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Clinical, Echocardiographic, and Surgical Correlates of Ventricular Septal Defect Size in a Pediatric Population from Pakistan: A Retrospective Cohort Study

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Abstract

Background: Ventricular septal defect (VSD) is a common congenital cardiac lesion with clinical outcomes influenced by defect anatomy, size, and hemodynamics. Evidence linking VSD characteristics with clinical severity, pulmonary artery pressure, and intervention timing remains limited in Pakistan. This study evaluated these associations among children at a tertiary pediatric cardiology center in Khyber Pakhtunkhwa.

Methodology: This retrospective cohort study included children aged 0–12 years evaluated at Lady Reading Hospital, Peshawar, between March and October 2025. Of 1,291 children undergoing echocardiography, 312 (24.2%) met the eligibility criteria. VSDs were classified by size relative to the aortic annulus as small (≤25%), medium (>25%–75%), or large (>75%). Clinical severity was assessed using the modified Ross classification. Systolic pulmonary artery pressure (SPAP) was estimated echocardiographically, with elevated SPAP defined as >40 mmHg. Clinical, echocardiographic, intervention, and postoperative outcomes were analyzed using univariable and multivariable methods.

Results: Of 312 children, 94 (30.1%) had small, 140 (44.9%) medium, and 78 (25.0%) large VSDs; 69.9% were perimembranous. Modified Ross Class III/IV symptoms increased across size categories (4.3%, 30.0%, and 78.2%, respectively; $p < 0.001$), as did elevated SPAP (8.5%, 32.1%, and 83.3%; $p < 0.001$). Mean SPAP increased from 28.5±8.2 mmHg in small to 58.6±14.8 mmHg in large VSDs. VSD size correlated with Ross class ($\rho = 0.72$), while the VSD/aortic-annulus ratio correlated with SPAP ($r = 0.72$; both $p < 0.001$). Surgical closure was performed in 122 (39.1%) children, including 72 (92.3%) with large VSDs. Among children with large VSDs, 42 (53.8%) underwent closure before 6 months. Postoperative 30-day mortality was 0.8%, and permanent pacemaker implantation occurred in 2.5%. Rural residence, low socioeconomic status, and large VSD size were associated with surgical closure after 6 months.

Conclusion: Larger VSDs were associated with greater clinical severity, impaired growth, higher estimated SPAP, and more frequent surgical intervention. These observational findings support locally adapted referral and intervention pathways, although prospective studies with standardized hemodynamic assessment are needed.

Keywords

Ventricular Septal Defect, Echocardiography, Systolic Pulmonary Artery Pressure, Congenital Heart Disease, Surgical Closure, Children, Pakistan.

Introduction

Congenital heart disease (CHD) is the most common congenital structural abnormality worldwide, with an estimated prevalence of approximately 17.9 cases per 1,000 live births.[1] Ventricular septal defect (VSD) is among the most frequently encountered congenital cardiac lesions and accounts for approximately 20%–40% of congenital heart defects.[2,3] VSDs comprise a heterogeneous group of lesions whose clinical consequences depend not only on anatomical location and defect size but also on the degree of restriction, magnitude and direction of shunting, pulmonary and systemic vascular resistance, ventricular volume loading, and the presence of associated cardiac abnormalities.[4]

Large, nonrestrictive VSDs are of particular clinical importance because substantial left-to-right shunting can produce pulmonary over circulation, congestive heart failure, impaired growth, recurrent respiratory morbidity, and progressive elevation of pulmonary artery pressure.[4] Persistent exposure of the pulmonary circulation to increased flow and pressure may eventually contribute to pulmonary vascular remodeling and, in advanced cases, irreversible pulmonary vascular disease. Consequently, early identification of children at increased risk and appropriate assessment of the timing of intervention are important components of pediatric VSD management.

The burden of CHD is particularly important in low- and middle-income countries (LMICs), where approximately 90% of children with congenital heart disease are born but access to specialized diagnostic, interventional, and surgical cardiac services remains limited.[5] In Pakistan, approximately 60,000 children are estimated to be born with CHD annually, while geographic, socioeconomic, diagnostic, and healthcare-system barriers may restrict timely access to specialized care.[6,7] In Khyber Pakhtunkhwa, facility-based studies have identified VSD and patent ductus arteriosus among the common acyanotic congenital cardiac lesions, with variation in disease distribution across different divisions of the province.[7,8] These regional differences emphasize the importance of locally generated clinical data.

Echocardiography is central to the diagnosis, anatomical characterization, hemodynamic assessment, and longitudinal evaluation of VSD. Anatomically, VSDs may be classified as perimembranous, muscular, inlet, or outlet defects.[4] Defect size can also be expressed relative to the diameter of the aortic annulus, providing a standardized approach to anatomical size classification. Previous approaches have categorized defects as small when the diameter is ≤25% of the aortic annulus, medium when >25% to ≤75%, and large when >75%.[9-11] Such classification provides a practical anatomical descriptor, although anatomical size should not be considered synonymous with hemodynamic significance because shunt magnitude is additionally determined by pressure gradients, vascular resistance, defect restrictiveness, and associated lesions.

Echocardiography also permits noninvasive estimation of pulmonary artery pressure. Tricuspid regurgitation velocity, interpreted using the modified Bernoulli equation, is commonly used to estimate right ventricular and systolic pulmonary artery pressures, while the pressure gradient across a VSD can provide additional information in appropriately selected patients.[12,13] However, these measurements remain estimates and may not correspond precisely to invasively measured pulmonary pressures in individual patients. Cardiac catheterization remains important when direct measurement of pulmonary vascular resistance and assessment of operability are clinically required.[12-15] Therefore, echocardiographically estimated pulmonary artery pressure should not be interpreted as equivalent to confirmed pulmonary vascular disease.

Defect size and hemodynamic consequences also influence clinical presentation and management. Large VSDs have been associated with early congestive heart failure, failure to thrive, increased pulmonary blood flow, and elevated pulmonary artery pressure.[16-19] Timely closure may be required in symptomatic children or those demonstrating significant hemodynamic consequences. Published literature commonly identifies early infancy as an important period for assessment of children with large symptomatic defects, although the decision to

intervene depends on the complete clinical and hemodynamic profile rather than anatomical diameter or chronological age alone.[18,19]

Access to timely intervention remains particularly challenging in resource-limited settings. Delayed diagnosis, referral, and surgical treatment of congenital cardiac lesions have been reported in LMICs. For example, data from a Nigerian series demonstrated that a substantial proportion of children underwent VSD repair at considerably older ages than typically reported in higher-resource settings.[19] Such delays may prolong exposure to heart failure, impaired growth, recurrent respiratory illness, and elevated pulmonary pressures. Understanding the clinical and healthcare characteristics associated with timing of intervention is therefore particularly relevant in settings where pediatric cardiac services are geographically concentrated. Although Pakistani studies have described the frequency and anatomical distribution of congenital heart disease,[6-9] comparatively limited data are available linking standardized echocardiographic VSD-size categories with clinical severity, growth status, echocardiographically estimated pulmonary artery pressure, and timing of intervention in children from Khyber Pakhtunkhwa. Furthermore, locally derived evidence is needed to determine whether routinely available echocardiographic parameters could contribute to pragmatic risk stratification and referral pathways in resource-constrained pediatric cardiac services.

Therefore, the present study aimed to evaluate the associations of VSD anatomical type and defect size with clinical severity, growth status, echocardiographically estimated systolic pulmonary artery pressure, and timing and mode of closure among children presenting to a tertiary pediatric cardiology center in Khyber Pakhtunkhwa, Pakistan. Secondary objectives were to describe short-term surgical outcomes and spontaneous closure or reduction during the available follow-up.

Methodology

Study Design

This retrospective cohort study was conducted to evaluate the relationships between ventricular septal defect (VSD) anatomical characteristics and size, clinical severity, echocardiographically estimated pulmonary artery pressure, timing and mode of intervention, and short-term clinical outcomes in children presenting with VSD. Data were obtained retrospectively through review of routinely maintained hospital clinical records and echocardiographic studies. No patient was contacted specifically for research purposes, and no additional diagnostic or therapeutic procedure was performed as part of the study. The study period extended for 8 months, from March 2025 through October 2025. During this period, 1,291 echocardiographic examinations for suspected congenital heart disease were performed in 1,291 individual children; each child contributed only one index echocardiographic examination and was therefore counted once. Children were screened consecutively as they presented, and 312 children meeting the eligibility criteria constituted the final analytical cohort.

Ethics

Ethical approval was obtained from the Ethical Review Committee of Lady Reading Hospital-Medical Teaching Institution (LRH-MTI), Peshawar, Khyber Pakhtunkhwa, Pakistan. Because the investigation involved retrospective analysis of routinely collected clinical and echocardiographic records without direct patient contact or additional procedures, the requirement for individual informed consent was waived by the reviewing committee. Patient information was anonymized before analysis to maintain confidentiality and protect participant identity.

Setting

The study was conducted in the Department of Pediatric Cardiology, Lady Reading Hospital-Medical Teaching Institution (LRH-MTI), Peshawar, Khyber Pakhtunkhwa, Pakistan. The source population consisted of children aged 0–12 years attending the pediatric cardiology outpatient department for evaluation of suspected congenital heart disease between March and October 2025. Clinical assessment and echocardiography were undertaken as part of routine care. Children requiring surgery or intervention subsequently underwent relevant clinical and postoperative follow-up. Follow-up for the study

was defined as the period between the index echocardiogram and the last documented clinical or echocardiographic assessment, with 31 October 2025 designated as the study closing date. Because recruitment occurred throughout the 8-month period, individual follow-up ranged from 1 to 8 months, with a median of approximately 4 months. Follow-up echocardiography was performed according to clinical indication rather than a prespecified fixed schedule.

Participants

Children aged 0–12 years with an echocardiographically confirmed isolated VSD or a VSD accompanied by a minor cardiac lesion, including patent ductus arteriosus, atrial septal defect, or mild pulmonary stenosis, were eligible. Children were excluded when the index echocardiogram demonstrated no VSD or a cardiac lesion other than VSD; the VSD formed part of complex cyanotic congenital heart disease; there was a history of previous cardiac surgery or intervention; an important extracardiac anomaly or syndrome other than trisomy 21 was present; the echocardiographic examination was incomplete or the defect could not be measured reliably; or no documented clinical follow-up was available. Of 1,291 children screened, 979 were excluded on one or more of these grounds and 312 (24.2%) were included in the final analysis, as illustrated in Figure 1. Because individual exclusion categories were not recorded separately during the original screening process, category-specific numbers could not be reconstructed retrospectively.

Children with a small patent ductus arteriosus, small atrial septal defect, or mild pulmonary stenosis were retained because these lesions were permitted by the eligibility criteria. Their presence was recorded from the echocardiographic report and they were clinically judged not to be independently responsible for the presenting clinical picture. However, a complete distribution of these associated lesions across the VSD-size categories could not be retrieved for all participants; therefore, formal adjustment or sensitivity analysis excluding these lesions was not undertaken.

Variables

The principal exposure variables were anatomical VSD type and VSD size. VSDs were anatomically categorized as perimembranous, muscular, inlet, or outlet/supracristal according to accepted echocardiographic criteria.[4,11] VSD size was expressed relative to the diameter of the aortic annulus and categorized as small (≤25% of aortic annulus diameter), medium (>25% to ≤75%), or large (>75%).[10,11] Clinical variables included age at presentation, sex, weight-for-age Z-score, modified Ross functional class, recurrent respiratory infections, area of residence, and socioeconomic status. Clinical severity was classified according to the modified Ross criteria as Class I (asymptomatic), Class II (mild tachypnea or diaphoresis during feeding), Class III (marked tachypnea, diaphoresis, prolonged feeding with growth failure), or Class IV (symptoms at rest with failure to thrive requiring hospitalization).[20] Failure to thrive was defined as a weight-for-age Z-score <−2 using WHO growth standards.

Echocardiographic variables included VSD location and diameter, VSD/aortic-annulus ratio, direction and velocity of shunt flow, peak instantaneous VSD gradient, and echocardiographically estimated systolic pulmonary artery pressure (SPAP). Intervention variables included whether closure was surgical or transcatheter and age at closure. Postoperative outcomes included residual shunt, reoperation, complete heart block, right bundle branch block, mechanical ventilation duration, intensive care unit stay, total hospital stay, and 30-day mortality. A secondary outcome was spontaneous closure or significant reduction in defect size among children managed without early closure.

Data Sources / Measurement

Clinical, demographic, echocardiographic, interventional, and postoperative information was extracted from routinely maintained hospital records and echocardiographic studies. Echocardiography was performed by trained pediatric cardiologists using standardized clinical protocols, including complete two-dimensional imaging, color Doppler, and continuous-wave Doppler interrogation using commercially available ultrasound systems. VSDs

were anatomically classified according to accepted criteria. Defect size was assessed in multiple imaging planes using two-dimensional imaging and color-flow mapping, with the maximum diameter recorded in the parasternal short-axis view. The defect diameter was expressed relative to the aortic annulus diameter measured in the parasternal long-axis view and classified as small, medium, or large using the prespecified thresholds described above.

Hemodynamic assessment included the direction and velocity of shunt flow and measurement of the peak instantaneous gradient across the VSD by continuous-wave Doppler. Qp:Qs was estimated clinically in selected children when ventricular outflow Doppler tracings permitted such assessment; however, these measurements had not been entered into a separate analyzable database and therefore were not included as quantitative study variables. Consequently, descriptions of hemodynamic severity were based on defect size relative to the aortic annulus, direction and velocity of flow, and the observed clinical and echocardiographic consequences rather than quantitatively measured shunt volumes.

SPAP was estimated primarily from peak tricuspid regurgitation (TR) velocity using the modified Bernoulli equation: SPAP = 4 × (TR peak velocity)² + estimated right atrial pressure.[12,13] Right atrial pressure was estimated from inferior vena cava diameter and collapsibility. When an adequate TR signal was unavailable and right ventricular outflow tract obstruction was absent, SPAP was estimated from the VSD gradient as SPAP = systolic blood pressure − 4 × (VSD peak velocity)² for left-to-right shunts. This calculation assumes simultaneous ventricular systole, approximation of left ventricular systolic pressure by cuff-measured systemic systolic pressure, an appropriate shunt for pressure-gradient estimation, and equivalence of right ventricular and pulmonary artery systolic pressures in the absence of outflow obstruction. VSD-gradient-derived estimates were interpreted with these limitations and were not used to classify pulmonary pressure when the defect was small and restrictive. When available, mean pulmonary artery pressure was additionally estimated using pulmonary regurgitation end-diastolic velocity or pulmonary acceleration time.[12,13]

Elevated pulmonary artery pressure was operationally defined as an echocardiographically estimated SPAP >40 mmHg, while severe elevation was defined as estimated SPAP >60 mmHg or at systemic level. These measurements were regarded as echocardiographic estimates rather than confirmation of pulmonary vascular disease. No invasive cardiac catheterization-based pulmonary vascular resistance measurements were available for the cohort.

For follow-up outcomes, spontaneous VSD closure required a follow-up echocardiogram demonstrating complete absence of flow across the ventricular septum. Significant reduction was defined as reduction of the measured defect diameter to ≤50% of its index measurement together with resolution of echocardiographic evidence of left-to-right shunt-related volume loading. Because the exact interval from index examination to closure or reduction was not consistently documented, time-to-event analysis was not performed and spontaneous closure/reduction was reported as a crude proportion.

Bias

Several measures were used to reduce potential measurement and analytical bias. Consecutive screening of children undergoing index echocardiography during the defined study period was used to minimize discretionary participant selection. Each child contributed only one index examination, preventing repeated examinations from being counted as independent observations. Standardized echocardiographic protocols, prespecified anatomical definitions, and predefined VSD-size thresholds were used to improve consistency of exposure classification. Clinical severity was assessed using the modified Ross classification,[20] while growth was evaluated using WHO growth standards.

Nevertheless, because this was a retrospective, single-center study, selection bias, referral bias, residual confounding, and incomplete

documentation could not be eliminated. Individual reasons for exclusion among the 979 excluded children were not separately recorded, associated minor cardiac lesions could not be fully adjusted for, and follow-up echocardiography was clinically indicated rather than scheduled at uniform intervals. Age at presentation also differed substantially among VSD-size categories, making unadjusted group comparisons susceptible to confounding. These limitations were considered when interpreting associations, and causal conclusions were avoided.

Study Size

The study size was determined by the number of eligible children available during the predefined 8-month study period rather than by prospective recruitment to a calculated target. Of 1,291 unique children undergoing an index echocardiogram for suspected congenital heart disease, 979 were excluded according to the eligibility criteria, leaving 312 children (24.2%) in the final analytical cohort. The cohort comprised 94 children with small VSDs, 140 with medium VSDs, and 78 with large VSDs. Of the total cohort, 122 children underwent surgical closure and 18 underwent attempted transcatheter closure. No prospective sample-size or power calculation is reported because the study used an available retrospective cohort.

Quantitative variables

Continuous variables included age at presentation, age at closure, weight-for-age Z-score, VSD/aortic-annulus ratio, estimated SPAP, mechanical ventilation duration, ICU stay, total hospital stay, cardiopulmonary bypass time, and aortic cross-clamp time. VSD size was analyzed both as an ordinal, three-level categorical variable (small, medium, and large) and, where appropriate, as the continuous VSD/aortic-annulus ratio. Modified Ross class was treated as an ordinal variable. Estimated SPAP was analyzed continuously and was additionally categorized as normal or elevated using the >40 mmHg threshold, with >60 mmHg or systemic-level pressure classified as severe elevation. Surgical timing was dichotomized for the multivariable analysis as closure after 6 months of age versus closure at or before 6 months. Categorical variables were summarized as frequencies and percentages, whereas continuous variables were summarized according to their observed distributions.

Statistical Methods

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Distribution of continuous variables was assessed using the Shapiro–Wilk test together with visual inspection of histograms. Normally distributed continuous variables were summarized as mean ± standard deviation, whereas skewed continuous variables were summarized as median and interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. Between-group comparisons for categorical variables were performed using the chi-square test or Fisher's exact test where appropriate. Normally distributed continuous variables, including weight-for-age Z-score and estimated SPAP, were compared using analysis of variance (ANOVA). Skewed variables, including age at presentation, age at closure, ventilation duration, ICU stay, hospital stay, cardiopulmonary bypass time, and aortic cross-clamp time, were compared using the Kruskal–Wallis test. When an overall group comparison was statistically significant, pairwise comparisons were performed with Bonferroni adjustment for multiple testing.

Correlation methods were selected according to variable type. The relationship between the three-level VSD-size category and modified Ross class was evaluated using Spearman rank correlation because both variables were ordinal. The association between the continuous VSD/aortic-annulus ratio and estimated SPAP was assessed using Pearson correlation. Analyses included children with complete information for the variables under consideration, and correlation coefficients were reported with the corresponding number of observations, two-sided p-values, and 95% confidence intervals.

Multivariable logistic regression was used to examine factors associated with surgical closure after 6 months of age among children who underwent surgical closure during the study period. The dependent variable was surgical closure after 6 months versus closure at or before 6 months.

Candidate predictors were selected a priori on clinical grounds and included sex, VSD-size category, VSD anatomical type, presence of an associated minor cardiac lesion, area of residence, and socioeconomic status. Candidate variables were entered simultaneously rather than through stepwise selection. Age at presentation was not entered into the final model because of its close relationship with age at operation. Multicollinearity was assessed using variance inflation factors, calibration using the Hosmer–Lemeshow test, and discrimination using the area under the receiver operating characteristic curve. Adjusted odds ratios were reported with 95% confidence intervals. No imputation was undertaken because the variables included in the reported analyses were complete after application of the study eligibility criteria. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Participants

During the 8-month study period from March to October 2025, 1,291 individual children underwent an index echocardiographic examination in the Pediatric Cardiology outpatient department for evaluation of suspected congenital heart disease. After application of the predefined eligibility criteria, 979 children were excluded and 312 (24.2%) children with an isolated ventricular septal defect (VSD) or a VSD accompanied by an eligible minor cardiac lesion constituted the final analytical cohort. Each participant contributed only one index echocardiographic examination. The participant selection process, distribution according to VSD size, and subsequent intervention status are summarized in Figure 1. The final cohort included 94 children (30.1%) with small VSDs, 140 (44.9%) with medium VSDs, and 78 (25.0%) with large VSDs. During the study period and available follow-up, 122 children (39.1%) underwent surgical closure, 18 (5.8%) underwent attempted transcatheter closure, and the remaining 172 (55.1%) did not undergo closure during the study period (Figure 1).

Descriptive Data

The median age at presentation for the overall cohort was 8 months (range 2–84 months), and 62.2% of children presented during infancy (<12 months). There was a slight male predominance, with a male-to-female ratio of 1.2:1. Geographically, 36.9% of participants were from Peshawar Division, 28.8% from Malakand Division, and 34.3% from other divisions of Khyber Pakhtunkhwa. Baseline demographic and clinical characteristics according to VSD size are presented in Table 1. Age at presentation differed substantially across the three size categories, with median ages of 18 [IQR 8–36], 8 [4–16], and 4 [2–8] months for small, medium, and large VSDs, respectively ($p<0.001$). In contrast, the proportion of males was similar across the three groups (55.3%, 55.0%, and 55.1%, respectively; $p=0.99$). Nutritional status progressively differed across VSD-size groups, with mean weight-for-age Z-scores of −0.5±1.2 for small, −1.8±1.5 for medium, and −2.5±1.3 for large VSDs ($p<0.001$) (Table 1).

Perimembranous VSD was the predominant anatomical subtype, accounting for 218 (69.9%) cases, followed by muscular VSD in 47 (15.1%), outlet VSD in 31 (9.9%), and inlet VSD in 16 (5.1%). Among the 78 children with large VSDs, 60 (76.9%) had perimembranous defects, eight (10.3%) muscular defects, eight (10.3%) outlet defects, and two (2.6%) inlet defects. The mean VSD/aortic-annulus ratio among children with large VSDs was 0.82±0.08, with absolute defect dimensions ranging from 8 to 16 mm. The anatomical distribution of VSDs and corresponding proportions with large defects, elevated estimated SPAP, surgical closure, and age at closure are presented in Table 2. Because anatomical type, defect size, and age were interrelated and the anatomical groups were unequal in size, these anatomical comparisons were treated descriptively rather than as evidence of independent effects (Table 2).

Outcome Data

Clinical severity increased across the VSD-size categories. Modified Ross Class III/IV symptoms were documented in 4 of 94 (4.3%) children with small VSDs, 42 of 140 (30.0%) with medium VSDs, and 61 of 78 (78.2%) with large VSDs ($p<0.001$). Failure to thrive, defined as a weight-for-age Z-score <-2, was present in 5 (5.3%), 45 (32.1%), and 56 (71.8%) children in the small, medium, and large VSD groups, respectively ($p<0.001$). Recurrent respiratory infections requiring hospitalization were also more

frequent among children with large defects, occurring in 55 of 78 (70.5%) children. These clinical patterns are summarized in Table 1 and illustrated in Figure 2. The between-group comparisons were unadjusted and should be interpreted in the context of the substantial differences in age at presentation among the three VSD-size groups.

Elevated echocardiographically estimated systolic pulmonary artery pressure (SPAP >40 mmHg) was identified in 118 (37.8%) children overall. Its frequency increased across VSD-size categories, from 8 of 94 (8.5%) children with small defects to 45 of 140 (32.1%) with medium defects and 65 of 78 (83.3%) with large defects ($p<0.001$). Severe elevation of estimated SPAP (>60 mmHg or systemic-level pressure) occurred in 27 of 78 (34.6%) children with large VSDs. Mean estimated SPAP was 28.5±8.2 mmHg in the small-VSD group, 42.3±11.5 mmHg in the medium-VSD group, and 58.6±14.8 mmHg in the large-VSD group ($p<0.001$), as shown in Table 1 and Figure 2. Anatomically, elevated estimated SPAP was documented in 39.0% of perimembranous, 25.5% of muscular, 51.6% of outlet, and 31.3% of inlet defects (Table 2). These measurements represent echocardiographic estimates; no participant underwent cardiac catheterization and pulmonary vascular resistance was not measured.

Surgical closure was performed in 122 of 312 children (39.1%), while transcatheter closure was attempted in 18 (5.8%). Surgical intervention differed markedly according to VSD size, occurring in 5 of 94 (5.3%) children with small defects, 45 of 140 (32.1%) with medium defects, and 72 of 78 (92.3%) with large defects ($p<0.001$) (Table 1). Median age at closure was 24 [IQR 12–36] months for small, 12 [8–18] months for medium, and 7 [4–12] months for large VSDs ($p<0.001$). Among all 78 children with large VSDs, 42 (53.8%) underwent surgical closure before 6 months of age. Outcomes of attempted transcatheter closure, including technical success, conversion to surgery, and residual shunt, were not consistently retrievable for all 18 children and therefore could not be reported.

Among the 122 children who underwent surgical closure, 104 (85.2%) had an uneventful postoperative course. Residual shunt of at least mild severity was identified in 10 (8.2%) children on predischarge echocardiography, with three (2.5%) requiring reoperation. Complete heart block requiring permanent pacemaker implantation occurred in three (2.5%) children, while right bundle branch block was documented in 18 (14.8%) postoperative electrocardiograms. One death occurred within 30 days of surgery, corresponding to a 30-day mortality of 0.8% (1/122). Postoperative outcomes according to preoperative pulmonary pressure status are detailed in Table 3 and Figure 3. Children with elevated preoperative estimated SPAP had longer postoperative mechanical ventilation (median 42 versus 16 hours, $p<0.001$), ICU stay (6 versus 3 days, $p<0.001$), and total hospital stay (13 versus 7 days, $p<0.001$) than those with normal estimated SPAP (Table 3; Figure 3).

During the available follow-up, spontaneous closure or significant reduction was documented in 35 of 94 (37.2%) children with small VSDs and two of 78 (2.6%) children with large VSDs. These percentages represent crude proportions rather than time-to-event estimates because follow-up varied from 1 to 8 months, with a median of approximately 4 months, and the precise interval between the index examination and spontaneous closure or reduction was not consistently recorded. Therefore, these findings should be interpreted as short-term observations rather than estimates of long-term spontaneous closure probability.

Main Results

VSD size category demonstrated a strong positive association with clinical severity. Spearman rank analysis showed a correlation between increasing VSD-size category and increasing modified Ross class ($\rho=0.72$, approximately 95% CI 0.66–0.77, $p<0.001$; $n=312$). This relationship was consistent with the marked increase in Ross Class III/IV symptoms, failure to thrive, recurrent respiratory morbidity, elevated estimated SPAP, and surgical intervention across increasing VSD-size categories (Table 1; Figure 2). However, these group comparisons were unadjusted, and age at presentation differed substantially among the small, medium, and large VSD groups; therefore,

the observed differences cannot be attributed to defect size alone.

A similarly strong positive relationship was observed between the continuous VSD/aortic-annulus ratio and echocardiographically estimated SPAP (Pearson r=0.72, approximately 95% CI 0.66–0.77, p<0.001; n=312). Children with large VSDs had substantially higher estimated SPAP and a higher frequency of severe pressure elevation than children with smaller defects (Table 1; Figure 2). Because pulmonary pressures were estimated noninvasively and no child underwent cardiac catheterization, these results indicate an association with echocardiographically estimated pulmonary pressure and should not be interpreted as confirmation of pulmonary vascular disease.

In the multivariable analysis of the 122 children who underwent surgical closure, rural residence (adjusted OR 3.2, 95% CI 1.8–5.7; p<0.001), low socioeconomic status (adjusted OR 2.8, 95% CI 1.5–5.2; p=0.001), and large VSD size (adjusted OR 4.5, 95% CI 2.1–9.6; p<0.001) were reported as independently associated with surgical closure after 6 months of age (**Table 4**). The outcome represented the age at which surgical closure occurred (>6 months versus ≤6 months) and should therefore be interpreted as delayed surgical closure rather than as the age at which the child first presented for medical care.

Table 1: Baseline Demographic and Clinical Characteristics by VSD Size.

Characteristics	Small VSD (≤25%) n=94	Medium VSD (>25-75%) n=140	Large VSD (>75%) n=78	p-value
Age at presentation, months, median [IQR]	18 [8-36]	8 [4-16]	4 [2-8]	<0.001*
Male, n (%)	52 (55.3%)	77 (55.0%)	43 (55.1%)	0.99
Weight-for-age Z-score, mean ± SD	−0.5 ± 1.2	−1.8 ± 1.5	−2.5 ± 1.3	<0.001*
Modified Ross Class III/IV, n (%)	4 (4.3%)	42 (30.0%)	61 (78.2%)	<0.001*
Recurrent pneumonia, n (%)	5 (5.3%)	35 (25.0%)	55 (70.5%)	<0.001*
Estimated SPAP, mmHg, mean ± SD	28.5 ± 8.2	42.3 ± 11.5	58.6 ± 14.8	<0.001*
Surgical closure, n (%)	5 (5.3%)	45 (32.1%)	72 (92.3%)	<0.001*
Age at closure, months, median [IQR]	24 [12-36]	12 [8-18]	7 [4-12]	<0.001*

Continuous variables are summarised as median [IQR] or mean ± SD according to the distribution of the variable, as described in the Statistical analyses. Categorical variables are summarised as n (%).
p-values are from the Kruskal-Wallis test for skewed continuous variables, analysis of variance for normally distributed continuous variables and the chi-square test for categorical variables.
Estimated SPAP refers to echocardiographically estimated systolic pulmonary artery pressure. IQR, interquartile range; SPAP, systolic pulmonary artery pressure; VSD, ventricular septal defect.
*p<0.05 is considered statistically significant.

Table 2: Coronary angiographic disease burden by parental history.

Anatomical Type	n (%)	Large Size, n (%)	Elevated SPAP, n (%)	Surgical Closure, n (%)	Age at Closure, months, median [IQR]
Perimembranous	218 (69.9%)	60 (27.5%)	85 (39.0%)	95 (43.6%)	7 [4-14]
Muscular	47 (15.1%)	8 (17.0%)	12 (25.5%)	12 (25.5%)	14 [8-24]
Outlet	31 (9.9%)	8 (25.8%)	16 (51.6%)	12 (38.7%)	5 [3-8]
Inlet	16 (5.1%)	2 (12.5%)	5 (31.3%)	3 (18.8%)	10 [6-18]

Percentages in columns 3 to 5 are of the number of children with that anatomical type.

Elevated SPAP indicates an estimated SPAP above 40 mmHg. Because anatomical type and defect size are related, and because the numbers in the outlet and inlet groups are small, this table is presented descriptively; formal adjustment of anatomical type for defect size was not performed in this retrospective dataset.

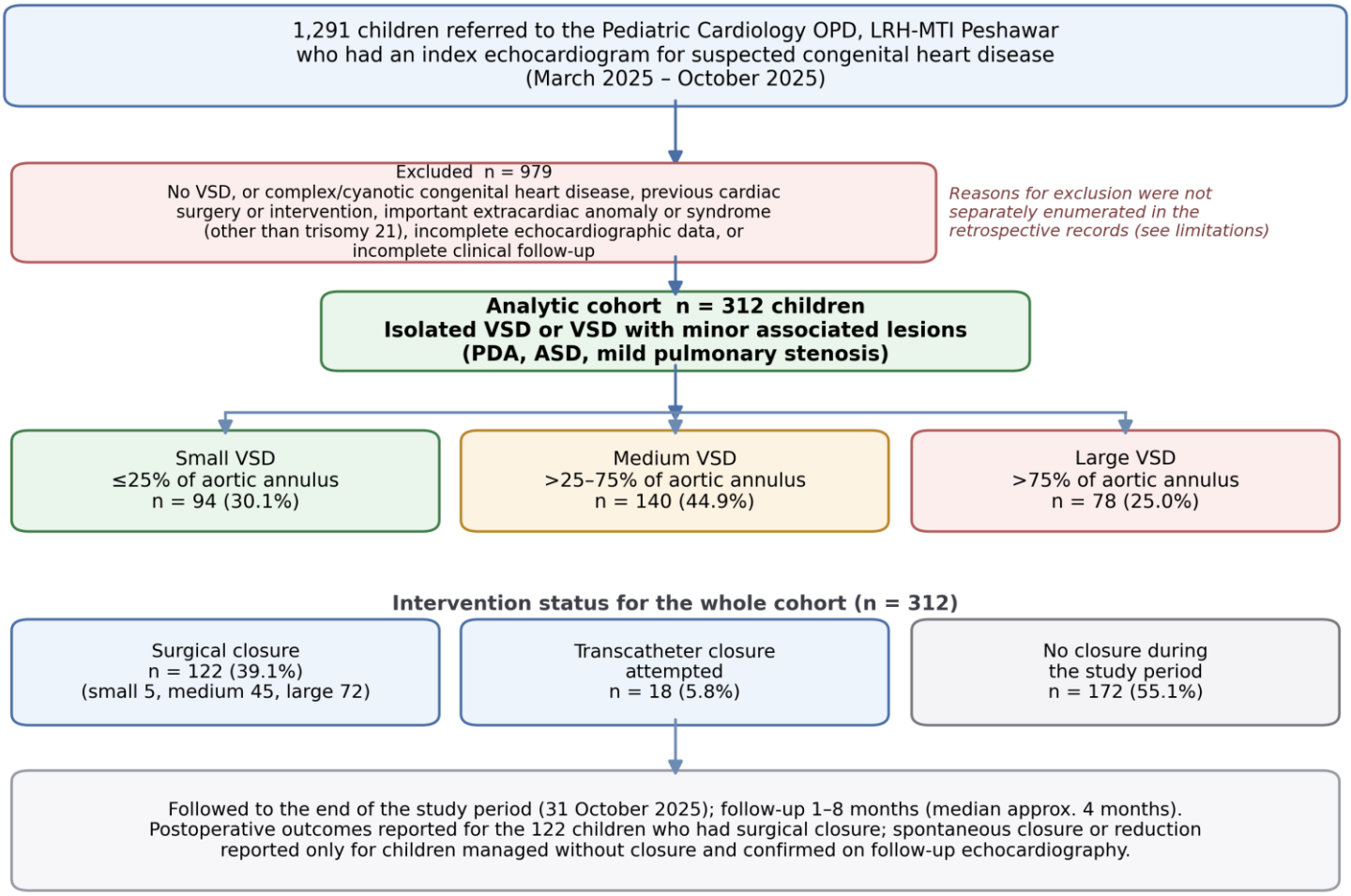


Figure 1: Flow of children through the study (source population, exclusions, analytic cohort and intervention status).

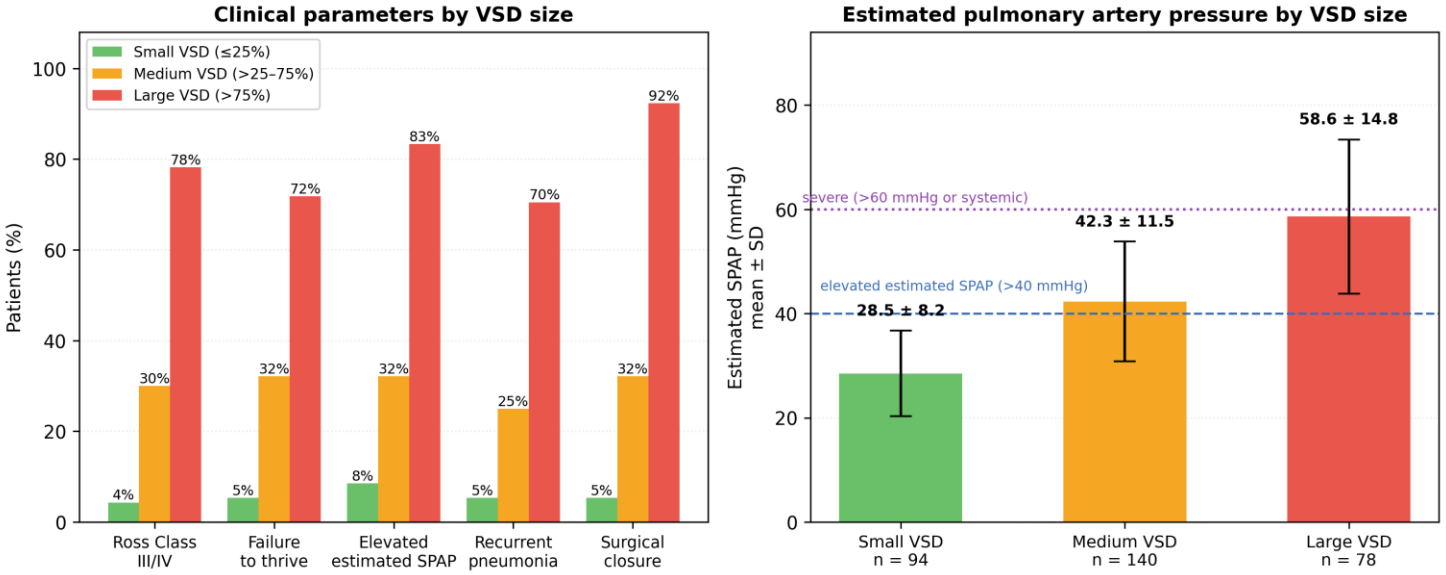


Figure 2: Clinical Correlates of VSD Size. These comparisons between size groups are unadjusted. They describe the children as they presented, and because the age at presentation differed substantially between the three size groups (median 18, 8 and 4 months for small, medium and large defects respectively), defect size alone cannot be said to account for the differences observed.

Table 3: Surgical Outcomes by Preoperative Pulmonary Pressure Status.

Outcome	Normal estimated SPAP n=45	Elevated estimated SPAP n=77	p-value
Cardiopulmonary bypass time, min, mean ± SD	82 ± 24	98 ± 28	0.002*
Aortic cross-clamp time, min, mean ± SD	52 ± 16	64 ± 20	0.001*
Postoperative ventilation, hours, median [IQR]	16 [10-22]	42 [24-68]	<0.001*
ICU stay, days, median [IQR]	3 [2-4]	6 [4-9]	<0.001*
Total hospital stay, days, median [IQR]	7 [6-10]	13 [9-18]	<0.001*
Residual shunt, n (%)	3 (6.7%)	7 (9.1%)	0.56
Complete heart block, n (%)	1 (2.2%)	2 (2.6%)	0.85
30-day mortality, n (%)	0 (0%)	1 (1.3%)	0.42

All outcomes are reported for the 122 children who underwent surgical closure, grouped according to whether the preoperative echocardiographic estimate of systolic pulmonary artery pressure was normal or elevated (defined as an estimated SPAP above 40 mmHg, see Methods). Continuous variables are summarised as mean ± SD or median [IQR] according to distribution. Mortality refers to death from any cause within 30 days of operation (30-day mortality); the single death in this series occurred after the first 24 hours and is counted in this way. There was no death in the operating theatre or within the first 24 hours after operation. ICU, intensive care unit; SPAP, systolic pulmonary artery pressure.

*p<0.05 is considered statistically significant.

Table 4: Multivariable Logistic Regression of Factors Associated with Surgical Closure After 6 Months of Age.

Variables	Reference category	Adjusted OR (95% CI)	p-value
Rural residence	Urban residence	3.2 (1.8-5.7)	<0.001*
Low socioeconomic status	Middle or upper socioeconomic status	2.8 (1.5-5.2)	0.001*
Large VSD (>75% of aortic annulus)	Small VSD (≤25%)	4.5 (2.1-9.6)	<0.001*

Surgical closure after 6 months of age versus closure at or before 6 months of age, analysed in the 122 children who underwent surgical closure during the study period. Candidate predictors entered simultaneously into the model were age at presentation, sex, VSD size category, VSD anatomical type, presence of an associated lesion (patent ductus arteriosus, atrial septal defect or mild pulmonary stenosis), area of residence and socioeconomic status. The three variables shown were the statistically significant predictors; the coding and reference categories for the variables shown are given in the table. Age at presentation was not entered as a covariate because it is collinear with the outcome (age at operation).
*p<0.05 is considered statistically significant.

Discussion

This retrospective cohort study provides clinically relevant data on the relationships between VSD size, anatomical subtype, clinical severity, growth status, echocardiographically estimated pulmonary artery pressure, and timing of intervention among children presenting to a tertiary pediatric cardiac center in Khyber Pakhtunkhwa, Pakistan. The principal finding was a consistent increase in clinical and echocardiographic disease burden across increasing VSD-size categories. Children with large VSDs presented at a younger age, had greater clinical severity, poorer growth, more frequent recurrent respiratory morbidity, higher estimated systolic pulmonary artery pressure (SPAP), and substantially greater use of surgical closure than children with smaller defects. Nevertheless, these associations should be interpreted within the observational nature of the study, particularly because age at presentation differed substantially between VSD-size groups and potentially important hemodynamic and anatomical confounders could not be fully adjusted.

The observed association between VSD size relative to the aortic annulus and clinical severity supports the practical value of standardized echocardiographic characterization of defect size. Classification according to the broad thresholds of ≤25%, >25% to ≤75%, and >75% of the aortic annulus provides an objective anatomical framework that can be incorporated into routine echocardiographic reporting [10,11]. In the present cohort, increasing VSD-size category correlated strongly with increasing modified Ross class, while large defects were accompanied by substantially higher frequencies of failure to thrive and recurrent respiratory morbidity. These observations are physiologically plausible and consistent with the recognized consequences of substantial left-to-right shunting and pulmonary overcirculation.[16,17] However, anatomical defect size should not be interpreted as a direct measure of hemodynamic significance. The physiological effect of a VSD also depends on defect restrictiveness, pulmonary and systemic vascular resistance, shunt magnitude, ventricular volume loading, and associated cardiac lesions. Because quantitative Qp:Qs measurements were not available for analysis in this study, the VSD/aortic-annulus ratio should be regarded as a useful anatomical descriptor rather than a stand-alone measure of shunt severity.

Perimembranous VSD was the predominant anatomical subtype, accounting for approximately 70% of defects, which is broadly consistent with established descriptions of VSD anatomy.[4] Outlet defects represented a smaller proportion but demonstrated relatively high estimated pulmonary

pressures in this cohort. The clinical importance of outlet VSDs extends beyond shunt magnitude because of their recognized association with aortic cusp prolapse and progressive aortic regurgitation, which may influence the timing of intervention.[2] Nevertheless, the present anatomical subgroup comparisons should be interpreted descriptively. Anatomical type, defect size, and age at presentation were interrelated, subgroup sizes were unequal, and formal multivariable adjustment for these factors was not undertaken. Therefore, the study does not establish an independent effect of VSD anatomical subtype on pulmonary pressure or clinical outcomes.

A major finding was the association between increasing VSD size and higher echocardiographically estimated SPAP. Elevated estimated SPAP was substantially more frequent among children with large defects, and the continuous VSD/aortic-annulus ratio correlated positively with estimated SPAP. This relationship is consistent with the expected physiology of larger left-to-right communications and increased pulmonary blood flow. However, several qualifications are essential when interpreting these observations. Echocardiographic estimation using tricuspid regurgitation velocity and the modified Bernoulli equation is an established noninvasive approach [17,18,20], but agreement with invasively measured pressures may be imperfect, particularly in children and in individuals with elevated right-sided pressures [21]. Furthermore, associated lesions such as patent ductus arteriosus and atrial septal defect can independently increase pulmonary blood flow. Accordingly, the observed relationship should not be interpreted as evidence that VSD size alone determines pulmonary pressure.

Importantly, no child in the present cohort underwent cardiac catheterization and pulmonary vascular resistance was not measured. The study therefore cannot distinguish elevated pulmonary artery pressure resulting predominantly from increased pulmonary blood flow from established pulmonary vascular disease. The SPAP values reported here should consequently be understood as echocardiographic estimates rather than confirmation of pulmonary arterial hypertension or pulmonary vascular disease. Where pulmonary pressures are markedly elevated and operability is uncertain, comprehensive hemodynamic assessment, including invasive assessment of pulmonary vascular resistance and reactivity where clinically indicated and available, remains important.[12-15]

The timing of intervention is another important finding. Large VSDs were associated with a high frequency of surgical closure, although not all children underwent surgery within early infancy. Published literature emphasizes early assessment and timely intervention for symptomatic large defects to reduce prolonged exposure to pulmonary overcirculation, growth failure, and elevated pulmonary pressures.[18,19] Nevertheless, a specific age threshold should not be applied independently of the child's complete clinical and hemodynamic profile. Symptoms, growth trajectory, degree of pulmonary overcirculation, estimated pulmonary pressures, pulmonary vascular resistance when clinically relevant, associated lesions, and overall surgical suitability must collectively inform the timing of intervention. In settings where children may first reach specialist care after infancy, the practical objective is therefore timely comprehensive assessment followed by intervention when clinically appropriate rather than adherence to chronological age alone.

The multivariable analysis identified rural residence, lower socioeconomic status, and large VSD size as factors associated with surgical closure after 6 months of age. These findings are relevant in the context of inequalities in access to specialized congenital cardiac services in Pakistan and other LMIC settings.[5-9] However, the modeled outcome was age at surgical closure, not age at first healthcare contact or referral. Consequently, these associations should not be interpreted as direct evidence that rural residence or socioeconomic disadvantage caused delayed presentation. They may instead reflect a combination of referral pathways, geographic

accessibility, financial constraints, disease characteristics, availability of specialized services, and other unmeasured factors. Similar challenges in obtaining timely VSD repair have been reported in resource-limited settings.[21] Future prospective studies should separately document age at symptom onset, first healthcare contact, diagnosis, referral, specialist assessment, and definitive intervention to identify where delays occur along the care pathway.

Short-term surgical outcomes were generally favorable within the available follow-up. Among the 122 children undergoing surgical closure, 30-day mortality was 0.8%, while complete heart block requiring permanent pacemaker implantation occurred in 2.5%. These findings are broadly consistent with the expectation that contemporary VSD repair can be performed with relatively low mortality in appropriately selected children.[16,17] Children with elevated preoperative estimated SPAP experienced longer postoperative mechanical ventilation and ICU stays, suggesting a greater perioperative resource requirement in this subgroup. However, these comparisons were observational and were not comprehensively adjusted for defect size, age, nutritional status, disease severity, or other perioperative factors. Therefore, elevated estimated SPAP should be regarded as an associated preoperative characteristic rather than an independently established cause of prolonged postoperative recovery.

Transcatheter closure was attempted in only a small proportion of the cohort. This reflects both anatomical considerations and the clinical selection of suitable defects. Transcatheter closure may provide an alternative to surgery in selected patients, and previous evidence has compared catheter-based and surgical approaches, particularly for muscular and selected perimembranous VSDs.[22] However, the present study cannot evaluate the effectiveness or safety of transcatheter closure because technical success, conversion to surgery, residual shunting, and procedure-related complications were not consistently retrievable for all 18 children undergoing attempted device closure. No comparative conclusions between surgical and transcatheter treatment should therefore be drawn from these data.

Spontaneous closure or substantial reduction was more frequently observed among children with small VSDs than among those with large defects. This pattern is consistent with the established natural history of VSD, particularly the greater tendency of small and muscular defects to close spontaneously.[23-25] However, the observed proportion should not be interpreted as an estimate of long-term spontaneous closure probability. Follow-up ranged from only 1 to 8 months, with a median of approximately 4 months, echocardiographic reassessment was performed according to clinical indication rather than at standardized intervals, and the precise time to closure was not consistently available. Consequently, crude proportions rather than time-to-event estimates were reported. Longer prospective follow-up using standardized echocardiographic intervals and survival-analysis methods would provide a more reliable assessment of spontaneous closure.

Taken together, these findings suggest that routinely available clinical and echocardiographic parameters may assist in identifying children who warrant closer surveillance and early specialist assessment in resource-constrained settings. Standardized reporting of VSD anatomy, VSD/aortic-annulus ratio, clinical severity, growth status, shunt characteristics, and estimated pulmonary pressure may improve consistency in clinical assessment. However, the present findings should be viewed as potential evidence for developing and prospectively evaluating locally adapted referral and management pathways rather than as definitive practice recommendations.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, its retrospective, single-center design introduces the possibility of selection, referral, information, and documentation bias and limits generalizability to

children managed in other healthcare settings. Although 1,291 children were screened, the individual reasons for exclusion of the 979 excluded children were not separately recorded, preventing a detailed assessment of potential selection effects. Second, the study was conducted over an 8-month period and may therefore not capture seasonal or longer-term variation in referral and disease presentation.

Third, pulmonary artery pressures were estimated echocardiographically rather than confirmed by invasive hemodynamic assessment. No participant underwent cardiac catheterization, and pulmonary vascular resistance and its reactivity were not measured. The study therefore cannot distinguish elevated pulmonary pressure due predominantly to increased pulmonary blood flow from established pulmonary vascular disease. Echocardiographic SPAP should consequently be interpreted as an estimate rather than a definitive diagnosis of pulmonary hypertension or pulmonary vascular disease.

Fourth, children with small patent ductus arteriosus, small atrial septal defect, or mild pulmonary stenosis were included, but their distribution across VSD-size categories could not be completely reconstructed and their effects could not be formally adjusted. These lesions may influence pulmonary blood flow or right-sided pressures and therefore represent potential residual confounders. Similarly, quantitative Qp:Qs data were unavailable for analysis, preventing direct assessment of shunt magnitude.

Fifth, age at presentation differed substantially among VSD-size categories. The principal comparisons between small, medium, and large defects were unadjusted, and therefore the observed differences in symptoms, growth, estimated pulmonary pressure, and intervention cannot be attributed solely to defect size. The study should consequently be interpreted as demonstrating associations rather than independent or causal effects.

Sixth, the number of surgically treated children was relatively limited for multivariable and postoperative analyses. The regression findings should therefore be interpreted cautiously, particularly given the possibility of residual confounding by factors not consistently available in retrospective records. In addition, the regression outcome represented surgical closure after 6 months of age and should not be interpreted as a direct measure of delayed presentation or delayed first healthcare contact.

Seventh, follow-up was relatively short and non-standardized, ranging from 1 to 8 months with a median of approximately 4 months. Follow-up echocardiography was performed according to clinical indication rather than at fixed intervals, and the exact interval to spontaneous closure or reduction was not consistently documented. Consequently, spontaneous closure was reported as a crude proportion rather than through time-to-event analysis, and longer-term natural history cannot be inferred.

Conclusion

In this tertiary-care pediatric cohort from Khyber Pakhtunkhwa, increasing VSD size was associated with greater clinical severity, poorer growth, recurrent respiratory morbidity, higher echocardiographically estimated systolic pulmonary artery pressure, and a greater frequency of surgical intervention. Large VSDs were particularly associated with symptomatic presentation and elevated estimated pulmonary pressures, while small defects more frequently demonstrated spontaneous closure or reduction during the available short-term follow-up.

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