VER
Vascular & Endovascular Review

Electrophysiological Sequelae Following Cardiac Surgery in Heterotaxy Syndrome

Samia A. Bekheet [1]*, Abdelmonem M. Helal [1,2], Ahmed F. Elmahrouk [3,4], Ahmed A. Jamjoom [3]

1 Pediatric Cardiology Section, Department of Pediatrics, Cairo University, Cairo, Egypt.
2 Pediatric Cardiology Section, Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia.
3 Cardiac Surgery Section, Department of Cardiovascular, King Faisal Specialist Hospital, Jeddah, Saudi Arabia.
4 Cardiothoracic Surgery Department, Faculty of Medicine, Tanta University, Egypt.

***Corresponding Author**
Pediatric Cardiology Section, Department of Pediatrics, Cairo University, Cairo, Egypt; e-mails: samiabekheet84@gmail.com

ABSTRACT

Background: Cardiac conduction system abnormalities often associated with heterotaxy syndrome predispose affected patients to a variety of cardiac arrhythmias. Although surgical palliation has contributed to improved survival, the burden of postoperative arrhythmia remains a critical concern. In the current study, electrophysiological outcomes were reviewed and risk factors for arrhythmia were identified in patients undergoing cardiac surgery for heterotaxy

Methods: A retrospective analysis of 33 patients with heterotaxy syndrome who underwent cardiac surgery at a single tertiary center was conducted. Main outcomes included the incidence of postoperative abnormal heart rhythm, defined as new-onset heart block, tachyarrhythmia, or nodal rhythm, and overall mortality. Risk factors for abnormal rhythm and mortality were examined using logistic regression and Cox proportional hazards modeling, respectively. The Kaplan-Meier method was used to estimate survival.

Results: The cohort had a median age of 28 months (IQR: 14-58) at the time of surgery. Right isomerism was predominant (75.8%). Most patients (87.9%) were palliated via a single ventricle pathway. Preoperatively, 87.9% of patients had a normal ECG. Postoperatively, the incidence of abnormal heart rhythm was 24.2% (12.1% heart block, 12.1% tachyarrhythmia). Over a median follow-up of 54 months (IQR: 27-90), overall mortality was 18.18%. Kaplan-Meier analysis revealed survival rates of 88% at 3 years and 74% at 10 years. Univariable analysis identified that left isomerism (OR 14.88, p=0.019) and absent inferior vena cava (IVC) (OR 7.00, p=0.033) were significantly associated with developing postoperative arrhythmia. Older age at the time of analysis was significantly associated with improved survival (HR 0.89, p=0.025).

Conclusion: Patients with heterotaxy syndrome undergoing cardiac surgery face a substantial risk of postoperative arrhythmia. Left isomerism and absent IVC are significantly associated with postoperative arrhythmias. Older age at surgery was associated with improved survival. These findings emphasize the importance of comprehensive electrophysiological evaluation and risk factor assessment in managing heterotaxy syndrome patients.

KEYWORDS: Heterotaxy; Cardiac Surgery; Electrophysiological Changes; Survival.

How to Cite: Samia A. Bekheet*, Abdelmonem M. Helal, Ahmed F. Elmahrouk, Ahmed A. Jamjoom, (2025). Electrophysiological Sequelae Following Cardiac Surgery in Heterotaxy Syndrome, Vascular and Endovascular Review, Vol.8, No.17s, 33-38.

BACKGROUND:

Heterotaxy syndrome, also termed situs ambiguous, represents the spectrum of congenital disorders characterized by abnormal lateralization of thoracic and abdominal organs, different from the usual situs solitus and situs inversus (1,2). The estimated incidence of heterotaxy is about 1 in 10,000 live births, comprising roughly 3% to 4% of all complex CHD cases (1). The syndrome is classified broadly into two major subtypes based on the morphology of the appendages of the atria, including right atrial isomerism (RAI)and left atrial isomerism (LAI) (1,2). The genetic etiology in heterotaxy is complex, with mutations identified in many genes related to laterality, such as ZIC3, NODAL, CFC1, and ciliary-related genes like DNAH5 and DNAH11 (2,3).

A critical aspect of heterotaxy syndrome is the intrinsic abnormality of the cardiac conduction system. The embryologic disorganization that affects organ situs also disrupts the normal development and location of the sinoatrial (SA) and atrioventricular (AV) nodes, thereby creating a substrate for a lifetime risk of both brady-arrhythmias and tachy-arrhythmias (4). Cardiac surgery can exacerbate the underlying electrophysiological vulnerability. The extensive incisions, cannulation, and patching required for complex repairs can directly damage conduction tissue or create lines of block that serve as circuits for re-entrant tachycardias (5). Furthermore, the altered hemodynamics of the Fontan circulation, characterized by elevated systemic venous pressure and chronic atrial dilation, contribute to the arrhythmogenic substrate over time (6).

Postoperative arrhythmias are a major source of morbidity and mortality in the long-term follow-up of heterotaxy patients, leading to heart failure, thromboembolism, and sudden death (5). Despite modern surgical techniques, outcomes for patients with

heterotaxy syndrome remain suboptimal, and the risk of postoperative arrhythmia remains substantial (7).

Although the association between heterotaxy, complex cardiac surgery, and arrhythmias is well-established, a continuing need exists to define the long-term outcome and identify specific predictors of adverse electrophysiological outcomes in the modern surgical era. This study aimed to investigate the electrophysiological outcomes and identify the risk factors for arrhythmia in patients with heterotaxy syndrome following cardiac surgery. Furthermore, the study evaluated the long-term survival in those patients and its association with postoperative arrhythmia.

PATIENTS AND METHODS

Study Design and population

We conducted a retrospective review of patients with heterotaxy syndrome who underwent cardiac surgery at a single tertiary center. Inclusion criteria were a definitive diagnosis of heterotaxy syndrome (either right or left isomerism) based on imaging (echocardiography, CT, or MRI) and a history of at least one cardiac surgical procedure. Surgical procedures were conducted between January 1995 and December 2024. Patients with incomplete medical records or those who were lost to follow-up immediately after surgery were excluded from the analysis. Additionally, we excluded patients who had surgery in other centers.

Data Collection

Data was extracted from electronic and paper medical records. Baseline data included:

- Demographics: Sex and age at the time of surgery
- Anatomical Characteristics: Isomerism type (right vs. left), inferior vena cava (IVC) status (present vs. absent/interrupted with azygous continuation), superior vena cava (SVC) anatomy (single vs. double), liver and spleen position, and cardiac position (levocardia vs. dextrocardia)
- Cardiac Pathway: Classification as single ventricle or biventricular pathway based on the intended surgical palliation strategy
- Preoperative Electrocardiogram (ECG): The last available 12-lead ECG prior to the first cardiac surgery was analyzed and categorized as normal sinus rhythm, heart block, tachyarrhythmia, or nodal/junctional rhythm
- Surgical Interventions: Type of surgical procedures was recorded, including pulmonary artery banding (PAB), bidirectional cavo-pulmonary shunt (BCPS), Fontan procedure, ventricular septal defect (VSD) repair, and unifocalization of major aortopulmonary collateral arteries
- Postoperative Abnormal Heart Rhythm: This was the primary electrophysiological outcome, defined as the first occurrence of any clinically significant, new-onset arrhythmia documented on a 12-lead ECG, Holter monitor, or telemetry strip after the initial cardiac surgery. It was a composite endpoint including: 1) high-grade or complete heart block requiring pacing, 2) sustained tachyarrhythmia (e.g., atrial flutter, atrial tachycardia, re-entrant tachycardia) requiring medical or electrical intervention, or 3) persistent nodal or junctional escape rhythm.
- Mortality: The secondary outcome was all-cause mortality, with the date of death obtained from hospital records or by phone calls

Follow-up time was calculated from the date of the indexed cardiac surgery (first procedure performed in our center) to the date of the last clinical encounter, death, or the study cut-off date (June 30, 2025).

Surgical Procedure

The surgical procedures were tailored to the specific cardiac anatomy and clinical status of each patient. The majority of patients were managed through a single ventricle palliation pathway. The primary surgical interventions included the Fontan procedure for completion of single ventricle palliation and the BCPS (Glenn procedure) as a staged procedure. Other less frequent procedures included pulmonary artery banding, ventricular septal defect (VSD) repair, and unifocalization of pulmonary blood supply. All surgical procedures were performed by consultant congenital heart surgeons.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of our institution. Due to the retrospective nature of the study, the requirement for individual patient consent was waived by the IRB.

Statistical Analysis

Statistical analysis was performed using Stata software (Version 18.0, Stata Corp., College Station, TX). Continuous variables are presented as median and interquartile range (IQR), while categorical variables are presented as numbers and percentages. The primary outcome was the incidence of postoperative arrhythmia, defined as new-onset heart block, tachyarrhythmia, or nodal rhythm. Overall mortality was a secondary outcome. Univariable logistic regression analysis was used to identify risk factors for developing postoperative arrhythmia. A Cox proportional hazards model was used to identify factors associated with overall mortality. Survival rates were estimated using the Kaplan-Meier method. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 33 patients with heterotaxy syndrome who underwent cardiac surgery were included in the analysis. The median age at surgery was 28 months (IQR: 14-58), and 51.5% (n=17) were male. The majority of patients (75.8%, n=25) had right isomerism. Anatomic and preoperative characteristics are summarized in Table 1. The most common anatomic findings were a double SVC (97.0%), left-sided liver (87.9%), and an absent IVC with azygos continuation (27.3%). Spleen status was variable, with 48.5% of patients having absent spleen, 24.2% having polysplenia, and 24.2% having a right-sided spleen. Preoperatively, 87.9% of

patients had a normal electrocardiogram (ECG).

Surgical Procedures and Postoperative Outcomes

The vast majority of patients (87.9%, n=29) were palliated via a single ventricle pathway. The most common surgical procedures were the Fontan completion (48.5%) and BCPS (27.3%). Postoperatively, the incidence of arrhythmia was 24.2% (n=8), comprising an equal distribution of heart block (12.1%) and tachyarrhythmia (12.1%). A permanent pacemaker was implanted in 12.1% (n=4) of patients (Table 2). No operative mortality was reported. Over a median follow-up of 54 months (IQR: 27-90), the overall mortality was 18.18% (n=6). Kaplan-Meier survival estimates were 88% at 3 years, 74% at 7 years, and 74% at 10 years (Figure 1).

Risk Factors for Postoperative Arrhythmia

Univariable logistic regression analysis identified two factors significantly associated with developing postoperative abnormal heart rhythm (Table 3). Patients with left isomerism had over 14-fold increased odds of postoperative arrhythmia (OR 14.88, 95% CI 1.56-142, p=0.019). Similarly, an absent inferior vena cava was associated with a 7-fold increase in odds (OR 7.00, 95% CI 1.17-41.76, p=0.033). Other factors, including sex, age at surgery, dextrocardia, and single ventricle pathway palliation, were not significantly associated with this outcome.

Factors Associated with Survival

Cox proportional hazards analysis identified older age at surgery as the only factor significantly associated with improved survival (HR 0.89 per unit increase in age in months, 95% CI 0.81-0.98, p=0.025) (Table 4). Notably, the occurrence of postoperative arrhythmia was not a significant predictor of mortality (HR 0.31, 95% CI 0.04-2.62, p=0.280). A descriptive analysis of the non-survivors revealed that all patients who died had right isomerism, a present IVC, a left-sided liver, and a normal heart position.

Table 1: Preoperative data of patients who had cardiac surgery for heterotaxy syndrome

Variables	(n= 33)
Sex (Male)	17 (51.52%)
Age (Months)	28 (14- 58)
Right isomerism	28 (75.76%)
Absent inferior vena cava	9 (27.27%)
Double superior vena cava	32 (96.97%)
Left liver	29 (87.88%)
Spleen	
Absent	16 (48.48%)
Right	8 (24.24%)
Left	1 (3.03%)
Polysplenia	8 (24.24%)
Dextrocardia	5 (15.15%)
Preoperative ECG	
Normal	29 (87.88%)
Heart block	1 (3.03%)
Tachy-arrhythmia	1 (3.03%)
Nodal rhythm	2 (6.06%)

Data are presented as numbers and percentages or median (25th- 75th percentiles)

Table 2: Surgical procedures and postoperative outcomes for patients with heterotaxy who had cardiac surgery

Variables	(n= 33)
Single ventricle pathway	29 (87.88%)
Surgery	
Pulmonary artery banding	4 (12.12%)
Superior Cavo-pulmonary shunt	9 (27.27%)
Fontan	16 (48.48%)
VSD repair	3 (9.09%)
Unifocalzation	1 (3.03%)
Postoperative ECG	
Normal	18 (54.55%)
Heart block	4 (12.12%)
Tachy-arrhythmia	4 (12.12%)
Nodal rhythm	7 (21.21%)
Permanent pacemaker	4 (12.12%)

Data are presented as numbers and percentages.

Table 3: Univariable logistic regression analysis for factors associated with new postoperative abnormal rhythm

Risk factors	Odds ratio (95% confidence interval)	P-value
Sex	0.42 (0.10- 1.72)	0.231
Age	1.004 (0.98- 1.02)	0.551
Left isomerism	14.88 (1.56- 142)	0.019*
Absent inferior vena cava	7 (1.17- 41.76)	0.033*
Left liver	0.24 (0.02- 2.54)	0.234
Polysplenia	9 (0.89- 91)	0.063
Dextrocardia	2 (0.28- 14)	0.484
Single ventricle pathway	0.81 (0.10- 6.58)	0.846
Surgical intervention	1.71 (0.75- 3.85)	0.200

*p value less than 0.05 is considered statistically significant.

Table 4: Univariable Cox regression analysis for factors associated with survival Factors

Factors	Hazard ratio (95% confidence interval)	p-value
Sex	1.02 (0.21- 5.05)	0.982
Age	0.89 (0.81- 0.98)	0.025*
Spleen position	0.69 (0.33- 1.45)	0.330
Single ventricle pathway	0.92 (0.10- 7.94)	0.942
Abnormal Rhythm	0.31 (0.04- 2.62)	0.280

*p value less than 0.05 is considered statistically significant.

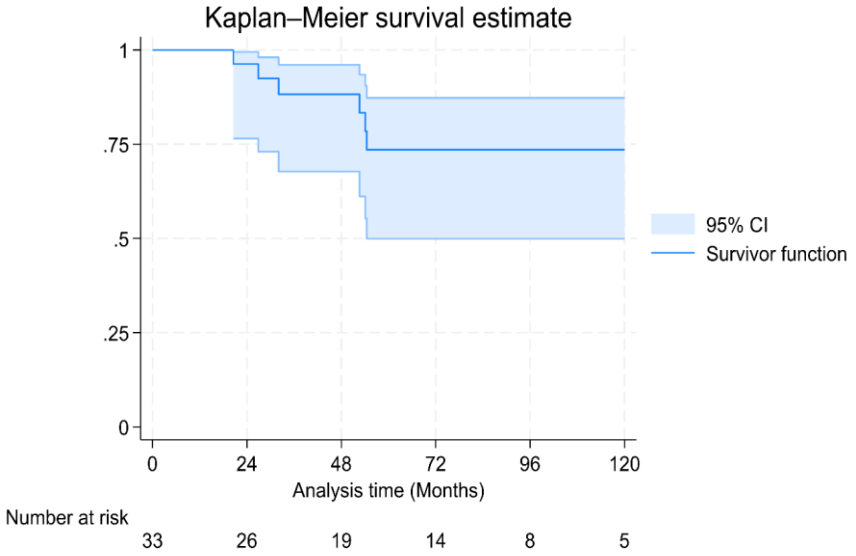

Figure 1: Kaplan-Meier survival curve for patients with heterotaxy syndrome who had cardiac surgery

DISCUSSION

This study investigated the long-term electrophysiological sequelae and survival in a cohort of patients with heterotaxy syndrome following cardiac surgery. Our data confirms that, although surgical palliation allows for long-term survival, it is associated with a significant burden of postoperative arrhythmia. The main conclusions from the present study are first, that left isomerism and absent IVC are particularly associated with the development of postoperative arrhythmia, and secondly, that older age is significantly associated with improved long-term survival.

The incidence of new-onset, clinically significant arrhythmia in our cohort was 24.2%. Various studies have reported differing incidences of postoperative arrhythmias in heterotaxy syndrome, largely depending on the specific type of arrhythmia and the presence of other complicating factors. After Fontan palliation, arrhythmias have been reported in about 25% of heterotaxy survivors versus 11% of non-heterotaxy cohorts (8). Petros and colleagues reported Sinus node dysfunction affecting up to 47% of patients with left atrial isomerism (9).

The high incidence of arrhythmias reflects the inherent electrophysiological instability of heterotaxy syndromes. Congenital conduction system anomalies, such as dual or absent sinus nodes and displaced atrioventricular nodes create a vulnerable substrate. Additionally, extensive atrial manipulation during Fontan-type surgery adds scarring and hemodynamic stress that may precipitate clinically significant arrhythmia.

The most striking finding of our analysis is the strong association between LAI and the development of postoperative arrhythmias (OR 14.88). However, this finding must be interpreted with considerable caution. The associated 95% confidence interval was extremely wide (1.56 to 142), a direct consequence of our small sample size. While this confirms that LAI is a statistically

significant risk factor, the true magnitude of the risk is poorly defined by our data and could range from modest to very large. This highlights the need for larger, multi-center studies to produce a more precise estimate of this risk.

Similarly, the association with absent IVC (with azygous continuation) is a significant finding. This venous anomaly is more commonly associated with LAI/polysplenia syndrome (10). Its role as a risk factor may be related to the altered systemic venous return pathways and the specific surgical modifications required to accommodate them during BCPS and Fontan procedures, potentially placing the conduction system at greater risk. These two markers, left isomerism and absent IVC, can be identified preoperatively and should alert clinicians to a patient's heightened electrophysiological risk.

In our survival analysis, the 10-year survival rate of 74% reflects the significant improvements in surgical and medical management for this complex patient group over the past few decades. Furthermore, no operative mortality has been reported. However, it also highlights the ongoing attrition that occurs even after successful initial palliation.

Survival rates vary significantly across studies and are heavily influenced by specific anatomical and clinical risk factors. Desai and colleagues reported 66% overall survival in a median follow-up of 2.2 years in patients with heterotaxy syndrome (7). In a study by Tanimoto et al, survival at 10 years for patients with functional single ventricle and heterotaxy was 47% (11). Lim et al reported 93% survival at 10 years after biventricular repair for patients with heterotaxy and 54% freedom from any arrhythmia at the same time point (12).

The finding that older age was associated with better survival (HR 0.89) is intriguing. This finding should be interpreted with caution. Delayed surgery may be advocated in heterotaxy syndrome; however, patients who underwent early surgery had first-stage palliation with a comparable risk of mortality compared to Fontan completion (13). Moreover, younger patients might have longer follow-up than those who had later surgery. The heterogeneity of the surgical procedures performed, and risk levels should also be considered (14).

Interestingly, the presence of postoperative arrhythmia was not a statistically significant predictor of mortality in our Cox model ($p=0.280$). This may seem counterintuitive, as arrhythmias are a known cause of death in this population. Several factors could explain this. First, our sample size of 33 patients (with six deaths) provides limited statistical power to detect such an association. A larger cohort might have revealed a significant relationship. Second, it may reflect successful management of arrhythmias in our cohort through medication, pacemaker implantation, and other interventions, thereby mitigating their direct impact on mortality.

STUDY LIMITATIONS

This study has several limitations. Its retrospective nature is subject to inherent biases in data collection and recording. This small cohort not only limits the statistical power to detect more subtle risk factors but, more importantly, leads to wide confidence intervals for the identified associations, reducing the precision of our effect estimates and necessitating cautious clinical interpretation. The definition of "abnormal heart rhythm" was a composite endpoint, and a more granular analysis of specific arrhythmia types (e.g., bradycardia vs. tachycardia) could yield further insights. Furthermore, the study spans a long period, during which surgical techniques and medical management have evolved considerably, potentially introducing confounding effects. Finally, as a single-center study, our findings may not be generalizable to all populations.

CONCLUSION

Patients with heterotaxy syndrome face a significant and enduring risk of developing major electrophysiological sequelae following cardiac surgery. Our study identifies left isomerism and absent inferior vena cava as risk factors for the development of postoperative arrhythmia. While long-term survival has improved, mortality remains a concern, with older age being associated with a better prognosis. These findings highlight the critical need for a proactive and risk-stratified approach to patient management. All patients with heterotaxy, particularly those with left isomerism or absent IVC, require lifelong, specialized surveillance with regular ECG and Holter monitoring to enable early detection and treatment of arrhythmias, with the ultimate goal of improving long-term, event-free survival

ABBREVIATIONS

SVC: Superior vena cava.
IVC: Inferior vena cava.
RAI: Right atrial isomerism.
LAI: left atrial isomerism.
CHD: Congenital heart disease.
BCPS: Bidirectional Cavo-pulmonary shunt.

REFERENCES

1. Agarwal R, Varghese R, Jesudian V, Moses J. The heterotaxy syndrome: associated congenital heart defects and management. Indian J Thorac Cardiovasc Surg [Internet]. 2021;37(1):67–81. Available from: https://doi.org/10.1007/s12055-020-00935-y
2. Ahmad Rafie NN, Yubbu P, Aissvarya S, Pujita R, Musa NH, Mohamed Ibrahim NH, et al. Genetic aspects of congenital heart disease in heterotaxy syndrome. Revista Portuguesa de Cardiologia [Internet]. 2025;44(10):633–48. Available from: https://www.sciencedirect.com/science/article/pii/S0870255125002586
3. Liu C, Cao R, Xu Y, Li T, Li F, Chen S, et al. Rare copy number variants analysis identifies novel candidate genes in

heterotaxy syndrome patients with congenital heart defects. Genome Med [Internet]. 2018;10(1):40. Available from: https://doi.org/10.1186/s13073-018-0549-y

4. Ozawa Y, Asakai H, Shiraga K, Shindo T, Hirata Y, Hirata Y, et al. Cardiac Rhythm Disturbances in Heterotaxy Syndrome. Pediatr Cardiol [Internet]. 2019;40(5):909–13. Available from: https://doi.org/10.1007/s00246-019-02087-2
5. Dai L, Liu W, Yildirim V, van Schie MS, Taverne YJHJ, de Groot NMS. Early Currents: Developmental Electrophysiology and Arrhythmia in Pediatric Congenital Heart Disease. J Cardiovasc Dev Dis [Internet]. 2025;12(10). Available from: https://www.mdpi.com/2308-3425/12/10/386
6. Lin HC, Wu MH, Wang JK, Lin MT, Chen CA, Lu CW, et al. Perioperative outcomes of Fontan operation: Impact of heterotaxy syndrome. Journal of the Formosan Medical Association [Internet]. 2022;121(1, Part 1):89–97. Available from: https://www.sciencedirect.com/science/article/pii/S092966462100036X
7. Desai MH, Ceneri NM, Dhari Z, Tongut A, Ozturk M, Staffa SJ, et al. Cardiac surgical outcomes of patients with heterotaxy syndrome. JTCVS Open [Internet]. 2023 Mar 1; 13:292–306. Available from: https://doi.org/10.1016/j.xjon.2022.12.004
8. Kim S-J, Kim W-H, Lim H-G, Lee C-H, Lee J Y. Improving Results of the Fontan Procedure in Patients with Heterotaxy Syndrome. Ann Thorac Surg. 2006 Oct;82(4):1245-1251. doi: 10.1016/j.athoracsur.2006.04.082.
9. Petros V. Anagnostopoulos, Jeffrey M. Pearl, Courtney Octave, Mitchell Cohen et al, Improved current era outcomes in patients with heterotaxy syndromes, European Journal of Cardio-Thoracic Surgery, Volume 35, Issue 5, May 2009, Pages 871–878, https://doi.org/10.1016/j.ejcts.2008.12.018
10. Chen SJ, Wu MH, Wang JK. Clinical implications of congenital interruption of inferior vena cava. Journal of the Formosan Medical Association [Internet]. 2022;121(10):1938–44. Available from: https://www.sciencedirect.com/science/article/pii/S0929664622000419
11. Tanimoto K, Hoashi T, Shibagaki K, Ono Y, Komori M, Okuda N, et al. Long-term outcomes of functional single ventricles associated with heterotaxy syndrome. European Journal of Cardio-Thoracic Surgery [Internet]. 2023 Dec 1;64(6): ezad311. Available from: https://doi.org/10.1093/ejcts/ezad311
12. Lim HG, Bacha EA, Marx GR, Marshall A, Fynn-Thompson F, Mayer JE, et al. Biventricular repair in patients with heterotaxy syndrome. J Thorac Cardiovasc Surg [Internet]. 2009 Feb 1;137(2):371-379.e3. Available from: https://doi.org/10.1016/j.jtcvs.2008.10.027
13. Dalén M, Odermarsky M, Liuba P, Johansson Ramgren J, Synnergren M, Sunnegårdh J. Long-Term Survival After Single-Ventricle Palliation: A Swedish Nationwide Cohort Study. J Am Heart Assoc [Internet]. 2024 Mar 19;13(6): e031722. Available from: https://doi.org/10.1161/JAHA.123.031722
14. AbdelAziz D, El-Sisi A, Mesalam A, Hasanin A, Salah Z. The ability of the RACHS-1 score to predict in-hospital mortality and morbidity in pediatric patients undergoing congenital heart surgery. The Cardiothoracic Surgeon [Internet]. 2025;33(1):28. Available from: https://doi.org/10.1186/s43057-025-00170-4