPad Prism version 8.3.0 was used for statistical analysis.

3. Findings and Results

Demographic data showed that a 100 patients were included in this study and the majority of them have no family history (77%) and only quarter of patients have positive family of any congenital heart diseases. Interestingly, the age of patient with family history was less than those without (Table 1).

Table 1

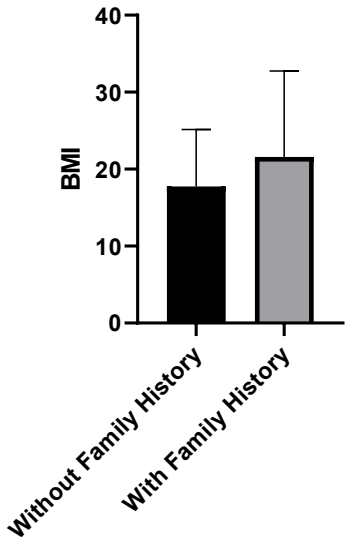
Demographic data of patient who were suffering from VSD at time of operation. BWT (body weight); Ht (Height). Data were presented as mean ± SD.

	n.	Male	Female	Age (year)	Weight (Kg)	Height (cm)
Patients without family history of VSD	77	35 (45.5%)	42 (54.5%)	7.13± 8.32	20.97± 17.72	101.5± 32.26
Patients with family history of VSD	23	9 (43.5%)	14 (56.5%)	8.52± 11.14	24.13± 20.56	106.6± 33.38

The body mass index (BMI) was calculated for each patients separately. A comparison between the studied groups found that patient without family history has lower BMI (17.75±7.4) than those without (21.59±11.2) at the time of surgical intervention. However, the difference was statistically insignificant (p=0.057, 95%CI (0.116 to 7.795), R^2 = 0.036).

Figure 1

illustrate a comparison the body mass index between the two studded group. BMI (body mass index), Data was presented as mean ± SD (p=0.057)

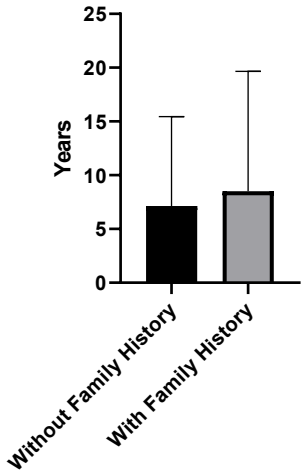


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Moreover, it was found that patients who had no family history of the disease, were more likely to require surgery earlier (7.129± 8.316 yr) compared to those who had a family history (8.515±1114 yr) although statistically, the difference was not significant (p>0.05 , .95%CI (- 2.87 to 5.643) $R^2 = 0.004$).

Figure 2

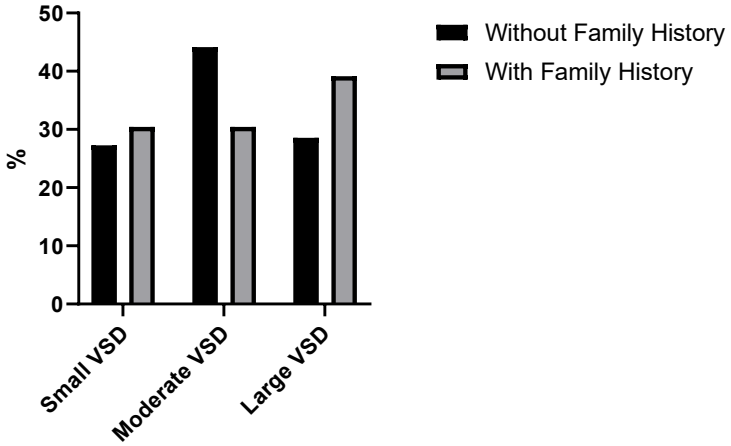
The age of the patient at the time of surgical intervention in both studied groups. Data was presented as mean ± SD (p>0.05).



Nevertheless, Figure 3, The results showed that the group of patients without a family history had a relatively lower percentage of small ventricular septal defects (27.27%) compared to the group of patients with a family history (30.43%). Additionally, patients without a family history had a relatively higher percentage of intermediate-type ventricular septal defects (44.156%) than those with a family history (30.43%). Furthermore, large ventricular septal defects were observed at a higher rate in patients with a family history (39.13% and 28.57%, respectively).Data were statistically non significant with p> 0.005.

Figure 3

A comparison of the size of the VSD between studied groups. Data was presented percentages.

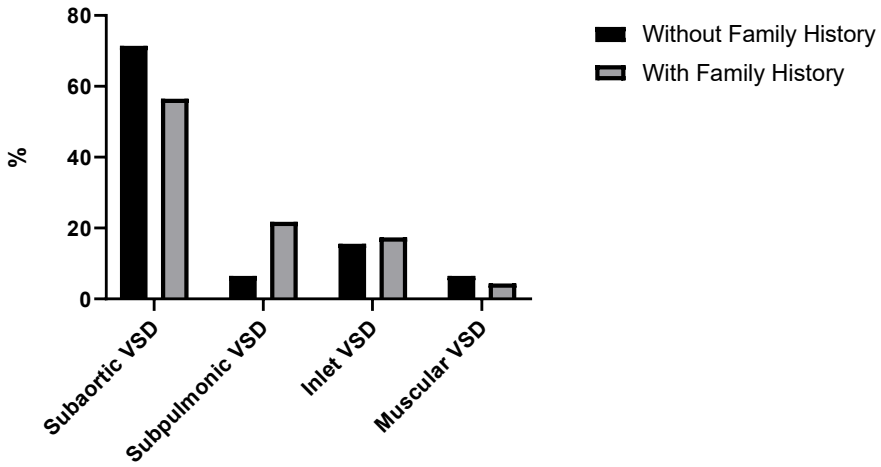


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The location of ventricular septal defects (VSDs) was examined in patients with VSDs in two groups: Group A (patients with no family history) and Group B (patients with a family history). After statistical analysis, Group A had a relatively higher percentage of defect locations (subaortic VSD and muscular VSD) (71.42% and 6.49%, respectively) compared to Group B (56.52% and 4.34%). Conversely, Group B had a relatively higher percentage of defect locations (subpulmonary VSD and inlet VSD) (21.73% and 17.39%) compared to Group A (6.49% and 15.58%) (Figure 4).

Figure 4

Comparison the site heart opening VSD (Subpulmonic VSD , Muscular VSD , Subaortic VSD , Inlet VSD) between (Group A patients with a family history of the disease, and Group B patients without any family history of the disease



The final conceptual structure demonstrated that ethical social media behavior among Olympic athletes operates through the interaction of three interconnected layers. At the foundational level, Islamic moral principles—including truthfulness, justice, trustworthiness, dignity, self-restraint, modesty, and avoidance of harm—provided the normative basis for ethical judgment. At the behavioral level, these values were operationalized through specific forms of conduct involving truthful communication, respectful interaction, protection of privacy, emotional regulation, accountability, responsible commercial engagement, and appropriate participation in digital communities. At the social and institutional level, athlete behavior was situated within the broader responsibilities associated with public visibility, role-model influence, Olympic participation, national representation, and cultural expectations. The framework therefore did not treat ethical behavior as a set of isolated prohibitions. Rather, it represented a relational model in which personal moral character, digital behavior, and public responsibility continuously influence one another. Self-restraint, for example, was linked not only to emotional regulation but also to the Islamic principle of controlling harmful speech, preservation of interpersonal dignity, and reduction of reputational damage during conflict. Similarly, truthfulness functioned simultaneously as a personal moral obligation, a requirement for responsible digital citizenship, and a professional responsibility in advertising and public communication. Respect for human dignity connected individual interpersonal conduct with broader concerns regarding discrimination, cyberbullying, hate speech, and public humiliation. The framework also positioned accountability as the mechanism through which athletes acknowledge the consequences of digital behavior, including correction of inaccurate information and appropriate response to misconduct. Overall, the resulting model indicated that culturally grounded ethical behavior on social media should be understood as a dynamic integration of Islamic ethical principles, contemporary digital

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responsibilities, professional sport expectations, and the distinctive social influence of Olympic athletes.

4. Discussion and Conclusion

The present study investigated whether a family history of congenital heart disease was associated with differences in the clinical phenotype of ventricular septal defect (VSD) among Iraqi patients undergoing surgical repair. Overall, 77% of the patients had no family history of congenital heart disease, whereas 23% reported a positive family history. Although several numerical differences were observed between the two groups in age at surgery, body mass index (BMI), VSD size, and anatomical location, none of these differences reached statistical significance. Patients without a family history underwent surgery at a somewhat younger mean age and had a lower mean BMI, whereas patients with a positive family history tended to have a higher proportion of large defects. In addition, subaortic and muscular VSDs were relatively more frequent among patients without a family history, whereas subpulmonary and inlet defects were relatively more frequent among those with a positive family history. Taken together, these findings suggest possible phenotypic variation according to familial background, but they do not provide sufficient statistical evidence to conclude that family history independently determines VSD severity or morphology.

The first important finding was that most patients with surgically treated VSD did not report a family history of congenital heart disease. This observation is consistent with the multifactorial nature of congenital cardiac abnormalities. Although familial clustering and heritable genetic factors are well established in congenital heart disease, a large proportion of affected individuals present as apparently sporadic cases (12). Congenital heart disease results from complex interactions among genetic susceptibility, developmental pathways, environmental exposures, maternal factors, and stochastic developmental events. Therefore, the absence of an identified family history does not indicate the absence of a genetic contribution. Rather, it may reflect incomplete penetrance, de novo variation, polygenic inheritance, unrecognized disease in relatives, or insufficient family information. Contemporary developmental research has reinforced this concept by showing that congenital cardiac abnormalities may arise from disturbances in multiple cardiac progenitor populations and interacting regulatory pathways rather than from a single inherited defect (8).

The observed proportion of patients with a positive family history is also biologically plausible in light of evidence concerning the inheritance of congenital heart disease. Previous work has demonstrated that the recurrence risk of congenital cardiac defects is higher among relatives of affected individuals than in the general population, although the specific anatomical phenotype may differ among members of the same family (12). Genetic heterogeneity and variable expressivity are particularly important because mutations or developmental abnormalities affecting cardiac transcription factors can produce a range of structural phenotypes. HAND family transcription factors contribute to chamber development and ventricular morphogenesis, and alteration of these regulatory mechanisms may influence cardiac structure in variable ways (9). Similarly, T-box genes regulate multiple stages of heart formation, including chamber specification, septation, and conduction-system development (10). These developmental mechanisms provide a reasonable biological basis for familial clustering while simultaneously explaining why family history may not correspond to a uniform VSD phenotype.

Another finding of the present study was that patients without a family history underwent surgical repair at a somewhat younger mean age than patients with a positive family history. Although this difference was not statistically significant, it may indicate that sporadic cases in this sample were not necessarily clinically milder than familial cases. The timing of VSD surgery is determined by several factors, including defect size, magnitude of left-to-right shunting, pulmonary arterial pressure, heart failure symptoms, growth failure, associated cardiac abnormalities, and the development of complications. Consequently, age at surgery should not be interpreted as a direct indicator of genetic severity. Small VSDs may remain asymptomatic and close spontaneously, whereas large defects can require intervention in infancy or early childhood because of pulmonary overcirculation and congestive heart failure (3, 4). The younger age at surgery observed among patients without a family history may therefore reflect differences in hemodynamic consequences, anatomical characteristics,

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referral patterns, symptom burden, or clinical decision-making rather than a protective or detrimental effect of familial predisposition itself.

The age-related pattern observed in this study is broadly compatible with clinical reports showing considerable variation in the timing of diagnosis and intervention among pediatric VSD patients. Manuel et al. described heterogeneous presentations of VSD among children and adolescents treated at a tertiary center, illustrating that age at presentation and clinical management can vary widely across patients (26). Such variation is expected because VSD represents a spectrum of lesions rather than a single uniform disorder. In addition, access to pediatric cardiology, timing of echocardiographic diagnosis, referral pathways, and local surgical capacity may influence the age at which an individual patient receives definitive treatment. Therefore, the absence of a significant difference in age between familial and non-familial cases in the present study suggests that family history alone may not be a sufficiently strong predictor of the timing of surgical intervention.

The study also showed that mean BMI was lower among patients without a family history of congenital heart disease than among those with a positive family history. Again, the difference approached but did not achieve statistical significance. Growth and nutritional status are clinically relevant in children with hemodynamically important congenital heart disease because increased metabolic demands, feeding difficulties, recurrent respiratory symptoms, and congestive heart failure can impair weight gain. Large VSDs with substantial left-to-right shunting may therefore contribute to poor somatic growth, especially before corrective intervention. The lower BMI observed in the non-familial group could consequently reflect greater preoperative hemodynamic burden in some patients, which is also compatible with their somewhat younger age at surgery. However, BMI is influenced by numerous non-cardiac determinants, including age, nutritional intake, socioeconomic circumstances, chronic illness, and overall growth patterns, and therefore cannot be interpreted as a specific marker of VSD severity.

This finding should also be considered in relation to the broader clinical management of congenital heart defects. Surgical outcomes are influenced by patient condition at the time of repair, and preoperative growth and nutritional status are among the variables that may complicate the clinical course (21). Nevertheless, because the current analysis did not demonstrate a statistically significant BMI difference, the results do not establish an association between familial status and nutritional phenotype. Rather, they indicate a pattern that deserves examination in a larger sample. Future investigation would benefit from incorporating weight-for-age, height-for-age, nutritional status, heart failure severity, feeding difficulties, pulmonary pressure, and shunt magnitude in addition to BMI.

VSD size was another major phenotype examined in the study. Both groups included patients with small, moderate, and large defects. Patients with a positive family history showed a relatively higher proportion of large VSDs, whereas intermediate defects were relatively more frequent among patients without a family history. Small defects were present in both groups at comparable proportions. These distributions, however, were not statistically significant. This finding indicates that a positive family history cannot be considered a reliable marker of larger defect size on the basis of the present data. VSD diameter represents only one dimension of clinical severity, and the physiological consequences of a defect depend on its relationship to body size, pulmonary vascular resistance, ventricular pressures, and associated lesions (3).

The absence of a significant association between family history and VSD size is consistent with the concept of variable phenotypic expression in congenital heart disease. Genetic susceptibility may increase the probability of abnormal cardiac development without determining the exact size or morphology of the resulting structural lesion (12). In addition, developmental disturbances affecting progenitor cells or transcriptional networks may lead to different anatomical outcomes even among individuals sharing a genetic predisposition (8, 9). Recent genomic reports similarly demonstrate that pathogenic variants associated with pediatric cardiovascular disease can produce highly variable clinical expression, ranging from structural abnormalities to severe cardiomyopathy and arrhythmia (15-17). Thus, familial inheritance may influence susceptibility without necessarily producing a predictable relationship with VSD diameter.

From a therapeutic perspective, the finding that both groups exhibited the full range of VSD sizes is important

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because the decision to close a VSD is not based exclusively on defect diameter. Patients with small or moderate lesions may require intervention if complications such as aortic cusp prolapse or aortic regurgitation develop, while selected defects can be treated using catheter-based approaches (19, 23). Conversely, even anatomically large defects must be evaluated in the context of overall hemodynamics, pulmonary vascular resistance, symptoms, and associated abnormalities. Surgical techniques are also adapted to defect complexity, including approaches designed for multiple VSDs (22). These considerations support the present finding that defect size alone is unlikely to explain differences in age at surgery between familial and non-familial patients.

Anatomical location represented one of the most notable descriptive differences between the groups. Subaortic VSD was the predominant anatomical type in both groups, but it was proportionally more frequent among patients without a family history. Muscular defects were also somewhat more frequent in the non-familial group. In contrast, subpulmonary and inlet VSDs were relatively more common among patients with a positive family history. Although these differences were not statistically significant, they are potentially meaningful because anatomical location is closely associated with developmental origin, complication profile, and treatment strategy. Classical pathological classification has long emphasized that VSDs arising in different regions of the septum represent anatomically distinct lesions (5).

The higher proportion of subaortic defects in the non-familial group may have contributed to earlier surgical referral in some cases because defects located near the aortic valve can predispose patients to cusp prolapse and aortic regurgitation. Ghosh et al. demonstrated the clinical importance of VSD-associated aortic valve prolapse and regurgitation and the potential role of defect closure in preventing progression of valve dysfunction (19). Similarly, VSD location is known to influence the risk of complications and the method of repair. Chaudhry et al. highlighted the range of complications associated with VSD, reinforcing the need to evaluate anatomy together with physiological consequences (18). Thus, the descriptive predominance of subaortic lesions among patients without a family history offers one possible explanation for their somewhat earlier age at surgery, although this interpretation remains speculative because statistical significance was not demonstrated.

The anatomical differences observed between familial and non-familial cases are also compatible with developmental evidence showing that septation depends on several distinct embryological processes. Differential contributions from cardiac progenitor populations and regulatory pathways could theoretically produce different locations of septal disruption (8). Expression of genes such as PITX2 and the activity of T-box and HAND transcription factors are spatially and temporally regulated during heart development (9-11). Accordingly, familial genetic predisposition might influence the location of a structural defect without necessarily determining its size or clinical severity. However, because no genetic testing was performed in the present study, this explanation should be regarded as a biologically plausible hypothesis rather than a demonstrated mechanism.

The findings should additionally be interpreted within the broader evolution of congenital cardiac medicine. Improvements in echocardiographic diagnosis, pediatric cardiac surgery, and transcatheter intervention have substantially changed the natural history of VSD (4, 23). Patients with unrepaired defects who survive into adulthood can still experience important complications, including pulmonary hypertension, infective endocarditis, arrhythmia, and aortic valve disease (6, 7). Rare acquired VSDs may also arise from severe pathological processes such as infective endocarditis (20). These observations emphasize that long-term outcome is determined by a combination of anatomy, physiology, associated complications, and treatment rather than by familial status alone.

The absence of statistically significant differences across the principal comparisons is itself clinically informative. The results suggest that family history should not be used in isolation to infer VSD severity, predict anatomical subtype, or determine the timing of surgical intervention. Familial information remains important because it can identify increased genetic susceptibility and may justify closer assessment of relatives or consideration of genetic counseling, particularly in families with multiple affected members. Maternal congenital heart disease is also relevant to reproductive counseling because congenital cardiovascular disorders can recur across generations (24).

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However, the clinical management of an individual patient should continue to be guided primarily by echocardiographic anatomy, hemodynamic significance, symptoms, growth, pulmonary pressures, and associated lesions.

Recent advances in genomic diagnosis reinforce the potential value of incorporating molecular investigation into future studies of familial VSD. Rapid exome sequencing is increasingly capable of identifying clinically relevant variants in children with serious cardiovascular disorders (15). Severe congenital heart abnormalities have also been recognized within defined molecular disorders such as SSR4-related congenital disorders of glycosylation (13), while syndromic cases can exhibit unusual combinations of congenital abnormalities (14). Such evidence suggests that family-history-based classification is useful but incomplete. Combining pedigree information with genomic data may eventually permit more precise distinction between truly sporadic VSD, monogenic familial disease, syndromic cases, and complex polygenic susceptibility.

Overall, the findings of this study indicate that Iraqi patients with and without a family history of congenital heart disease can exhibit broadly overlapping VSD phenotypes. Numerical differences were observed in BMI, age at surgery, defect size, and anatomical distribution, but these patterns did not reach statistical significance. The results therefore support a cautious interpretation in which familial predisposition may contribute to phenotypic variability but does not appear to be a dominant determinant of clinical presentation in this sample. The study contributes locally relevant evidence from Iraq and provides a basis for larger investigations integrating detailed family pedigrees, echocardiographic variables, hemodynamic measures, and genetic testing.

Several limitations should be considered when interpreting these findings. First, the study was conducted at a single specialized cardiac center and included only 100 surgically treated patients, which restricts the generalizability of the results and limits statistical power, particularly because only 23 participants had a positive family history. Second, family history was based on reported clinical information rather than systematic echocardiographic screening or genetic confirmation of relatives, creating the possibility of misclassification, especially when family members had mild or undiagnosed congenital defects. Third, the study did not incorporate molecular genetic testing, detailed pedigree analysis, consanguinity, maternal exposures, socioeconomic characteristics, pulmonary arterial pressure, shunt fraction, symptoms, nutritional indices other than BMI, or associated extracardiac abnormalities. Fourth, restricting the sample to patients who underwent surgery may have introduced selection bias because patients with small spontaneously closing VSDs or lesions managed conservatively were not represented. Finally, postoperative and long-term outcomes were not evaluated, preventing assessment of whether family history is related to complications, residual defects, reintervention, functional status, or survival.

Future studies should recruit substantially larger samples through multicenter collaboration involving pediatric and congenital cardiac centers across different regions of Iraq and, where feasible, neighboring populations. Prospective recruitment should include both surgically and conservatively managed patients so that the full clinical spectrum of VSD can be examined. Family history should be documented through standardized three-generation pedigrees and, when possible, supported by echocardiographic assessment of first-degree relatives. Future research should incorporate genomic approaches such as targeted congenital heart disease panels, chromosomal microarray analysis, or exome sequencing to determine whether specific genetic variants are associated with defect size, anatomical location, age at presentation, or treatment requirements. Detailed hemodynamic variables, pulmonary arterial pressure, shunt magnitude, growth measures, feeding status, associated cardiac lesions, consanguinity, maternal and prenatal exposures, and socioeconomic characteristics should also be examined. Longitudinal follow-up would be particularly valuable for determining whether familial status predicts postoperative complications, spontaneous closure, residual shunting, reintervention, arrhythmia, pulmonary hypertension, exercise capacity, or long-term quality of life.

In clinical practice, family history of congenital heart disease should be routinely obtained as part of the assessment of every child diagnosed with VSD, but it should not be used alone to classify disease severity or determine the timing of intervention. Clinical decisions should remain based on comprehensive echocardiographic evaluation,

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defect location and size, hemodynamic significance, pulmonary pressure, symptoms, growth trajectory, associated cardiac abnormalities, and the risk of complications. Patients from families with multiple congenital cardiac cases should receive more detailed pedigree assessment and may benefit from genetic counseling and evaluation of first-degree relatives when clinically appropriate. Particular attention should be paid to early recognition of poor growth, heart failure symptoms, aortic valve involvement, pulmonary hypertension, and other indicators of clinically important shunting. Strengthening referral pathways between primary care, pediatric services, echocardiography units, genetic services, and congenital cardiac surgery centers could facilitate earlier diagnosis, individualized monitoring, and timely intervention for Iraqi patients with VSD.

Authors' Contributions

All authors contributed substantially to the study and to manuscript development, and all approved the final version.

Declaration

The authors declare that artificial intelligence tools were used only to assist with language editing, translation, and improvement of the manuscript's readability. All conceptualization, study design, data collection, data analysis, interpretation of findings, and final approval of the manuscript were performed by the authors. The authors take full responsibility for the accuracy, integrity, and originality of the content.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

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Declaration of Interest

The authors report no conflict of interest.

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Ethics Considerations

The study placed a high emphasis on ethical considerations. Informed consent obtained from all participants, ensuring they are fully aware of the nature of the study and their role in it. Confidentiality strictly maintained, with data anonymized to protect individual privacy. The study adhered to the ethical guidelines for research with human subjects as outlined in the Declaration of Helsinki.

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