


RESEARCH

Open Access



# Long-term surgical outcomes after repair of multiple ventricular septal defects in pediatrics

Abdullah A. Alshehri<sup>1\*</sup> , Abdulaziz M. Alshehri<sup>2</sup>, Aisha A. Muthanna<sup>3</sup>, Aitizaz Uddin Syed<sup>4</sup>, Ayman R. Abdelrehim<sup>4</sup>, Azzahra M. Edrees<sup>1</sup>, Ahmed M. Dohain<sup>5,6</sup>, Ahmed F. Elmahrouk<sup>1,7</sup>, Ahmed A. Jamjoom<sup>1</sup> and Osman O. Al-Radi<sup>1,8</sup>

## Abstract

**Background:** Surgical closure of multiple ventricular septal defects (VSDs) is challenging and associated with a high complication rate. Several factors may affect the outcomes after surgical repair of multiple VSDs. We aimed to report the outcomes after surgical repair of multiple VSDs before and after 1 year and identify the factors affecting the outcomes. We have studied forty-eight patients between 2016 and 2017 who had surgical repair of multiple VSDs. We grouped them according to the age at the time of repair. Study outcomes were hospital complications, prolonged hospital stay, and reoperation.

**Results:** There were 18 females (60%) in group 1 and 13 (72.22%) in group 2 ( $P = 0.39$ ). There were no differences in the operative outcomes between the groups. Prolonged postoperative stay was associated with group 1 (OR 0.23 (0.055–0.96);  $P = 0.04$ ) and lower body weight (OR 0.76 (0.59–0.97);  $P = 0.03$ ). Hospital mortality occurred in 2 patients (6.67%) in group 1 and 1 patient (5.56%) in group 2 ( $P > 0.99$ ). Five patients had reoperations: two for residual VSDs, two for subaortic membrane resection, and one for epicardial pacemaker implantation. All reoperations occurred in group 1 (log-rank  $P = 0.08$ ). Two patients had transcatheter closure of the residual muscular VSDs; both were in group 2.

**Conclusions:** Surgical repair of multiple VSDs was associated with good hospital outcomes. The outcomes were comparable in patients younger or older than 1 year of age. Young age at repair could lead to prolonged postoperative stay and a higher reoperation rate.

**Keywords:** Multiple ventricular septal defects, Staged repair, One-stage repair, VSD repair age

## Background

Ventricular septal defects (VSDs) are the most common congenital cardiac anomaly in children, and it accounts for 20–40% of all congenital heart diseases [1, 2]. Surgical repair of multiple VSDs is challenging and associated with residual defects, heart block, and mortality [3, 4]. Younger age and lower body weight at the time

of multiple VSD repairs were associated with prolonged hospital stay and postoperative complications [5].

Despite the advancement of surgical techniques for managing multiple VSDs [3, 6], the complications and mortality rates remain high. While transcatheter approaches to VSD closure have been established, surgical repair remains the gold standard [7]. Early reports advocated the staged repair of multiple VSDs by performing pulmonary artery banding; however, this approach was associated with high mortality and septal hypertrophy; therefore, several authors recommended

\*Correspondence: J1514715@kfsshr.edu.sa

<sup>1</sup> Division of Cardiac Surgery, Cardiovascular Department, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia  
Full list of author information is available at the end of the article

single-stage repair of multiple VSDs [3, 8]. The effect of age and staged approach on the outcomes after multiple VSD repairs is still the subject of ongoing research. Our objective was to report the outcomes after repairing multiple VSDs before and after 1 year of age and assess the factors that influenced the results.

## Methods

### Design and patients

A retrospective multicenter study was conducted to compare the outcomes of multiple VSD repairs in patients aged  $\leq 1$  year and  $> 1$  year. We included all patients who underwent surgical repair of multiple VSDs between 2016 and 2017. Multiple VSDs were defined as the presence of more than one VSD with or without concomitant intracardiac or extracardiac malformations. All the patients with missing important data and who underwent single VSD repair were excluded from the study. Medical records of these patients were retrospectively reviewed with permission from the Institutional Review Board, and the consents to participate in the study were waived.

Forty-eight patients met the inclusion criteria and were grouped according to age into two groups. Group 1 included patients aged 1 year or younger ( $n = 30$ ), and group 2 included patients older than 1 year ( $n = 18$ ).

### Data

Study data were collected and categorized into preoperative, operative, and postoperative variables. Data were collected from the echocardiography reports, clinic, inpatient, perfusion, and operative notes. Data collected were gender, weight at operation, other associated cardiac anomalies, cardiopulmonary bypass time, cross-clamp time, number of VSDs closed, and staged approach with pulmonary artery (PA) banding before and after surgery. Study endpoints were postoperative hospital complications, length of hospital stay, and long-term survival and reoperation. Hospital outcomes were defined as those occurring within the same hospital admission or within 30 days from surgery. Prolonged hospital stay was defined as the post-procedure stay of more than 10 days.

### Techniques

The indications of surgical repair of multiple VSDs were pulmonary hypertension, congestive heart failure, or associated congenital cardiac anomalies. We performed the surgical repair under cardiopulmonary bypass using aortic and bi-caval cannulation. All patients had repair through median sternotomy. We used moderate hypothermia with antegrade cold cardioplegia and approached the VSDs through right atriotomy. Inlet or perimembranous VSDs were repaired with a bovine pericardial patch, and muscular VSDs were closed with the approximation

of the surrounding trabeculae with direct sutures or using synthetic patches. Intraoperatively, we pressurized the left ventricle to detect leakage from the ventricular septum and confirm the satisfactory repair. Significant residual VSDs were excluded using transesophageal or epicardial echocardiography and by measuring oxygen saturation in the superior vena cava and pulmonary artery. An increase in the saturation of 5% or more indicated a hemodynamically residual shunt.

### Statistical analysis

To test the normality of the quantitative variables, we used the Shapiro-Wilk test, and normally distributed variables were presented as mean and standard deviations, while non-normal variables were presented as median (Q1 and Q3). The frequency and percentage of qualitative data were presented. We used the Student *t*-test or Mann-Whitney test to compare the quantitative data and the chi-square or Fisher exact test to compare the qualitative data. Univariable logistic regression was used to identify the factors associated with a prolonged hospital stay and residual shunt. Kaplan-Meier curve was used to plot survival and freedom from reoperation. The log-rank test was used to compare the survival distribution. Stata 16.1 was used for statistical analysis (Stata Corp, College Station, TX, USA).

## Results

### Preoperative and operative data

There were 18 females (60%) in group 1 and 13 (72.22%) in group 2 ( $P = 0.39$ ). The distribution of the associated cardiac anomalies was significantly different between both groups ( $P = 0.04$ ). Four patients in group 1 had concomitant chronic diseases (bronchial asthma, Dandy-Walker syndrome, bilateral hydronephrosis, pulmonary hypertension), compared to three in group 2 (DiGeorge syndrome, Down syndrome, and renal failure) ( $P > 0.99$ ).

There were no differences in cardiopulmonary bypass (CPB) and aortic cross-clamp times and the number of VSDs closed between the groups. Five patients (10.42%) had staged repair with PDA banding before or after VSD repair surgery (Table 1).

### Operative outcomes

There were no differences in the operative outcomes between the groups (Table 2). Twenty-one patients (48.84%) of those who had staged repair had a residual shunt; three of them had a moderate shunt. However, none of the patients with pulmonary artery (PA) banding had a moderate residual shunt, and three had tiny shunts. The age group ( $P = 0.55$ ), the number of VSDs closed ( $P = 0.63$ ), and the method of VSD closure ( $P = 0.75$ ) were not related to the residual shunt. Mortality

**Table 1** Preoperative and operative variables

	Group 1 (age ≤ 1 year) (n = 30)	Group 2 (age > 1 year) (n = 18)	P
Age (days)	179 (112–234)	1370.5 (563–2560)	< 0.001
Female	18 (60%)	13 (72.22%)	0.39
Weight (kg)	4.3 (3.4–5.3)	10.3 (8.5–17.5)	< 0.001
Height (cm)	60.35 (50–63.5)	91.45 (73–108)	< 0.001
<b>Associated anomalies</b>			0.04
Coarctation	3 (10%)	1 (5.56%)	
Patent ductus arteriosus	10 (33.33%)	2 (11.11%)	
Atrial septal defect (secundum)	4 (13.33%)	1 (5.56%)	
Mitral regurgitation	1 (3.33%)	0	
Mitral ring	0	1 (5.56%)	
Pulmonary valve stenosis	0	3 (16.67%)	
Pulmonary artery stenosis	0	1 (5.56%)	
TGA	3 (10%)	0	
DORV (subpulmonary VSD)	0	1 (5.56%)	
DORV (remote/inlet VSD)	0	1 (5.56%)	
Hypoplastic aortic arch	1 (3.33%)	0	
Hypoplastic right ventricle	1 (3.33%)	0	
Symptomatic heart failure	12 (40%)	12 (66.67%)	0.07
Infective endocarditis	1 (3.33%)	1 (5.56%)	> 0.99
Cardiopulmonary bypass (min)	77.5 (65–103)	95 (66–142)	0.16
Aortic cross-clamp time (min)	54 (43–62)	67.5 (47–82)	0.09
<b>Number of VSD closed</b>			0.27
Two	19 (63.33%)	13 (72.22%)	
Three	3 (10%)	3 (16.67%)	
Four	7 (23.33%)	1 (5.56%)	
Five	1 (3.33%)	0	
Six	0	1 (5.56%)	
<b>Method of VSD closure</b>			0.41
Patch	14 (46.67%)	12 (66.67%)	
Primary closure	4 (13.33%)	2 (11.11%)	
Patch and primary closure	12 (40%)	4 (22.22%)	
PA banding before surgery	0	4 (22.22%)	0.016
PA banding after surgery	1 (3.33%)	0	> 0.99

We presented continuous data as median (Q1–Q3) and binary or ordinal data as frequency and percentage

PA pulmonary artery, TGA transposition of great arteries, VSD ventricular septal defect

**Table 2** Operative complications

	Group 1 (n = 30)	Group 2 (n = 18)	P
Heart block	2 (6.67%)	2 (11.11%)	0.62
Ventricular dysfunction	5 (16.67%)	2 (11.11%)	0.70
Residual shunt	14 (46.67%)	10 (55.56%)	0.55
Moderate residual shunt	2 (6.67%)	1 (5.56%)	> 0.99
Length of stay (days)	9.5 (7–18)	8 (7–9)	0.14
Hospital mortality	2 (6.67%)	1 (5.56%)	> 0.99

We presented continuous data as median (Q1–Q3) and binary or ordinal data as frequency and percentage

occurred in patients who had associated transposition of great arteries (TGA), hypoplastic right ventricle (RV), and pulmonary valve and right infundibular stenosis.

**Factors associated with prolonged hospital stay**

Prolonged postoperative stay was associated with group 1 (OR 0.23 (0.055–0.96); *P* = 0.04), lower body weight (OR 0.76 (0.59–0.97); *P* = 0.03), and the closure of 4 or more VSDs (OR 6.53 (1.41–30.27); *P* = 0.02). Prolonged hospital stay was not related to gender, staged repair, or heart failure symptoms (Table 3).

**Table 3** Factors associated with a prolonged hospital stay

	OR (95% CI)	P
Age group	0.23 (0.055–0.96)	0.04
Gender	0.66 (0.18–2.35)	0.52
Staged repair	0.42 (0.04–4.11)	0.46
Weight	0.76 (0.59–0.97)	0.03
Height	0.97 (0.93–1.0)	0.06
Number of VSDs closed	6.53 (1.41–30.27)	0.02
Method of VSD closure	1.3 (0.37–4.54)	0.69

VSDs ventricular septal defects

**Long-term outcomes**

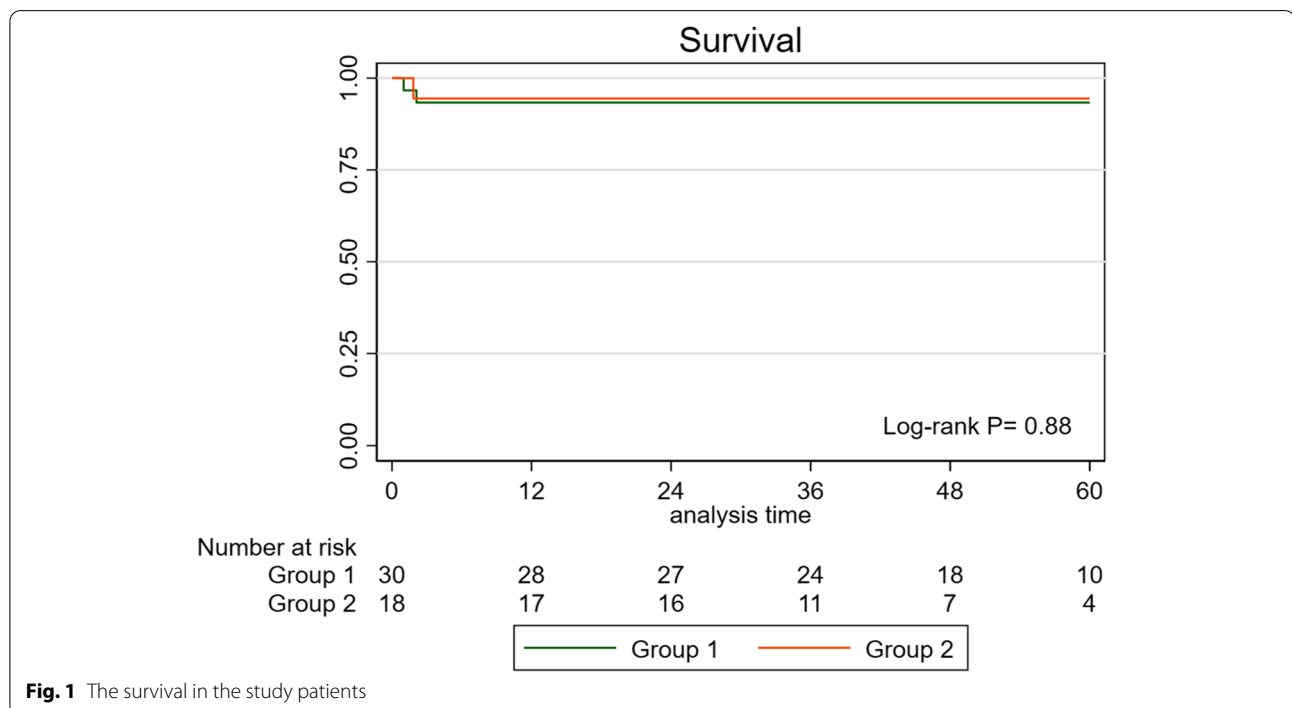
The median follow-up was 49 months (34–62). There was no difference in survival between both groups (Fig. 1). One patient had infective endocarditis after 24 months and was managed medically. Five patients had reoperations: two for residual VSDs, two for subaortic membrane resection, and one for epicardial pacemaker implantation. Two patients required a second reoperation: one had Ross-Konno, and one had epicardial pacemaker implantation. All reoperations occurred in group 1 (log-rank  $P = 0.08$ ). Freedom of reoperation was 91.39% at 1 year and 89.08% at 5 years (Fig. 2). Two patients had transcatheter closure of the residual muscular VSDs; both were in group 2.

**Discussion**

Repair of multiple VSDs is surgically challenging, and visualization of multiple muscular VSDs could be difficult from the right ventricle because of the trabeculations. Several approaches were proposed to manage multiple VSDs, including primary or staged surgical repair or transcatheter closure [9, 10]. Several factors could affect the outcomes after surgical repair of multiple VSDs, including the age at the time of repair, staged approach, and number of VSDs.

This study evaluated the outcomes after surgical repair of multiple VSDs in 48 patients with or without associated cardiac anomalies. The most common concomitant cardiac defect found in our patients was patent ductus arteriosus (25%). Schipper and colleagues reported that patent foramen ovale (PFO) was the most common anomaly associated with VSDs (22.6%) [11].

Mortality after repair of multiple VSDs had improved in recent years. We reported an overall mortality rate of 6%, with no difference in mortality rates between patients younger or older than 1 year. In a study by Serraf and associates on 130 patients with multiple isolated VSDs, they reported a mortality rate of 8%, and in other series, the mortality was 9% [7, 12]. The difference in mortality between our study and others could be attributed to the time era with the recently improved surgical techniques. Recent studies reported a lower mortality rate [3], and Daley and coworkers had 2% hospital mortality after the repair of multiple VSDs [13]. Similar to our study,



**Fig. 1** The survival in the study patients



**Fig. 2** Freedom from reoperation

the reported mortality was highest during the hospital admission and low during follow-up [3, 13].

Heart block and the need for a permanent pacemaker are common after the repair of VSDs. Our reported rate of heart block was 8%, which is similar to other series. Alsofi and colleagues reported a 12% incidence of heart block after repair of multiple VSDs [7], and Konstantinov and Coles had a rate of 11% [14]. The rate of pacemaker insertion remains high in recent studies, and Daley and associates reported a rate of 9% for pacemaker insertion [13]. Anderson and associates reported a 6% heart block after VSD repair in a multicenter study [15]. Postoperative ventricular dysfunction occurred in 15% of our patients, and it was not related to age. In another study, postoperative ventricular dysfunction was related to the size of the VSD and the use of synthetic material for closure [16].

The management considerations of multiple VSD repairs can vary among surgeons. Several factors affect the natural history, presentation, and management of multiple VSDs patients, such as the patient’s age, the clinical status, surgeon’s experience, and the presence of associated anomalies or risk factors [17–20]. The hospital stay in our series was affected by the age, weight, and number of VSDs closed. Anderson and colleagues found a nearly double-fold increase in the length of hospital stay in patients who had repair below 6 months of age, and every 1-kg increase in the

patients’ weight decreased hospital stay by 2 days [15]. Similar to our results, a study found that age did not increase the risk of complications, but younger age was associated with prolonged hospital stay [21]. Lower age and weight could lead to difficult visualization and extensive dissection with an increased surgical risk and prolonged hospital stay. Despite these findings, the prognostic effect of age and weight of children with multiple VSDs remains controversial [22, 23].

In our cohort, reoperations were required in five patients in group 1. However, only two patients had surgical closure of residual VSDs in group 1, and two patients in group 2 had transcatheter VSD closure. Daley and associates found that the overall freedom from reoperation after multiple VSD repairs was 52% at 16 years, and the survival was 95% at 18 years [13]. They also reported an improved reoperation rate in patients who underwent surgery in the recent era. A significant residual shunt was not frequent in our cohort, and we succeeded in managing it interventionally in two patients. Transcatheter closure of residual VSDs was successfully reported in the literature and can be used as adjunctive to surgical correction [24–26].

This study’s limitations are primarily defined by the limitations of all retrospective studies as a retrospective study depends on the medical records and written documentation of several doctors. Additionally, the study is limited by the sample size, which limited the statistical analysis.

## Conclusions

Surgical repair of multiple VSDs was associated with good hospital outcomes. The outcomes were comparable in patients younger or older than 1 year of age. Young age at repair could lead to prolonged postoperative stay and a higher reoperation rate.

## Abbreviations

VSDs: Ventricular septal defects; PDA: Patent ductus arteriosus; PFO: Patent foramen ovale; PA: Pulmonary artery; TGA: Transposition of great arteries; RV: Right ventricle.

## Acknowledgements

Not applicable

## Authors' contributions

AAA and AE projected the study, analyzed and interpreted the data, and wrote the manuscript. OA carried out the statistical analysis. OA and AAJ performed the surgical interventions and were major contributors in writing the manuscript. AUS and AFE revised the final version of the manuscript. ARA, AMA, and AM contributed to collecting the data for analysis. The authors read and approved the final manuscript.

## Funding

Not applicable

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

The study was approved by the local ethics committee at King Faisal Specialist Hospital & Research Centre, Jeddah, Saudi Arabia

### Consent for publication

Not applicable.

### Competing interests

All authors declare that they have no competing interests.

### Author details

<sup>1</sup>Division of Cardiac Surgery, Cardiovascular Department, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia. <sup>2</sup>Department of Pediatrics, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. <sup>3</sup>Ibn Sina National College, Jeddah, Saudi Arabia. <sup>4</sup>Department of Cardiac Surgery, Madinah Cardiac Center, Medina, Saudi Arabia. <sup>5</sup>Department of Pediatrics, Cardiology Division, Cairo University, Cairo, Egypt. <sup>6</sup>Department of Pediatrics, King Abdulaziz University Hospital, Jeddah, Saudi Arabia. <sup>7</sup>Cardiothoracic Surgery Department, Tanta University, Tanta, Egypt. <sup>8</sup>Division of Cardiac Surgery, Department of Surgery, King Abdulaziz University Hospital, Jeddah, Saudi Arabia.

Received: 16 August 2021 Accepted: 14 October 2021  
Published online: 26 October 2021

## References

1. Kenny D (2018) Interventional cardiology for congenital heart disease. *Korean Circ J* 48(5):350–364
2. Penny DJ, Vick GW 3rd. (2011) Ventricular septal defect. *Lancet* (London, England) 377(9771):1103–1112

3. Shetty V, Shetty D, Punnen J, Chattuparambil B, Whitlock R, Bohra D (2017) Single-stage repair for multiple muscular septal defects: a single-centre experience across 16 years. *Interact Cardiovasc Thorac Surg* 25(3):422–426. <https://doi.org/10.1093/icvts/ivx105>
4. Kitagawa T, Durham LA 3rd, Mosca RS, Bove EL (1998) Techniques and results in the management of multiple ventricular septal defects. *J Thorac Cardiovasc Surg* 115(4):848–856
5. Du ZD, Roguin N, Barak M, Bihari SG, Ben-Elisha M (1996) High prevalence of muscular ventricular septal defect in preterm neonates. *Am J Cardiol* 78(10):1183–1185
6. Scully BB, Morales DLS, Zafar F, McKenzie ED, Fraser CDJ, Heinle JS (2010) Current expectations for surgical repair of isolated ventricular septal defects. *Ann Thorac Surg* 89(2):541–544
7. Alsoufi B, Karamlou T, Osaki M, Badiwala MV, Ching CC, Dipchand A et al (2006) Surgical repair of multiple muscular ventricular septal defects: the role of re-endocardialization strategy. *J Thorac Cardiovasc Surg* 132(5):1072–1080
8. Yoshimura N, Matsuhisa H, Otaka S, Kitahara J, Murakami H, Uese K et al (2009) Surgical management of multiple ventricular septal defects: the role of the felt sandwich technique. *J Thorac Cardiovasc Surg* 137(4):924–928
9. Houeijeh A, Godart F, Jalal Z, Ovaert C, Heitz F, Mauran P et al (2020) Transcatheter closure of a perimembranous ventricular septal defect with Nit-Occlud Lè VSD Coil: a French multicentre study. *Arch Cardiovasc Dis* 113(2):104–112
10. Eroğlu AG, Oztunç F, Saltik L, Bakari S, Dedeoğlu S, Ahunbay G (2003) Evolution of ventricular septal defect with special reference to spontaneous closure rate, subaortic ridge and aortic valve prolapse. *Pediatr Cardiol* 24(1):31–35
11. Schipper M, Slieker MG, Schoof PH, Breur JMPJ (2017) Surgical repair of ventricular septal defect; contemporary results and risk factors for a complicated course. *Pediatr Cardiol* 38(2):264–270
12. Serraf A, Lacour-Gayet F, Bruniaux J, Ouaknine R, Losay J, Petit J et al (1992) Surgical management of isolated multiple ventricular septal defects. Logical approach in 130 cases. *J Thorac Cardiovasc Surg* 103(3):437–442 discussion 443
13. Daley M, Brizard CP, Konstantinov IE, Brink J, Kelly A, Jones B et al (2019) Outcomes of patients undergoing surgical management of multiple ventricular septal defects. *Semin Thorac Cardiovasc Surg* 31(1):89–96
14. Konstantinov IE, Coles JG (2003) The role of intraoperative device closure in the management of muscular ventricular septal defects. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 6:84–89
15. Anderson BR, Stevens KN, Nicolson SC, Gruber SB, Spray TL, Wernovsky G et al (2013) Contemporary outcomes of surgical ventricular septal defect closure. *J Thorac Cardiovasc Surg* 145(3):641–647
16. Matsuhisa H, Yoshimura N, Higuma T, Misaki T, Onuma Y, Ichida F et al (2013) Ventricular septal dysfunction after surgical closure of multiple ventricular septal defects. *Ann Thorac Surg* 96(3):891–897
17. Elmahrouk AF, Ismail MF, Arafat AA, Dohain AM, Helal AM, Hamouda TE, Galal M, Edrees AM, Al-Radi OO, Jamjoom AA (2021) Outcomes of biventricular repair for Shone's complex. *J Card Surg* 36(1):12–20. <https://doi.org/10.1111/jocs.15090> Epub 2020 Oct 8. PMID: 33032391
18. Alamri RM, Dohain AM, Arafat AA, Elmahrouk AF, Ghunaim AH, Ellassal AA, Jamjoom AA, Al-Radi OO. Surgical repair for persistent truncus arteriosus in neonates and older children. *J Cardiothorac Surg*. 2020;15(1):83. doi: <https://doi.org/10.1186/s13019-020-01114-1>. PMID: 32393289; PMCID: PMC7216609.
19. Arafat AA, Elatafy EE, Elshedoudy S, Zalat M, Abdallah N, Elmahrouk A. Surgical strategies protecting against right ventricular dilatation following tetralogy of Fallot repair. *J Cardiothorac Surg*. 2018;13(1):14. doi: <https://doi.org/10.1186/s13019-018-0702-0>. PMID: 29357937; PMCID: PMC5778645.
20. Al-Radi OO, Elmahrouk A, Ismail M et al (2020) Total anomalous pulmonary venous drainage repair: the effect of anatomical type and pulmonary vein stenosis on outcomes. *Cardiothorac Surg* 28:7. <https://doi.org/10.1186/s43057-020-0016-6>
21. Ashfaq A, Zia HA, Amanullah MM (2010) Is early correction of congenital ventricular septal defect a better option in a developing country? *J Pak Med Assoc* 60(4):324–327
22. Brizard CP, Olsson C, Wilkinson JL (2004) New approach to multiple ventricular septal defect closure with intraoperative echocardiography

- and double patches sandwiching the septum. *J Thorac Cardiovasc Surg* 128(5):684–692
23. Vaidyanathan B, Roth SJ, Rao SG, Gauvreau K, Shivaprakasha K, Kumar RK (2002) Outcome of ventricular septal defect repair in a developing country. *J Pediatr* 140(6):736–741
  24. Dua JS, Carminati M, Lucente M, Piazza L, Chessa M, Negura D et al (2010) Transcatheter closure of postsurgical residual ventricular septal defects: early and mid-term results. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 75(2):246–255
  25. Kouakou NYN, Song J, Huh J, Kang I-S (2019) The experience of transcatheter closure of postoperative ventricular septal defect after total correction. *J Cardiothorac Surg* 14(1):104. <https://doi.org/10.1186/s13019-019-0933-8>
  26. Zhou W, Li F, Fu L, Gao W, Guo Y, Liu T et al (2016) Clinical experience of transcatheter closure for residual ventricular septal defect in pediatric patients. *Congenit Heart Dis* 11(4):323–331 Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/chd.12357>

### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Submit your manuscript to a SpringerOpen<sup>®</sup> journal and benefit from:**

- ▶ Convenient online submission
- ▶ Rigorous peer review
- ▶ Open access: articles freely available online
- ▶ High visibility within the field
- ▶ Retaining the copyright to your article

---

Submit your next manuscript at ▶ [springeropen.com](https://www.springeropen.com)

---