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Congenital heart disease: A lifelong chronic condition

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Congenital heart disease: A lifelong chronic condition

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CASE REPORT
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A Rare Complication During Transcatheter Closure of Double Atrial Septal Defects With Incomplete Cor Triatriatum Dexter: A Case Report

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The cor triatiatum dexter is an embryologic remnant derived from the right atrium and totally separate from the right atrium. An incomplete cor triatiatum dexter (iCTD) means a partially obstructive remnant at the right atrium. It is usually formed by a remnant of the Eustachian valve (EV), Thebesian valve (ThV), or Chiari network (CN). This anatomic variant is usually asymptomatic but is often associated with other heart abnormalities including atrial septal defects (ASDs), and has the potential to hamper percutaneous heart procedures such as electrophysiological study or ASD closure. Herein, we report a rare complication, transient heart ischemia, in transcatheter closure of double ASDs in a 55-year-old woman with EV. This rare complication was thought to be caused by coronary sinus obstruction during device placement. The ischemic change was resolved spontaneously after we withdrew the device. For a second attempt, we adjusted the position of the device to avoid coronary sinus obstruction under transesophageal echocardiogram guidance and the device was smoothly deployed in a good position with a minimal residual shunt. This case suggests that anatomy details in percutaneous heart procedures are important, and this rare and dangerous complication, heart ischemia, should be identified immediately during the procedure.

Keywords: atrial septal defect, cor triatiatum dexter, percutaneous catheterization, complication, heart ischemia

INTRODUCTION

Anatomic variants of the remnants of the right sinus venous valve are commonly observed in the right atrium (RA). They can be classified as normal structures or pathologic entities. Normal structures include the crista terminalis, taenia sagittalis, Chiari network (CN), Eustachian valve (EV), Thebesian valve (ThV), and coumadin ridge. An example of a pathologic entity is the cor triatriatum dexter (CTD) (1).

CTD is a rare congenital malformation of the RA in which the right venous valve is not resorbed, causing the RA to have two distinct chambers (2). The prevalence of CTD is rare, as it represents approximately only 0.025% of cases of all congenital heart diseases reported in previous literature (3). If the remnants that connect to the atrial

septum are non-obstructive, it can be defined as incomplete CTD (iCTD) (4, 5). The symptoms of iCTD depend on the size of the septation between the two distinct chambers in the RA. When the septation is mild, most patients are often asymptomatic and these anomalies are mostly incidental findings during echocardiography. However, severe septation can cause generalized edema and even right-sided heart failure owing to inflow obstruction. It is often associated with other heart abnormalities, including atrial septal defect (ASD), tricuspid valve abnormality, and Ebstein anomaly.

Surgery is usually needed for ASD closure in patients with obstructive iCTD. In non-obstructive iCTD, few successful percutaneous procedures have been reported. These right atrial remnants may increase the difficulty to close the ASDs in percutaneous catheterization. More anatomic detail images, including transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), computed tomography (CT), and magnetic resonance imaging (MRI), may be helpful in these patients before any percutaneous procedure (1).

CASE PRESENTATION

A 55-year-old female patient came to our hospital with a complaint of chest discomfort for 2 days. The electrocardiogram (ECG) revealed an incomplete right bundle branch (iRBBB) without ST segment elevation. Troponin-I, creatine kinase (CK), and creatine kinase-MB (CK-MB) levels were in the normal range. Chest X-ray revealed right ventricle hypertrophy (RVH) with prominent pulmonary congestion. Two secundum type ASDs with membranous remnants at the right atrium were noted in TTE. TEE was arranged for the membranous remnants at the right atrium and revealed double ASDs with iCTD at the connection of the right atrium and inferior vena cava (**Figures 1A,B**). Cardiac CT showed double ASDs, which were 21.2 and 13.6 mm in size, with iCTD (**Figures 2A,B**). During catheterization, no pulmonary hypertension was found, and the size of the larger ASD under balloon sizing was 29.2 mm. The ratio of pulmonary flow to systemic flow was 1.9:1. Therefore, a 30-mm Lifetech device was chosen to close these two ASDs. We chose a 7 French sheath to pass the larger ASD from the RA to LA and deploy the device to close the ASDs without detachment. However, transient heart ischemia with presence of ST segment elevation (**Figure 3A**) was noted and coronary sinus obstruction by the device was thought to be the cause. The shape of the device was also not feasible and many residual shunts were noted. Partial involvement of iCTD in the process of device deployment, which resulted in the obstruction of coronary sinus, was determined (**Figure 4A**). Hence, we withdrew the device immediately and the ST segment elevation recovered (**Figure 3B**).

For the second attempt, a 7 French sheath passed the larger ASD using the same method as last time. The position of the device was adjusted more accurately than the first time to avoid iCTD involvement under TEE guidance. After deployment, the device was more stable than the first time, and no bradycardia or ST segment elevation were found on the electrocardiogram monitor. After device movement, we detached the device smoothly, and a minimal residual shunt without iCTD and tricuspid valve clamping was noted (**Figure 4B**). After the procedure, no complication was noted. Her chest tightness was improved and no residual shunt was noted in TTE during 6 months follow-up.

DISCUSSION

iCTD is an embryologic remnant deriving from the valve of the sinus venosus (3, 6). During embryogenesis, the right horn of the sinus venosus incorporates into the right atrium forming the smooth posterior portion. The left horn is the future coronary sinus (3, 7). This remnant is usually close to the ASD. As a result, it may influence the process of percutaneous closure of ASDs, especially the right disk of the device deployment (1, 2). The complications of ASD device malposition are residual atrial septal leak, bacterial endocarditis in the presence of a foreign body, and paradoxical embolism (8). Good preparation before the percutaneous catheterization is important to avoid these complications. Nowadays, TTE, TEE, cardiac CT, and MRI are valuable tools to help us find these remnants and recognize the morphology prior to the procedure. In the last 20 years, only a few case reports mentioned the effect of iCTD in percutaneous closure of ASDs (7, 9, 10). No clinical guideline describes the standard treatment of ASD closure with right atrial remnants. McMahon et al. reported four cases which had redundant EV in percutaneous closure of a secundum-type ASD (11). They used the steerable radiofrequency ablation catheter to deflect the EV toward the lateral wall of the RA. Three of these four patients underwent successful ASD closure by using this technique. Nevertheless, this skill is still not popular because few hospitals are equipped with steerable radiofrequency ablation.

Recently, McMahon CJ et al. reported the result of percutaneous ASD closure in six ASDs in children with iCTD. Two patients used the oversized device to close the ASD because of detachment. In two patients, it was difficult to trap the anterior border of the defect in the percutaneous closure. The other two patients were unable to receive percutaneous catheterization (5). This report reminds us of the difficulty of percutaneous catheterization with remnants in the RA. In our case, we chose a larger device to cover these two ASDs and open the right-side disc of the device more carefully under TEE guidance to avoid clamping the EV. During catheterization, the position of the RA remnants and the device are important to avoid device malposition and coronary sinus obstruction (12, 13). The unique point of our case is two ASDs with prominent iCTD, which is rarely reported. Besides, the occlusion of the coronary sinus causing the ischemic change during closure of the ASD has not been reported previously. Fortunately, we managed this case under TEE guidance by percutaneous catheterization and solved this rare but critical complication.

In conclusion, the importance of recognizing this remnant during anatomical study of ASDs is highlighted. This peculiar structure produces a diagnostic dilemma in echocardiography and it may bring about technical challenges and complications

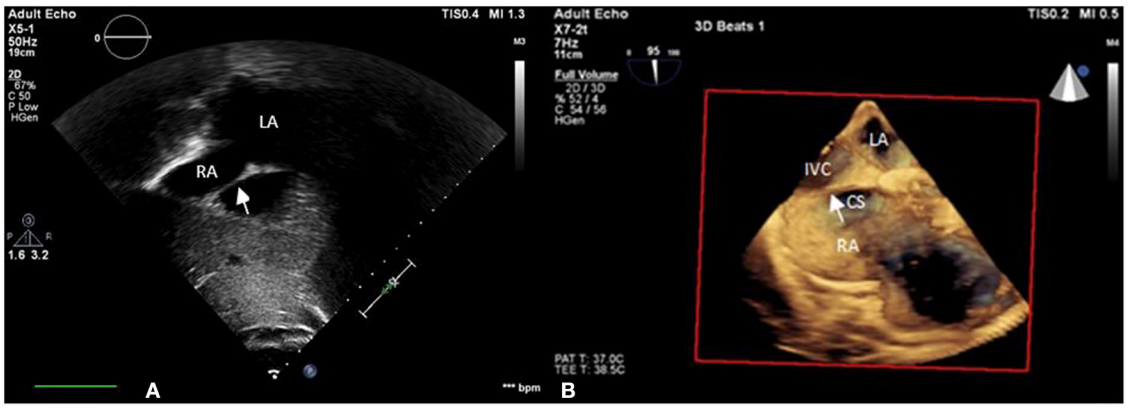

FIGURE 1 | iCTD (arrow) at the connection of the right atrium and inferior vena cava is shown in **(A)** transthoracic echocardiogram (TTE) and **(B)** three-dimensional TEE. LA, left atrium; RA, right atrium; CS, coronary sinus; IVC, inferior vena cava.

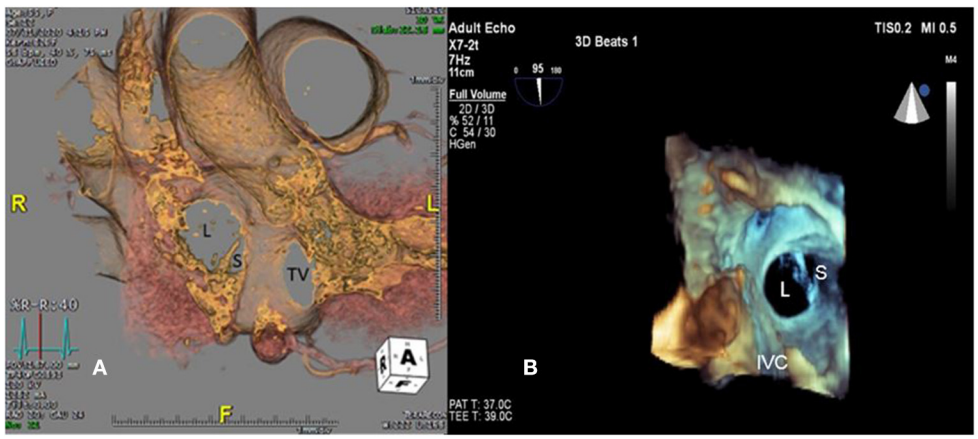

FIGURE 2 | Large (L) and small (S) ASDs are revealed in **(A)** cardiac computed tomography and **(B)** three-dimensional transesophageal echocardiogram. TV, tricuspid valve.

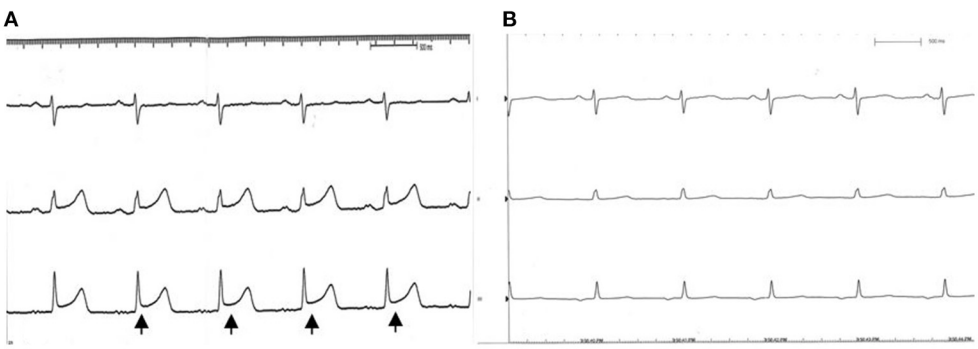

FIGURE 3 | EKG during catheterization. **(A)** ST segment elevation (black arrow) is noted while the coronary sinus was obstructed by the occluder. **(B)** Recovery to sinus rhythm after we withdrew the device.

such as ischemic change during interventional procedures. Cardiac CT and MRI are important tools to differentiate between CTD, EV, ThV, or Chiari network. TEE guidance and device selection were important during intervention.

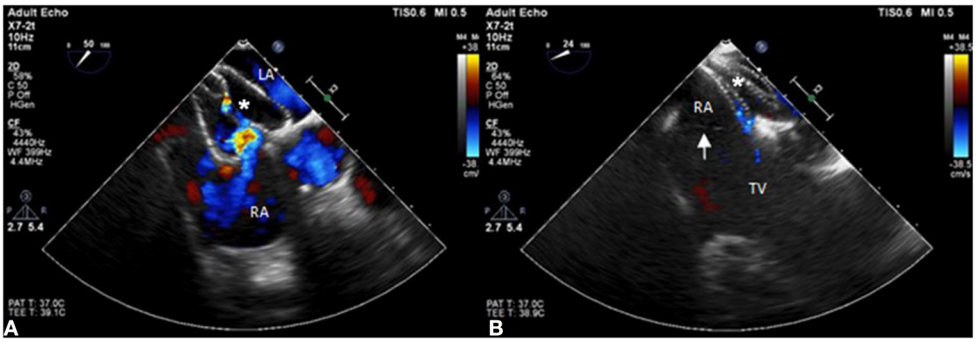

FIGURE 4 | The position of the ASD occluder. **(A)** The position of the ASD device is initially incorrect with part of the incomplete cor triatiatum dexter clamped and many residual shunts noted under TEE. **(B)** The position of the ASD occluder is good with a minimal residual shunt and the incomplete cor triatiatum dexter (arrow) is free from clamping by the device.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

J-HH carried out the studies. Y-CL, Z-KD, and I-CC participated in collecting data. P-HC drafted the manuscript. J-RW and Y-HW helped to draft the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Residual Atrial Shunt Lesions in Aging Adults With Congenital Heart Disease: An Underestimated Risk of Stroke?

Matthias Schneider[1,2], Varius Dannenberg[3], Bernd Opgen-Rhein[4], Felix Berger[2,4], Burkert Pieske[1,2,5,6], Harald Gabriel[3] and Leif-Hendrik Boldt[1,5]*

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We report two cases of paradoxical cerebral embolism in adults with congenital heart disease (ACHD) with residual atrial shunt lesions, a 59 year-old male patient with partial detachment of a surgical ASD closure patch, and a 57 year-old male patient with Ebstein's anomaly and a large patent foramen ovale. Considering these mechanisms and the increasing incidence of venous thrombosis with age, a higher prevalence of paradoxical embolism in ACHD patients with residual atrial shunts may be suspected. Regular follow-up of patients with ACHD remains important throughout life even in seemingly stable lesions.

Keywords: embolic stroke, adults with congenital heart disease, echocardiography, cardioembolic and cryptogenic stroke, Ebstein anomaly, ASD, case report

INTRODUCTION

The number of aging adults with congenital heart disease (ACHD) is constantly growing, as are late sequelae in this cohort (1). The risk for ischemic stroke is eleven times higher in young patients with CHD when compared to controls (2), the cumulative risk between the ages of 18 and 64 years is 6–8% (3). The majority of events occur in patients with cyanotic defects and in those without sinus rhythm (4). Arrhythmias are common in ACHD patients (5), in particular there is a high prevalence of atrial arrhythmias (6, 7). While paradoxical embolism *via* a patent foramen ovale (PFO) is associated with cryptogenic stroke in the general population and PFO closure reduces the rate of subsequent events in selected patients (8–10), up to now cryptogenic stroke has not been investigated systematically in ACHD patients.

CASE PRESENTATION

We report two cases of paradoxical cerebral embolism in ACHD patients with residual atrial shunt lesions (**Figure 1**). The first patient is a 59 year-old male who had received surgical repair of

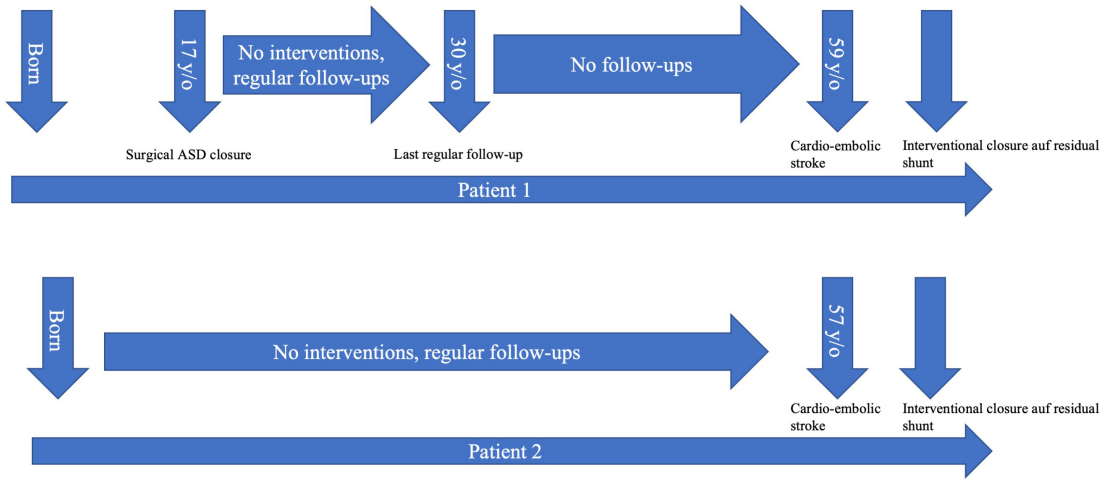

FIGURE 1 | Timeline depicting the medical history of both presented patients. ASD, atrial septum defect.

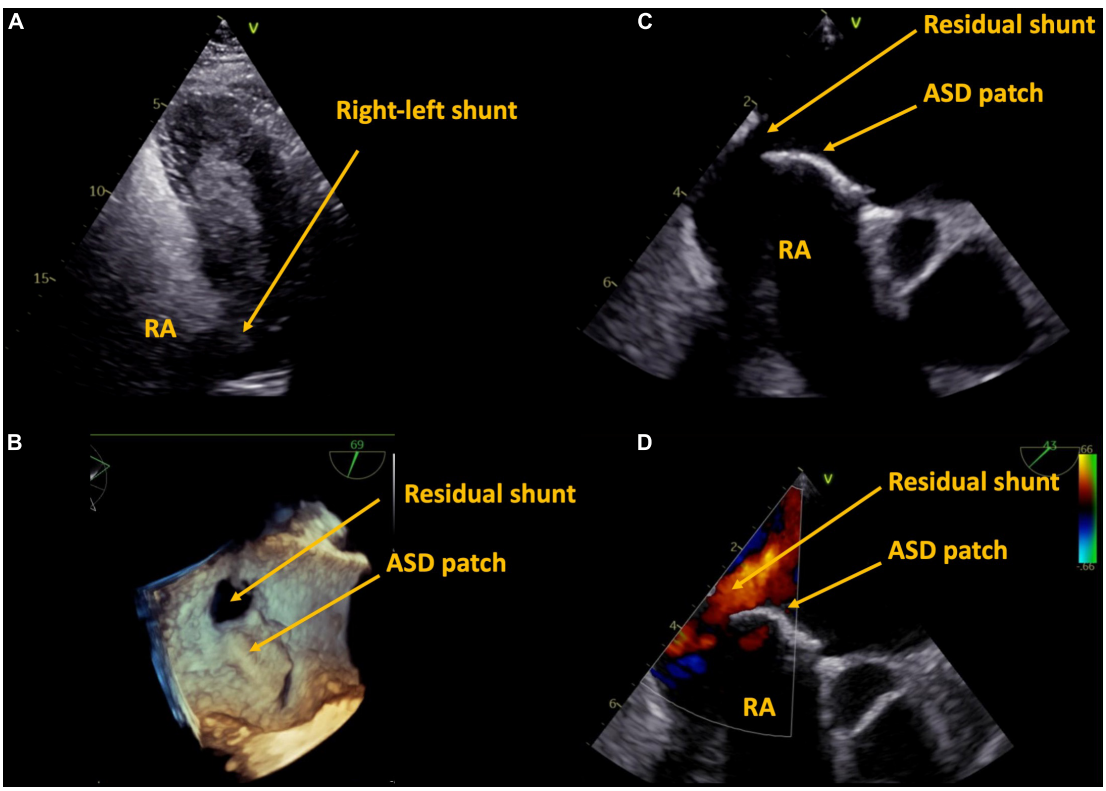

FIGURE 2 | Case 1, 59 year-old patient with a history of surgical ASD closure with partial detachment of the patch. Residual shunt shown by right-heart contrast agent **(A)**, and by transesophageal echocardiography in 3D **(B)**, 2D **(C)**, and 2D color **(D)**. ASD, atrial septum defect, RA, right atrium.

secundum atrial septum defect (ASD) 42 years ago. There were no regular follow-ups after the age of 30, his further medical history was unremarkable, exercise capacity was excellent. The patient presented to our hospital with acute embolic stroke. Transesophageal echocardiography revealed a residual atrial septal defect in the posterior inferior region due to partial detachment of the surgical patch (**Figure 2**) with spontaneous transfer of ultrasound contrast agent from right to left. The right ventricle was of borderline size, calculated Qp:Qs was 1.4:1. In absence of other reasons for embolic stroke (non-smoker, no dyslipidemia, no arterial hypertension, no history of atrial fibrillation, and unremarkable carotid ultrasound), paradoxical

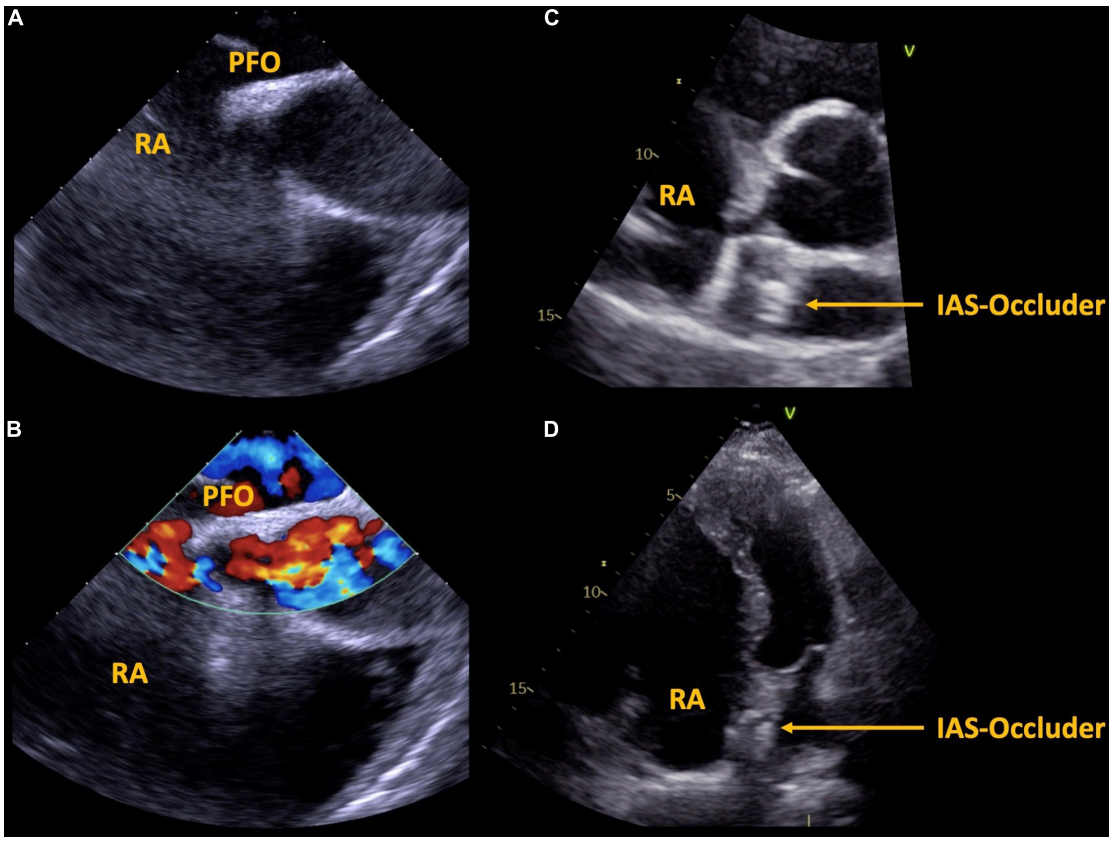

FIGURE 3 | Case 2, 57 year-old patient with Ebstein's anomaly. A large PFO is shown via transesophageal echocardiography without **(A)** and with **(B)** color Doppler imaging. Interventional septal occluder implantation was performed, the result is shown in panels **(C,D)**. PFO, patent foramen ovale, IAS, inter atrial septum, RA, right atrium.

embolism was assumed and interventional closure of the residual atrial septum defect was performed with a 25 mm septal occluder device.

The second patient is a 57 year-old male with known Ebstein's anomaly. Exercise capacity had been unchanged for years as were right heart dimensions. This patient also presented with embolic stroke. The patient was a non-smoker, there was no history of dyslipidemia, arterial hypertension, or atrial fibrillation, carotid ultrasound was unremarkable). TEE revealed a large PFO with spontaneous transfer of ultrasound contrast agent from right to left (**Figure 3**). Paradoxical embolism was assumed and the PFO was closed interventionally with a 25 mm PFO closure device. Exercise capacity remained unchanged after PFO closure.

The two presented cases of paradoxical embolism illustrate that mechanisms of stroke in ACHD patients can be different from those of the general population (e.g., high right atrial pressure in Ebstein's anomaly, large shunt in partial detachment of ASD patch). Considering these mechanisms and the increasing incidence of venous thrombosis with age (11), a higher prevalence of paradoxical embolism in ACHD patients with residual atrial shunts may be suspected and should be investigated in prospective trials.

CONCLUSION

With the increasing number of aging ACHD patients, late sequelae not directly related to the initial congenital heart disease significantly influence their morbidity and mortality. Regular follow-up of patients with ACHD remains important throughout life even in seemingly stable lesions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MS: conceptualization and visualization. MS and VD: writing – original draft preparation. HG, VD, FB, BO-R, BP, and L-HB: writing – review and editing. BP, HG, and L-HB: supervision. All authors have read and agreed to the published version of the manuscript.

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BRIEF RESEARCH REPORT
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Long-Term Survival of Adult Patients With Atrial Septal Defect With Regards to Defect Closure and Pulmonary Hypertension

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Background: Atrial septal defect (ASD) is the most common congenital heart disease (CHD) in adults and pulmonary hypertension (PH) is an established risk factor. A decision whether to perform ASD closure, especially in elderly patients with PH, is a complex dilemma. The aim of our study was to compare long-term survival in patients with closed and open ASD.

Methods: A retrospective cohort study was performed on 427 patients with ASD (median age at diagnosis 38 years, IQR 18–56) out of which 186 patients (44%) manifested PH. ASD closure in patients with PH was only considered in patients without Eisenmenger syndrome with pulmonary vascular resistance < 5 WU. Median follow-up duration was 18 years (IQR 9–31 years). Kaplan-Meier and Cox proportional hazards survival analyses were performed to evaluate 12 potential predictors of survival.

Results: Defect closure was associated with improved long-term survival in ASD patients both with ($P < 0.001$) and without PH ($P = 0.01$) and this association was present also in patients over 40 years. The 20-year survival since diagnosis was significantly higher in patients with PH and closed ASD compared to those with PH and open ASD (65% vs. 41%). ASD closure was a significant independent predictor of long-term survival ($P = 0.003$) after accounting for age at diagnosis, PH, NYHA class, Eisenmenger syndrome, and mitral regurgitation. Significant negative independent predictors of survival were older age at diagnosis ($P < 0.001$), Eisenmenger syndrome ($P < 0.001$), and PH ($P = 0.03$).

Conclusion: ASD closure appears to be associated with improved long-term survival independently of age, PH, and other clinical variables.

Keywords: atrial septal defect, long-term survival, pulmonary hypertension, defect closure, congenital heart disease

INTRODUCTION

Atrial septal defect (ASD) is the most common congenital heart disease (CHD) in adults and is often diagnosed late in adulthood. Identification of patients who would benefit from a closure of atrial septal defect (ASD) in adulthood remains a crucial, but complicated question (1). One particularly important group with unclear closure benefit comprises patients with pulmonary hypertension (PH). ASD closure appears safe in young patients without PH or even with PH meeting the criteria for defect closure (2–6). However, the presence of PH in older patients is associated with increased mortality following ASD closure compared to patients without PH (3, 4). It is not known whether the poor prognosis of the PH patients results from the ASD closure itself, or if their outcome would have been similar or even worse if the ASD closure was not carried out. As highlighted in the latest ESC guidelines, the impact of shunt closure on long-term outcome of patients with PH remains an area of uncertainty and requires further research (6).

We therefore sought to compare long-term survival of adults with and without ASD closure, with respect to PH, age, and other clinical variables.

METHODS

Patients

Following institutional ethics committee approval, we performed a retrospective observational cohort analysis of isolated ASD patients in our database. The consecutive patient data were collected between 1995 and 2020. Mortality data were obtained from the national mortality register. The inclusion criteria were: adults with ASD type secundum, sinus venosus or coronary sinus defect diagnosed in adulthood or childhood, with accessible information concerning presence of PH and defect closure. The exclusion criteria were: ASD type primum, patent foramen ovale, missing data on ASD closure or on PH, or presence of another hemodynamically important congenital heart disease.

Clinical Variables

For the purpose of this analysis, pulmonary hypertension (PH) was defined as mean pulmonary arterial pressure $\geq$ 25 mmHg, as determined by catheterization (if available) or echocardiography (7, 8). Patients suspected to have moderate or severe PH based on echocardiography have undergone right heart catheterization (RHC) with pulmonary vascular resistance (PVR) assessment. ASD size was measured by transesophageal echocardiography in 74% patients. The contraindications for ASD closure were: (a) Eisenmenger syndrome or non-indexed PVR > 5 Wood Units (WU) not responding to vasodilatation testing with epoprostenol or advanced therapy treatment (5, 6), (b) an increase in left atrial mean pressure during temporary balloon occlusion > 10 mmHg compared to baseline (9). In some patients, ASD was not closed in accordance with their wish.

Statistical Analysis

Comparisons between cohorts (with and without PH) were performed with the Fisher's exact test for binary variables and Mann-Whitney *U*-test for continuous variables, with Benjamini-Hochberg correction for multiple testing (false-discovery rate 0.05) applied on the reported *P*-values. Kaplan-Meier estimates and Cox proportional hazards model were used to analyze survival. All covariates were assessed that they fulfill the proportional hazards assumption, using the MATLAB fitcox function, which is based on the scaled Schoenfeld residuals, as derived by Grambsch and Therneau (10). The following variables were included in the univariable model: ASD closure, age at diagnosis, sex, New York Heart Association (NYHA) functional class, PH, moderate or severe mitral regurgitation (MR), Eisenmenger syndrome, ASD types (ASD secundum, sinus venosus, coronary sinus defect), ASD size, and advanced pulmonary vasodilator therapy. NYHA was used as a binary variable (NYHA > 2) to fulfill the proportional hazards assumption. The variables significant in univariable Cox proportional hazards model were then included in a multivariable model. Both the Kaplan-Meier and the multivariable Cox proportional hazards analyses were performed first in all patients (model A) and second in patients without Eisenmenger syndrome (model B). Values of $P < 0.05$ were considered statistically significant ($^{***}P < 0.001$; $^{**}P < 0.01$; $^{*}P < 0.05$). Statistical tests were two-sided. Data were analyzed using MATLAB (R2021b).

RESULTS

Patient Characteristics

Data analysis was performed in 427 patients from our database meeting the inclusion criteria. Median age at diagnosis of the whole group was 38 (IQR 18–56) years and 74% of patients were female (**Table 1**). The age at diagnosis was higher in patients with PH compared to patients without PH: 50 (IQR 30–60) vs. 29 (IQR 13–46) years for closed defects ($P < 0.001$) and 53 (IQR 29–70) vs. 39 (IQR 28–57) for open defects ($P = 0.3$), (**Table 1**). Median follow-up was 18 years (IQR 9–31). Sinus venosus defect was present in 77 patients (18%) and coronary sinus defect in 8 patients (2%). Catheterization was performed in 60% of patients with PH and in 22% of patients without PH, altogether in 166 patients. ASD closure was performed in 367 patients (86%); out of which 58% by sternotomy, 14% video-assisted mini-thoracotomy, 10% robotic cardiac surgery, and 17% transcatheter.

Pulmonary Hypertension

PH was present in 186 patients (44%), out of which 150 have undergone ASD closure (81%) and 36 have not (19%), (**Table 1**). The group of 36 patients with PH and open ASD comprised 12 patients who refused a recommended ASD closure (7 of them died), 7 patients with Eisenmenger syndrome (5 of them died), 4 patients with high PVR without Eisenmenger syndrome (3 died), 2 patients with small defects and PH (1 died), and 11 patients with various reasons for leaving ASD open (lung

TABLE 1 | Patient characteristics.

Feature	No PH closed (*n* = 223)	PH closed (*n* = 144)	*P*-value closed no PH vs. PH	No PH open (*n* = 25)	PH open (*n* = 35)	*P*-value open no PH vs. PH	All (*n* = 427)
Age at diag. (years)	29 [13–46] (*n* = 217)	50 [30–60] (*n* = 150)	1×10^{-8} (***)	39 [28–57] (*n* = 24)	53 [29–70] (*n* = 36)	0.3	38 [18–56] (*n* = 427)
NYHA > 2	11.5% (25/217)	54.7% (82/150)	3×10^{-18} (***)	16.7% (4/24)	61.1% (22/36)	0.007 (**)	31.1% (133/427)
MR	12.0% (26/217)	28.9% (43/149)	1×10^{-4} (***)	12.5% (3/24)	31.4% (11/35)	0.2	19.5% (83/425)
Eisenmenger	*NA*	0.0% (0/150)	1	*NA*	19.4% (7/36)	0.1	1.6% (7/427)
ASD secundum	82.9% (180/217)	80.7% (121/150)	0.7	95.8% (23/24)	80.6% (29/36)	0.2	82.7% (353/427)
Sinus venosus	17.5% (38/217)	19.3% (29/150)	0.8	4.2% (1/24)	25.0% (9/36)	0.1	18.0% (77/427)
Coronary sinus	0.5% (1/217)	2.7% (4/150)	0.2	0.0% (0/24)	8.3% (3/36)	0.4	1.9% (8/427)
ASD size	16 [11–20] (*n* = 147)	20 [14–25] (*n* = 126)	0.001 (**)	6 [4–12] (*n* = 16)	19 [12–28] (*n* = 25)	9×10^{-4} (***)	18 [12–23] (*n* = 314)
Advanced therapy	0.0% (0/217)	4.7% (7/150)	0.003 (**)	0.0% (0/24)	8.3% (3/36)	0.4	2.3% (10/427)
Sex (male)	28.1% (61/217)	22.0% (33/150)	0.3	20.8% (5/24)	30.6% (11/36)	0.7	25.8% (110/427)
10-year survival	98.2% (166/169)	86.5% (109/126)	2×10^{-4} (***)	90.5% (19/21)	63.6% (21/33)	0.1	90.3% (315/349)
20-year survival	94.8% (110/116)	65.1% (56/86)	2×10^{-7} (***)	69.2% (9/13)	40.6% (13/32)	0.2	76.1% (188/247)
40-year survival	80.5% (33/41)	44.3% (27/61)	5×10^{-4} (***)	0.0% (0/5)	23.3% (7/30)	0.4	48.9% (67/137)
TVP	7.8% (17/217)	40.7% (61/150)	5×10^{-13} (***)	*NA*	*NA*	*NA*	*NA*
MVP + MVR	6.5% (14/217)	20.7% (31/150)	2×10^{-4} (***)	*NA*	*NA*	*NA*	*NA*
antiarrhythmic MAZE + CTI	4.6% (10/217)	24.0% (36/150)	2×10^{-7} (***)	*NA*	*NA*	*NA*	*NA*

*Binary variables are given as percentage (positive/all cases). Continuous variables are given as median [interquartile range] (n), where n is the number of patients in the group with available data. ASD, atrial septal defect; MR, moderate or severe mitral regurgitation; NYHA, New York Heart Association class; PH, pulmonary hypertension; TVP, tricuspid valvuloplasty; MVP, mitral valvuloplasty; MVR, mitral valve replacement; CTI, ablation of cavo-tricuspid isthmus. (***P < 0.001; **P < 0.01; *P < 0.05).*

disease, left heart failure with high pulmonary capillary wedge pressure (PCW), age or increased PVR between 3 and 5 WU), 10 of them died.

Concomitant Surgical Procedures

Concomitant surgical procedures were performed in moderate or severe valve regurgitations: tricuspid valve repair (TVP), mitral valve repair (MVP) or replacement (MVR) or documented supraventricular arrhythmias: MAZE procedure or cryo-ablation of cavo-tricuspid isthmus (CTI). The concomitant surgical procedures were significantly more frequent in the group of 150 closed defects with PH compared to the group of 217 closed defects without PH (TVP: 41% vs. 8%, MVP/MVR: 21% vs. 6%, MAZE/CTI: 24% vs. 5%, respectively, **Table 1**).

Advanced Pulmonary Vasodilator Therapy

Advanced pulmonary vasodilator therapy was administered to 10 patients with ASD and PH in our study (5.4%): three patients with Eisenmenger syndrome and open ASD, six patients after ASD closure (all with persistent PH and PVR $\geq$ 2.9 WU), and one patient with PVR > 5 WU received the therapy both before and after the ASD closure. The remaining 4 patients with Eisenmenger syndrome died before the specific therapy was available.

Pulmonary Hypertension and Atrial Septal Defect Closure as Predictors of Mortality

As expected, PH was associated with higher all-cause mortality of ASD patients with closed defects (log-rank $P < 0.001$) as well as with open defects (log-rank $P = 0.01$ for model A and log-rank $P = 0.006$ for model B with Eisenmenger patients excluded) (**Figure 1A** and **Supplementary Figure 1A**). At the same time, defect closure was associated with improved survival not only in patients without PH (log-rank $P = 0.01$), but also in patients with PH and PVR < 5 WU (log-rank $P < 0.001$ for model A and log-rank $P < 0.001$ for model B) (**Figure 1A** and **Supplementary Figure 1**). Finally, this difference was present also in patients older than 40 years at diagnosis (**Figure 1B** and **Supplementary Figure 1B**).

The 20-year survival since diagnosis was higher in closed ASD than open ASD both in patients with PH (65% vs. 41%, $P = 0.02$) and without PH (95% vs. 69%, $P = 0.01$).

Univariable Analysis of Mortality Prediction

Six variables significantly predicted mortality in a univariable model. While defect closure was negatively associated with mortality (hazard ratio 0.2, 95% confidence interval 0.1–0.4, $P < 0.001$), positive association with mortality was found for

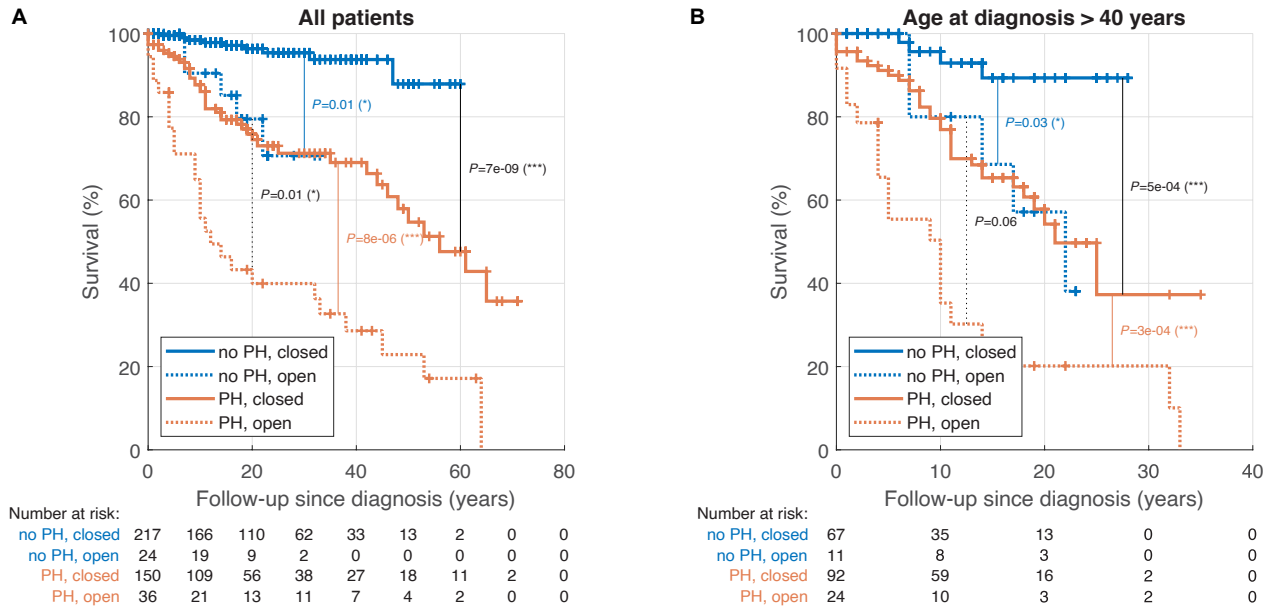

FIGURE 1 | Kaplan-Meier survival analysis of atrial septal defect (ASD) patients stratified by pulmonary hypertension (PH) and ASD closure; all patients (model A). **(A)** Patients of all ages. **(B)** Patients diagnosed at the age above 40. ASD, atrial septal defect; MR, moderate or severe mitral regurgitation; NYHA, New York Heart Association class; PH, pulmonary hypertension.

older age at diagnosis, PH, Eisenmenger syndrome, NYHA class, and MR (**Table 2** and **Figure 2A**). The remaining variables were not significantly predictive of mortality: ASD secundum, sinus venosus defect, coronary sinus defect, advanced therapy, ASD size, and sex.

Multivariable Analysis of Mortality Prediction

The six variables significant in univariable analysis were subsequently included in a multivariable model A, in which four of them remained significantly predictive of mortality: ASD closure negatively (P = 0.003), while older age at diagnosis (P < 0.001), Eisenmenger syndrome (P < 0.001), and PH (P = 0.03) positively (**Table 2** and **Figure 2B**). Finally, even when patients with Eisenmenger syndrome (as they are contraindicated for ASD closure) were completely excluded from this analysis (multivariable model B), the better long-term survival in patients with closed defects remained significant (P = 0.003) (**Table 2**).

DISCUSSION

The decision concerning ASD closure is particularly difficult in elderly patients with PH given the increased mortality risk in this group after ASD closure compared to young patients or patients without PH (3, 4, 11, 12).

The previous studies were missing a control group of patients without ASD closure, and thus could not distinguish whether the worsened survival is due to ASD closure itself, or PH and older age (3). Other previous studies have indicated that older patients with moderate or severe PH benefit from transcatheter closure of ASD with regards to improvement of symptoms and reduction of PH; however, these studies did not report a survival analysis (9, 13, 14).

A study of ASD and trisomy 21 showed a significantly higher mortality in uncorrected ASD including those with severe pulmonary vascular disease (PVD) compared to those with ASD closure. However, this study comprised only children and the group with PH before ASD closure was not analyzed (15).

Here, we conducted a retrospective study comparing long-term mortality in ASD patients with and without defect closure, with respect to PH, age, and other clinical variables. In line with previous studies (3, 4), we observed PH to be associated with higher all-cause mortality. The frequency of PH was high in our cohort (44%). This reflects the fact that our patients were older with late ASD diagnosis (they were followed-up since 1995). There could be also a selection bias resulting from the fact that high-risk patients with PH were sent to our tertiary referral center, while simple ASD patients were frequently treated at the local level.

A key finding of our study is that ASD closure (with adherence to the contraindication criteria) is associated with improved long-term survival in patients with or without PH and this holds also for patients over 40 years of age. ASD closure was a significant independent predictor of survival even after adjusting for age at diagnosis, PH, NYHA, MR, and Eisenmenger syndrome (which was present only in patients with open defects). In particular, ASD patients with PH had significantly better long-term survival after defect closure (65% after 20 years since diagnosis) compared to patients with PH and open ASD (41% after 20 years since diagnosis). Therefore, our data do not support the hypothesis that closure itself increases mortality risk for patients at high

TABLE 2 | Cox-proportional hazards models for mortality prediction.

	Univariable analysis (n = 427)		Multivariable model A (n = 425)		Multivariable model B (n = 418)	
Feature	**Hazard ratio**	***P*-value**	**Hazard ratio**	***P*-value**	**Hazard ratio**	***P*-value**
Age at diag. (decades)	2.9 [2.4–3.5]	1×10^{-27} (***)	2.8 [2.3–3.5]	7×10^{-22} (***)	2.7 [2.2–3.4]	6×10^{-20} (***)
Eisenmenger	4.3 [1.7–10.8]	0.002 (**)	16.4 [4.9–54.3]	3×10^{-06} (***)		
ASD closure	0.2 [0.1–0.4]	2×10^{-10} (***)	0.5 [0.3–0.8]	0.003 (**)	0.5 [0.3–0.8]	0.003 (**)
PH	6.2 [3.4–11.1]	8×10^{-10} (***)	2.0 [1.1–3.8]	0.03 (*)	2.0 [1.0–3.7]	0.03 (*)
NYHA > 2	4.6 [2.9–7.4]	8×10^{-11} (***)	1.3 [0.8–2.2]	0.2	1.4 [0.8–2.3]	0.2
MR	2.1 [1.3–3.4]	0.001 (**)	1.4 [0.9–2.3]	0.2	1.4 [0.9–2.3]	0.2
ASD secundum	1.9 [1.0–3.8]	0.06				
Sinus venosus	0.7 [0.4–1.2]	0.2				
Coronary sinus	2.0 [0.6–6.6]	0.2				
Advanced therapy	0.9 [0.2–3.8]	0.9				
ASD size	1.0 [1.0–1.0]	0.4				
Sex (male)	1.0 [0.6–1.6]	1				

*In the univariable analysis, all variables were assessed independently, and the significant variables were then included in the multivariable analysis (models A and B). In the multivariable model A, all 425 patients with non-missing values for the seven variables were included. In the multivariable model B, patients with Eisenmenger syndrome were excluded and all 418 patients with non-missing values for the remaining six variables were included. ASD, atrial septal defect; MR, moderate or severe mitral regurgitation; NYHA, New York Heart Association class; PH, pulmonary hypertension. (***P < 0.001; **P < 0.01; *P < 0.05).*

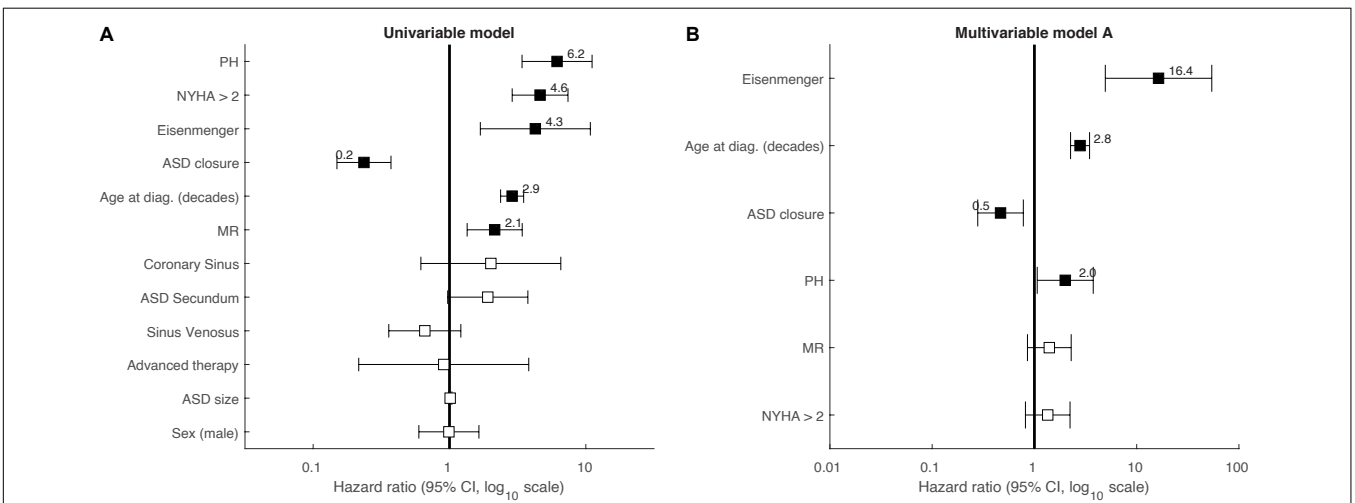

FIGURE 2 | Forest plot of Cox-proportional hazards survival analysis in ASD patients. **(A)** univariable analysis. **(B)** Multivariable analysis (all patients, i.e., model A). The forest plot shows the hazard ratios and their 95% confidence intervals at a $\log_{10}$ scale. Significant variables are highlighted by a filled black square. ASD, atrial septal defect; MR, moderate or severe mitral regurgitation; NYHA, New York Heart Association class; PH, pulmonary hypertension.

age or with PH, but rather that these patients are at high risk even without the closure. Our finding of the benefit of ASD closure is in line with results of a large nationwide study showing that patients with closed ASD have lower mortality compared to patients with open ASD (16).

It should be emphasized that the association of improved survival with ASD closure is relevant only for patients who fulfill the indication criteria for defect closure, with PVR $\leq$ 5 WU at baseline or after pulmonary vasodilator therapy (5, 6). Patients with PVR above 5 WU were shown to develop pulmonary arterial hypertension (PAH) late after defect closure, with poor prognosis (17). However, some case reports in the literature and also one of our patients suggest the possibility of "treat and repair" strategy with the use of advanced pulmonary vasodilator therapy in ASD patients with higher baseline PVR than 5 WU (18).

Patients with Eisenmenger syndrome are rare in ASD (1.6% in our study). Since Eisenmenger syndrome is a contradiction for defect closure, we designed our analysis with a special care to account for this potential confounding factor and performed all analyses with and without inclusion of patients with Eisenmenger syndrome. In our study, Eisenmenger syndrome was a strong predictor of mortality in univariable as well as in multivariable analysis (**Table 2**). However, ASD closure was a significant independent predictor of survival both in the analysis with Eisenmenger syndrome patients included (model A) and excluded (model B).

The presence of PH is sometimes erroneously considered to be a contraindication for defect closure on the basis of the study by Manes et al. (19). The authors observed the worst survival in patients with closed defects and PH, while the best survival was observed in Eisenmenger syndrome with open defects (most of them treated by advanced therapy). On the contrary, in our study, the highest long-term mortality was observed in open ASD with PH, including Eisenmenger syndrome. Eisenmenger syndrome, age at diagnosis, and PH were independent positive predictors of mortality in our study, while defect closure was a significant independent negative predictor of mortality. The discrepancy between the studies may be explained by the fact that the study of Manes et al. comprised predominantly post-tricuspid defects with unknown and potentially high preoperative PVR due to PAH and PVD. Therefore, the conclusions of Manes study are not applicable to ASD patients with PH and PVR $\leq$ 5 WU considered for closure. Moreover, the favorable long-term survival in patients with Eisenmenger syndrome in Manes et al. study could have been influenced by the use of advanced pulmonary vasodilator therapy. This therapy could only be used in a minority of our patients. While we observed general stabilization of clinical state in patients treated with advanced therapy, the numbers were too low to evaluate a potential significant benefit in the survival analysis.

The results of our study support the strategy of active screening of the ASD in adults with timely closure of hemodynamically significant defects early after diagnosis. ASD closure should be performed even in asymptomatic patients and on the other side even in older patients with PH if they comply with the indication criteria for ASD closure specified in the guidelines (5, 6). Transcatheter closure is preferred because of its lower invasiveness; however, if a patient with ASD and PH has concomitant severe tricuspid or MR or large defect without appropriate rims, we believe there is still place for surgery as recommended by the guidelines (5, 20).

High-risk patients should always be assessed for risks and benefits of ASD closure in a specialized expert center (6). ASD closure may prevent further deterioration of PH and improve survival, however in patients with severe PH and advanced PVD, the shunt closure may be detrimental. Therefore, the catheterization with PVR assessment is crucial (5, 6, 21). The current recommended cut-off value of PVR for ASD closure is 5 WU (6). In high-risk patients with PAH, a small fenestration may be useful to prevent right heart failure after ASD closure. In postcapillary and combined PH, we aimed to remove the cause of postcapillary PH (mitral regurgitation, coronary artery disease, left heart failure, etc.) before or during the ASD closure and to leave a small fenestration to prevent left heart failure.

Mortality and morbidity (stroke or heart failure) are significantly increased by atrial arrhythmias (22). The risk of atrial arrhythmias and stroke is increased in patients with ASD (23, 24) and the prevalence of atrial arrhythmias in ASD increases with age (22). In our study, we performed the antiarrhytmic surgery (MAZE and/or CTI) in the case of documented atrial arrhythmias. This procedure was significantly more frequent in patients with PH compared to defects without PH (24% vs. 5%, $p < 0.001$). Close long-term follow-up of patients with open as well as closed ASD is important. It should include clinical examination with assessment of symptoms, especially arrhythmias, repeated echocardiogram, and ECG monitoring. Some of the small defects may increase their hemodynamic relevance with increasing age and such defects should be closed in time.

Our study confirmed that ASD patients with PH had higher mortality and suffered more often from mitral and tricuspid regurgitation and arrhythmias, compared to patients without PH. This is in line with the literature; patients with PH had more comorbidities, were older and had a significantly higher risk of developing major cardiac and cerebrovascular adverse events after transcatheter ASD closure (25).

In conclusion, our study on 427 ASD patients identified ASD closure as a positive independent predictor of survival. In contrast, older age at diagnosis, Eisenmenger syndrome, and PH were independent negative predictors of survival. Patients with PH and closed ASD had significantly lower long-term mortality compared to patients with PH and open defects. ASD closure thus appears to be beneficial even in older patients with PH and PVR < 5 WU, who are not contraindicated for closure for other reasons.

LIMITATIONS OF THE STUDY

(A) Due to the retrospective nature of our study, the groups with and without ASD closure could not be matched. Patients with open ASD and PH formed a heterogenous group comprising patients contraindicated for ASD closure (Eisenmenger syndrome, small defects with severe PH), and patients who refused ASD closure despite PVR < 5 WU. However, the mortality was high in all subgroups of open ASD and PH patients. (B) While the long-term follow-up (and data collection since 1995) is of a general advantage of our study, it brings two inherent limitations. First, catheterization was not performed in all patients, but preferentially in those with suspicion of moderate or severe PH based on echocardiography. Second, not all patients with high PVR had the possibility of advanced pulmonary vasodilator therapy treatment. However, as soon as the advanced therapy was accessible, it was administered to all patients with Eisenmenger syndrome or high PVR who were still alive. The impact of advanced vasodilator therapy on the long-term survival of ASD patients with high PVR and open or closed defects therefore remains to be assessed in future research.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Na Homolce Hospital, project

5.6.2019/25 and 26. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JR conceived the study, collected the patient data, and was the guarantor of the study. RŽ contributed to data collection. MT and JT carried out data analysis and visualization. MT and JR wrote the initial draft, with all authors subsequently carrying out critical revisions.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.867012/full#supplementary-material

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Clinical Characteristics of Congenital Atresia of the Left Main Coronary Artery in 12 Children

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Background: Left main coronary artery atresia (LMCAA) is an extremely rare abnormality and only <100 cases have been reported worldwide. We describe the clinical manifestations, imaging features, prognosis, and treatments of LMCAA who were admitted in our department, which aimed to improve the clinical diagnosis and treatments of LMCAA in children.

Methods: A retrospective study identified 12 patients diagnosed with congenital left coronary artery atresia at Pediatric Heart Center of Beijing Anzhen Hospital from June 2010 to June 2019. The clinical characteristics, imaging data, and treatment follow-up were analyzed.

Results: Among the 12 cases, 8 were boys and 4 were girls; the age of onset was 2 months to 2 years old (median age 7 months); the age of diagnosis was 7 months to 6 years old (median age 2 years and 11 months). At the initial diagnosis, there were 4 cases of respiratory tract infection with cardiac murmur, 3 cases of cardiac shadow enlargement, 1 case of recurrent syncope, 2 cases of feeding difficulty with cardiac enlargement, and 2 cases of simple cardiac murmur. In 12 cases of electrocardiogram examination, 7 cases showed pathological Q waves of lead I, AVL and v4–v6; in 12 cases of chest X-ray examination, 8 cases showed cardiac shadow enlargement; in 12 cases of our hospital's first cardiac ultrasound examination, 4 cases were definitely diagnosed, and 8 cases showed the possibility of left coronary artery abnormality; in 5 cases of cardiac coronary CT angiography examination, 2 cases were confirmed, 2 cases reported suspected left coronary artery abnormality, and 1 case did not report abnormality; All cases were definitely diagnosed in 8 cases of angiography. Follow-up was performed from 1 to 8 years; one case died suddenly, one case of syncope after activity was treated by oral medication, 3 cases received open coronary angioplasty and mitral valvuloplasty, recovered well after operation, the rest of the children were treated by oral medication, and the symptoms are stable at present.

Conclusions: Left main coronary artery atresia is difficult to diagnose and can result in heart failure early in life. Timely diagnosis and reasonable treatment are the keys to improve the prognosis.

Keywords: atresia of the left main coronary artery, congenital, children, coronary angiography, coronary angioplasty

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INTRODUCTION

The incidence of congenital coronary abnormalities was 0.6–1.3% in patients undergoing coronary angiography and 0.3% at autopsies (1). Among them, left main coronary artery atresia (LMCAA) is an extremely rare abnormality, and only <100 cases have been reported worldwide (2). LMCAA is characterized by the absence of left coronary ostium and the proximal left main trunk ends blindly, blood flows from the right coronary artery to the left *via* small collateral arteries. The symptoms of LMCAA can be different, and infants and children may be manifested as heart failure while some adults may be had no symptoms. The severity of symptoms is related to the degree of myocardial ischemia. This study retrospectively analyzed the clinical data of 12 children with congenital LMCAA referred to our department from June 2010 to June 2019, summarized the clinical features, imaging manifestations, treatments, and follow-up data of these children, to make early and correct diagnosis and to understand the prognosis of this disease.

METHODS

A retrospective study was performed to identify 12 patients diagnosed with congenital left coronary artery atresia at Pediatric Heart Center of Beijing Anzhen Hospital from June 2010 to June 2019. The patients met the following inclusion criteria: (1) The diagnosis was confirmed by cardiac coronary CT angiography (CTA) or coronary angiography in our hospital; (2) age of onset ≤14 years. Exclusion criteria were as follows: (1) left main coronary artery occlusion secondary to other diseases, such as Kawasaki disease, Takayasu arteritis, etc., and (2) complicated with other congenital heart malformations.

In this study, the relevant data and examinations that include medical history, laboratory examinations, electrocardiograms, and imaging examinations of the patients were collected by reviewing the cases. After a definite diagnosis, all the 12 children were given medicine therapy, and 3 of them underwent surgery. Regular outpatient follow-up was performed. All the children's guardians signed the informed consent. This study was approved by the hospital medical ethics committee.

RESULTS

Among the 12 patients, 8 were boys and 4 were girls. The onset age ranged from 2 months to 2 years (median age 7 months). The age of diagnosis was 7 months to 6 years (median age 2 years and 11 months). At the initial diagnosis, the manifestations were pneumonia, respiratory tract infection with cardiac murmur in 4 cases, cardiac shadow enlargement in 3 cases, recurrent syncope in 1 case, feeding difficulty with cardiac enlargement in 2 cases, and simple cardiac murmur in 2 cases. Among the 12 patients, the first visiting hospital was our hospital. Correct diagnosis was made in 1 case, and incorrect diagnosis was made in other 11 cases during their initial visit at other hospitals: 7 cases were misdiagnosed as valvular disease, of which 1 case was diagnosed as mitral valve prolapse and severe regurgitation who had received mitral valvuloplasty in other hospitals, 1 case was misdiagnosed as endocardial fibroelastosis, 1 case was misdiagnosed as left ventricular non-compaction, 1 case was misdiagnosed as dilated cardiomyopathy, and 1 case was misdiagnosed as the anomalous origin of the left coronary artery from pulmonary artery.

All the 12 patients underwent laboratory examination, electrocardiogram, chest radiography, and echocardiogram, five underwent cardiac CTA examinations, and 8 underwent coronary angiography.

In regard to laboratory examination, Creatine Kinase, MB Form (CK-MB) was abnormal in 2 cases. Brain natriuretic peptide (BNP) was slightly higher in 6 cases. Electrocardiogram was done in all patients. Then, 7 patients showed the presence of pathological Q waves and ST segment changes in lead I, AVL, and V4-V6 (**Figure 1**). The cardiothoracic ratio increased in 8 cases (≥0.55) (**Figure 2**).

A number of 4 cases diagnosed, and 8 cases suspected left coronary artery abnormality at the first-time echocardiogram was done in our hospital. Echocardiographic signs include the following: ① left ventricular enlargement in all 12 cases with *Z*-value of left ventricular end-diastolic diameter >2; ②ejection fraction of left ventricle decreased (<60%) in 3 cases (25%) and normal in 9 cases (75%); ③ the origin of the right coronary artery is normal and its inner diameter was slightly widened. The ratio of the right coronary artery to aortic root was 0.19 ± 0.02 (0.17–0.21); ④fibrosis of mitral tendinous cord and papillary muscle; ⑤mitral valve prolapse with medium to large amount of reflux signals at the mitral valve orifice during systole; ⑥collateral circulation between the right coronary artery may be observed; ⑧ the dysplasia left coronary artery may be observed if the image is clear enough but there was no connection between left coronary artery (LCA) and the left coronary ostium, and abnormal reflux signals in the dysplasia LCA may be observed by color doppler flow imaging (CDFI) (**Figure 3**).

A number of 5 patients underwent cardiac CTA examinations. LMCAA was confirmed in 2 of the 5 children. Suspicious left coronary artery abnormalities were reported in 2 children, and no abnormalities were reported in 1 child. The main signs of cardiac CTA with LMCAA are the enlargement of left atrium and ventricle, normal opening of right coronary artery in right sinus and unobstructed coronary artery lumen, and proximal atresia of left main coronary artery. Furthermore, the left anterior descending coronary artery and the left circumflex coronary artery develop intermittently, with light development and thin lumen (**Figure 4**).

A number of 8 patients underwent coronary angiography. Coronary angiography can clearly show the shape and developmental sequence of coronary arteries. Aortic root angiography shows that the origin and course of the right coronary artery are normal, the diameter is slightly thicker, and the left coronary sinus is a blind end. Selective right coronary angiography shows that the branches of the left coronary artery are inversely perfused through the lateral branches of the right coronary artery, and the hypoplasia left coronary artery was finally developed and showed a blind end. No contrast agent

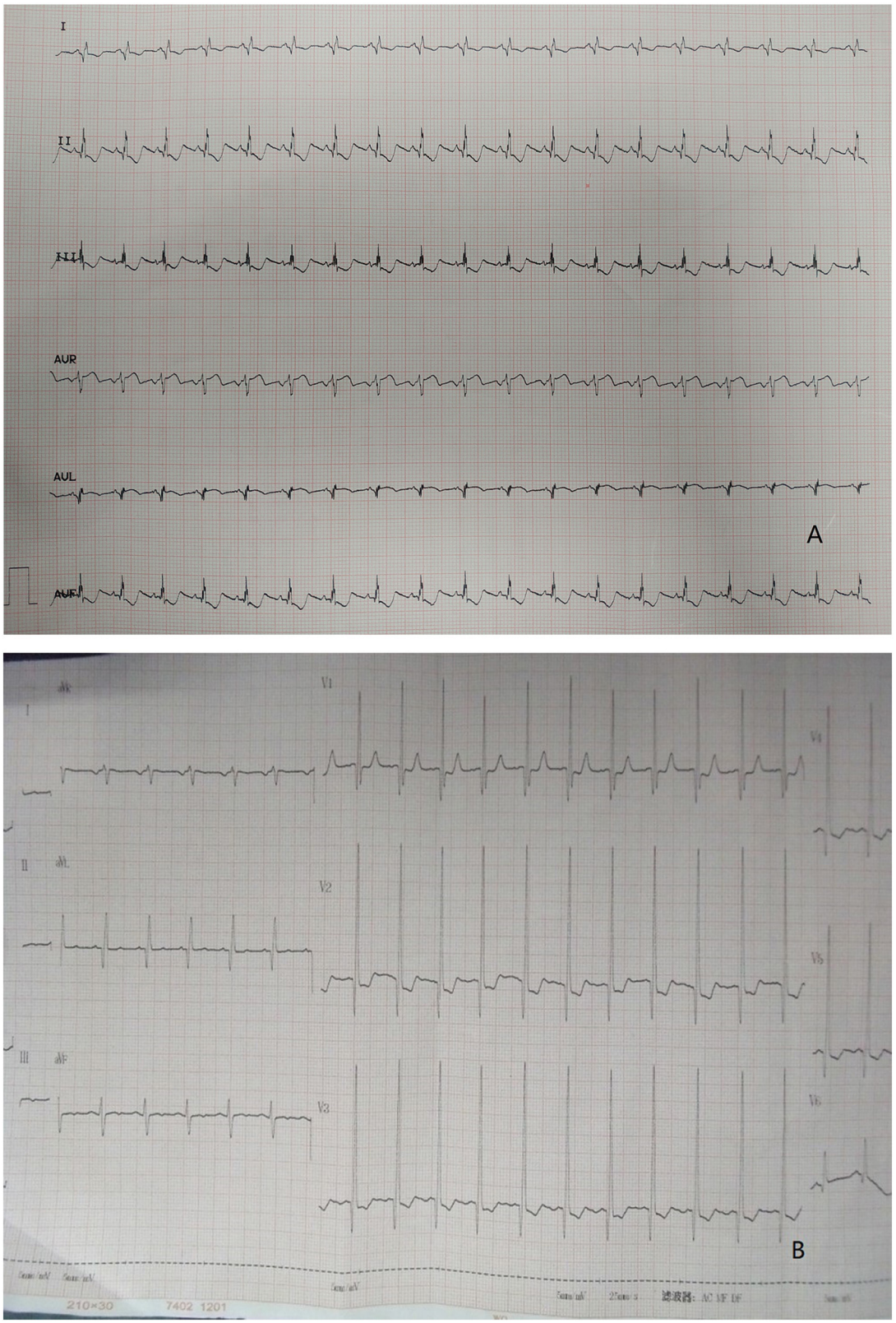

FIGURE 1 | (A) ECG: pathological Q waves in lead I, AVL. **(B)** ECG: pathological Q waves in lead AVL and ST segment depression in lead V2, V3.

developed in the pulmonary artery sequentially which means that there is no connection between LMCAA and pulmonary artery (PA) that often seen in the angiography of anomalous left coronary artery from the pulmonary artery (ALCAPA) (**Figure 5**). The right cardiac catheterization data showed the normal range of pulmonary artery pressure in these 8 children. The calculation of Qp/Qs did not indicate left to right shunt.

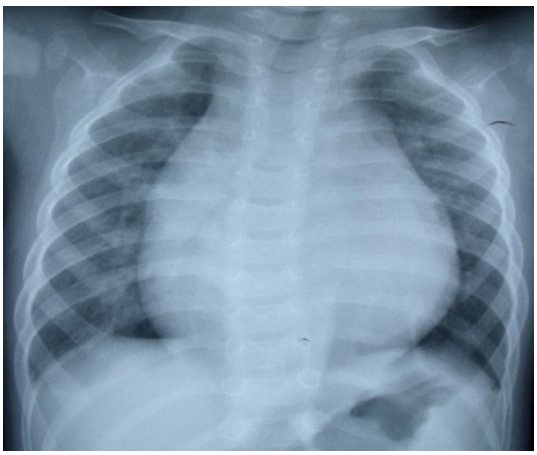

FIGURE 2 | Chest X-ray:cardiac enlargement and cardiothoracic ratio 0.68.

TREATMENT AND FOLLOW-UP

The children with congenital left main coronary artery atresia (CLMCAA) mainly showed the symptoms as myocardial ischemia, mitral regurgitation, and cardiac insufficiency. After diagnosis, the heart failure treatment started, such as digoxin, diuretics, and captopril. Follow-up time was 1–8 years. The symptoms were stable in 8 patients. One child who was diagnosed at 7 months died of heart failure at the age of 9 years. A number of 3 children underwent coronary angioplasty and mitral valvuloplasty after the definite diagnosis. They were followed up for 11–25 months, and the results were good until now. No symptoms happened in the cases, blood flow at the opening of the left coronary artery was unobstructed, and the cardiac function was normal. The electrocardiogram showed normal results. Due to the high surgical difficulty of LMCAA, the

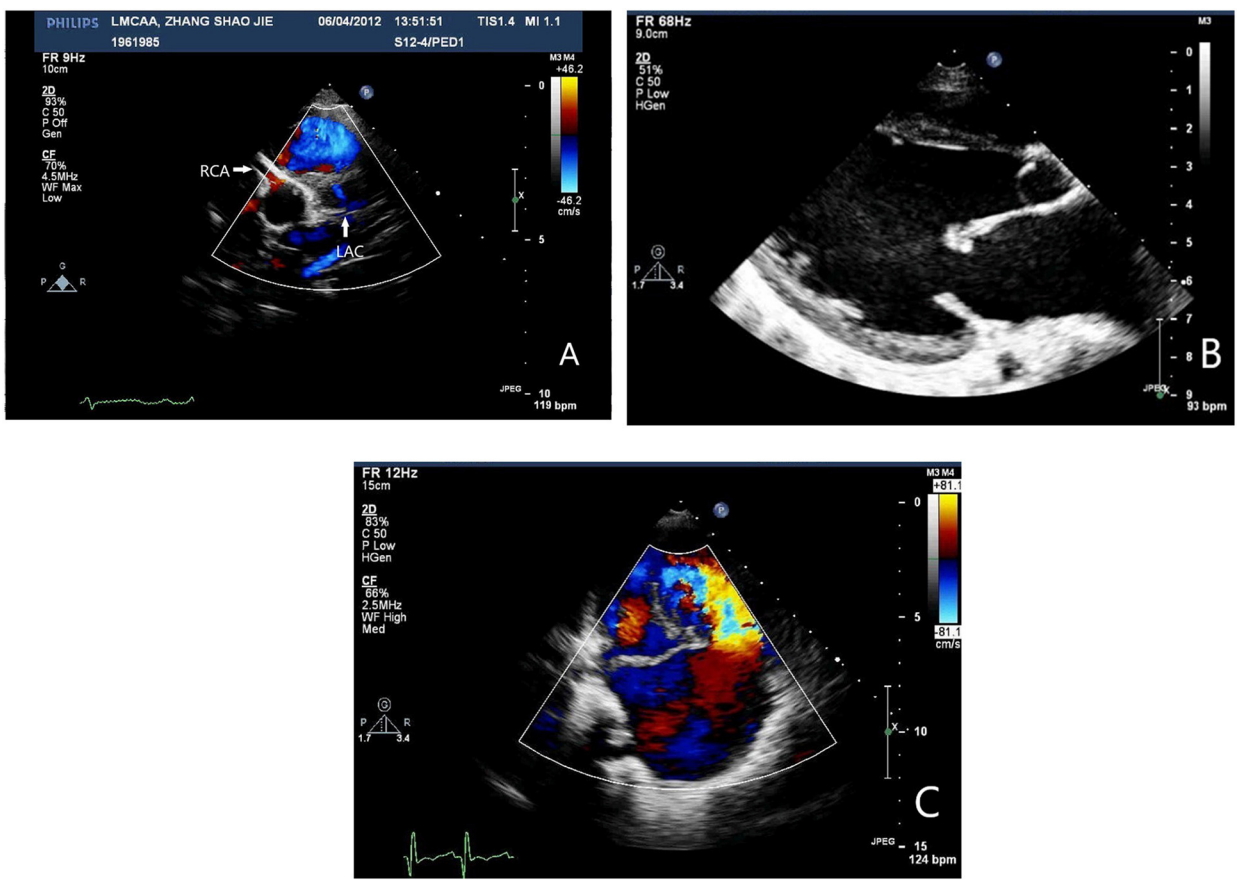

FIGURE 3 | (A) Echocardiography: No left coronary artery opening in the left coronary sinus, the origin and course of RCA is normal. RCA dilated the signal of reverse perfusion blood flow can be seen in the slender left main coronary artery. **(B)** Echocardiography: Echo enhancement of mitral valve, papillary muscle, and endocardium. **(C)** Echocardiography: Massive mitral regurgitation.

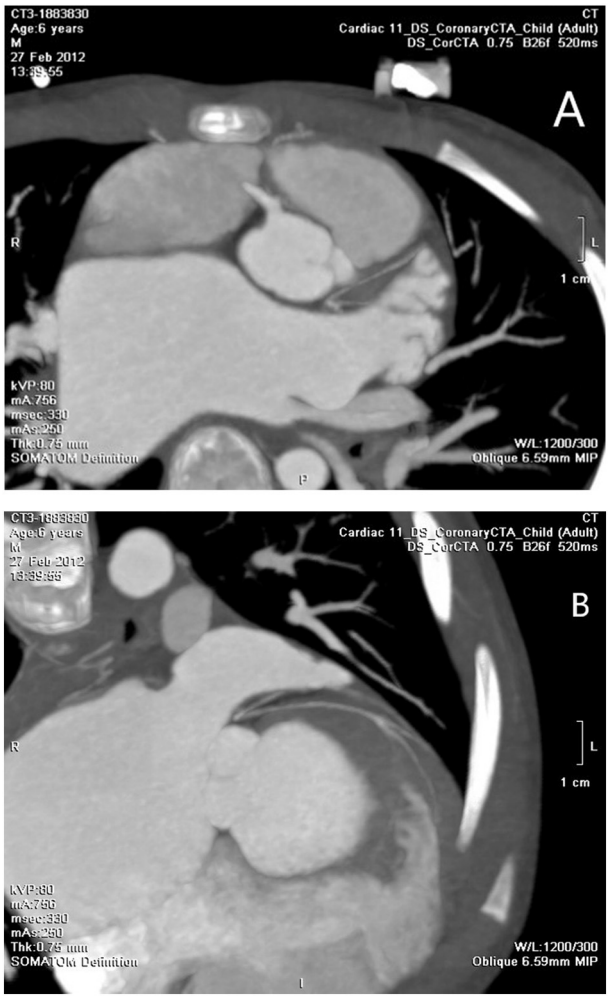

FIGURE 4 | (A) Cardiac CTA: No left coronary artery opening in the left coronary sinus. **(B)** Cardiac CTA: hypoplasia of left anterior descending coronary artery and left circumflex coronary artery.

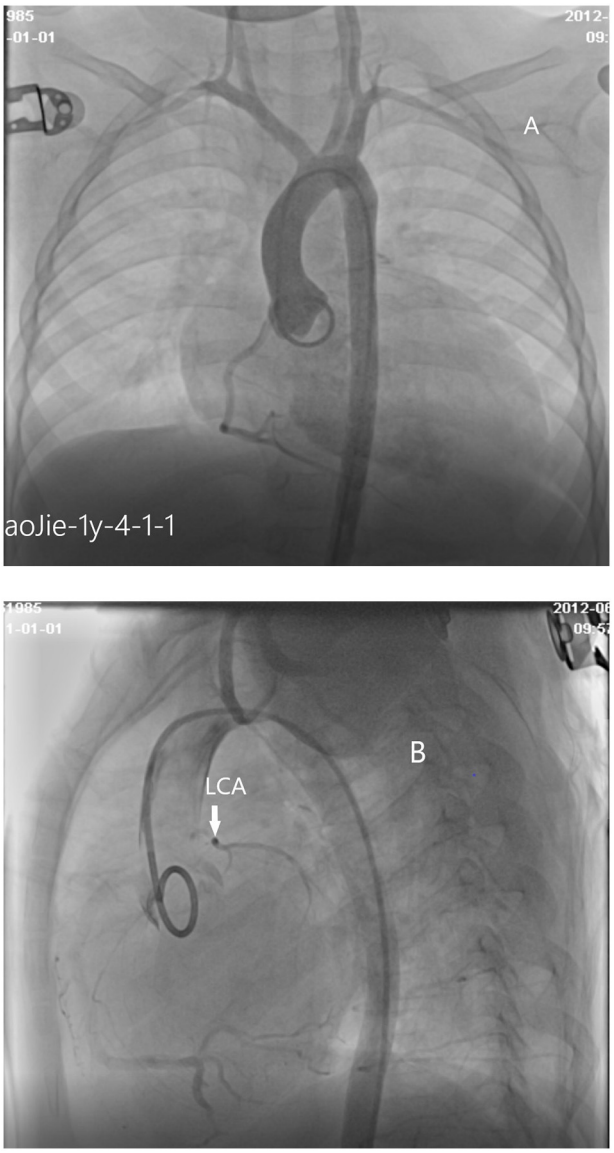

FIGURE 5 | (A) Cardiac angiography: No left coronary artery opening is found in the left coronary sinus by aortography. **(B)** Cardiac angiography:atresia of left coronary ostium and hypoplasia of main stem of left coronary artery.

number of cases of operation in China was small. Some of the children's families could not accept the risk of surgery, so the remaining children continued to take oral medication, and their symptoms were stable at present. The clinical condition, examination, and diagnosis results of 12 children are shown in **Tables 1**, **2**.

DISCUSSION

There are various classification methods for congenital coronary abnormalities. Angelini (3) proposed a classification based on the anatomical features of abnormal coronary artery development, which includes anomalies of origination, course, and termination. CLMCAA is classified as the type of abnormal coronary course. At present, the pathogenesis of CLMCAA is not clear. The possible mechanisms include congenital loss or displacement of left coronary artery primordium, failure of left coronary artery opening, an extension of aortic mediator fiber to left coronary artery opening, or early embryonic coronary artery obstruction (4).

Upon to the reports (5), the onset age of LMCAA varies from 2 months to 85 years and the clinical manifestations of different ages are also different. Infants mostly show the symptoms as chronic heart failure, such as dyspnea, recurrent pneumonia, feeding difficulty, and so on Syncope and chest pain are the main symptoms in elder children and adults. In this group, the cases were all young and had onset early in infancy. The main complaints were cardiac enlargement, cardiac insufficiency, cardiac murmur, and syncope. Owing

TABLE 1 | Clinical data of atresia of the left main coronary artery in 12 children.

Case	Gender	Age of onset	Age of diagnosis	Weight (kg)	Preliminary diagnosis	Symptoms	Treatment and follow-up outcome
1	M	2 m	7 m	6.5	LVNC	Recurrent Respiratory infection, Heart murmur Feeding difficulty	Followed up for 8 years with medicine treatment, and died at the age of 9
2	F	1 y	6 y	24	EFE	Pneumonia, Recurrent syncope	Followed up for 5 years, recurrent syncope, improved after 3 years with medicine treatment
3	M	1 y	5 y	19.2	Mitral regurgitation (severe)	Respiratory infection, Heart murmur	**Followed up for 3 years with medicine treatment. Left ventricular aneurysm occurred at the age of 6 years and received surgical treatment at 8 years old**
4	F	2 y	5 y	15	Mitral regurgitation (severe)	Respiratory infection, Cardiac enlargement	Followed up for 7 years, with medicine treatment, stable at present
5	M	5 m	1 y 5 m	11.3	Mitral regurgitation (moderate)	Respiratory infection, Cardiac enlargement	Followed up for 7 years, with medicine treatment, stable at present
6	F	2 y	2 y 11 m	12.2	Abnormal origin of left coronary artery?	Pneumonia, Cardiac enlargement	Followed up for 4 years, with medicine treatment, stable at present
7	M	5 m	7 m	7	LMCAA	Pneumonia, Heart murmur	Followed up for 4 years, with medicine treatment, stable at present
8	F	7 m	10 m	7.3	Mitral regurgitation (severe)	Heart murmur	Followed up for 4 years, with medicine treatment, stable at present
9	M	3 m	1 y	10	Mitral valve prolapse and insufficiency	Respiratory infection, Heart murmur	Followed up for 2 years, and received surgical treatment at the age of 3, recovered well and continue to take medicine
10	M	1 y 6 m	3 y 6 m	13	DCM	Feeding difficulty, Cardiac enlargement	Followed up for 2 years, with medicine treatment, stable at present
11	M	6 m	11 m	10	Mitral regurgitation	Heart murmur	Followed up for 1 years, with medicine treatment, stable at present
12	M	7 m	8 m	8	Mitral regurgitation (severe)	Feeding difficulty, Cardiac enlargement	Followed up for 2 years, and received surgical treatment at the age of 2, recovered well and continue to take medicine

to the lack of specificity in the clinical manifestations and rare morbidity of the disease, LMCAA has a higher rate of false initial diagnosis. The patients had been misdiagnosed as valvular disease, endocardial fibroelastosis, left ventricular non-compaction, dilated cardiomyopathy, and anomalous origin of the left coronary artery from the pulmonary. The misdiagnosis rate of an initial visit of our patients was as high as 91.7% (11/12). The reason is mainly because LMCAA is extremely rare, and always confused with other diseases of cardiac disfunction such as endocardial fibrolastosis, dilated cardiomyopathy, ALCAPA, valvular diseases et al, and doctors lacked experience. The first case we diagnosed was suspected as abnormal origin of left coronary artery from echocardiogram, but different from ALCAPA, and the diagnosis was at last done by aorta root angiography.

The combination of clinical manifestations and imaging is the basis for the diagnosis of LMCAA. Chest X-ray shows enlarged heart shadow and pulmonary congestion in 8/12 cases, which is non-specific but can indirectly suggest heart disfunction in children. Electrocardiogram (EKG) is commonly and easily used in clinic but sometimes is ignored. In our groups,7/12 patients showed abnormal deep Q waves in leads I, AVL, and V4–V6 in EKG, which was also often seen in ALCAPA (6) and suggest severe myocardial ischemia.

Echocardiogram has good repeatability and is valuable for the diagnosis of LMCAA (7) although it is very difficult to distinguish the origin of coronary especially in infants. It can provide evidence for whether further examination such as angiography or cardiac CTA is needed (8). Some details can be found in echocardiogram, which suggests the abnormality coronary origin. In our group, we noticed that sign of echo enhancement of mitral chordae tendineae and papillary muscles which suggest severe myocardial ischemia might distinguish LMCAA from other non-coronary diseases. Right coronary artery widened slightly and the opening was normal. Various degrees of coronary collateral arteries are the important signs of abnormality origin of coronary artery, which can distinguish with the diseases without coronary abnormality such as EFE and cardiomyopathy. If possible, the origin of coronary artery should be detected carefully, hypoplasia LCA with atresia ostium may be demonstrated in 2D echocardiogram, and the abnormal reflux blood signals in hypoplasia main left coronary attery (MLCA) showing in CDFI also suggest the possibility of LMCAA.

For patients with suspected coronary artery abnormalities, further examination such as CTA or coronary angiography should be recommended. With recent improvements in coronary artery visibility on CT in children, the diagnostic accuracy and the resultant clinical utility of coronary CTA are noticeably

TABLE 2 | Echocardiogram, ECG, and X-ray cardiogram in 12 children.

Case	Gender	Age of diagnosis	ECG	CXR	Echocardiogram					
					LVEDD *Z*-Value	LVEF (%)	Mitral regurgitation	RCA/AO	Collateral formation	Diagnosis
1	M	7 m	Abnormal Q waves in I, AVL, V3, V5 leads, extensive ST-T depression	0.61	7.44	46	Severe	0.17	Little	Non-compaction cardiomyopathy
2	F	6 y	No obvious abnormality	0.52	2.05	62	Moderate	0.17	Little	Endocardial fibroelastosis
3	M	5 y	Abnormal Q waves in I, AVL leads	0.53	4.05	64	Severe	0.17	Little	Mitral regurgitation
4	F	5 y	Abnormal Q waves in V5,V6 leads, ST segment depression in v4–v6 leads	0.51	2.06	74	Severe	0.21	Abundant	Mitral regurgitation
5	M	1 y 5 m	abnormal Q waves in I, AVL,V4–V6 leads	0.68	4.86	50	Moderate	0.20	Little	Mitral regurgitation
6	F	2 y 11 m	No obvious abnormality	0.57	4.43	61	Severe	0.19	Medium	Anomalous origin of left coronary artery
7	M	7 m	abnormal Q waves in I, AVL leads	0.58	7.05	59	Severe	0.21	Medium	Congenital atresia of the left main coronary artery
8	F	10 m	No obvious abnormality	0.62	7.13	65	Severe	0.20	Little	Anomalous origin of left coronary artery
9	M	1 y	No obvious abnormality	0.67	4.49	64	Severe	0.18	Medium	Mitral regurgitation
10	M	3 y 6 m	Abnormal Q waves in I, AVL leads	0.53	4.41	40	Moderate	0.17	Little	Dilated cardiomyopathy
11	M	11 m	No obvious abnormality	0.65	4.02	73	Severe	0.21	Medium	Mitral regurgitation
12	M	8 m	Abnormal Q waves in I, AVL leads	0.64	3.57	63	Severe	0.19	Medium	Mitral regurgitation

increasing in children (9). It had been reported (10) that cardiac CTA was a very effective and non-invasive examination for the diagnosis of this disease, which could clearly show the opening and course of the left and right coronary arteries, as well as the widening degree of the right coronary artery. In our group, 5 cases underwent cardiac CTA, and 2 elder cases had clear CT imaging, which showed that the proximal segment of the left coronary artery was blind and dysplastic. However, cardiac CTA examination had limitations on infant coronary artery examination because breath shortness in some patients and rapid heart rate may affect image quality to a certain extent. Aortic root angiography and selective angiography are the golden indexes for the diagnosis of LMCAA. A number of eight children in our group underwent angiography. Angiography could clearly show the course and lumen shape of coronary artery (11). The developing sequence is the right coronary artery develops first, and then collateral artery, at last hypoplastic left main coronary artery, and the atresia ostium can be shown clearly. No development of pulmonary artery was the important sign to distinguish with ALCAPA. Selective right coronary angiography was required for elder patients with an unclear display.

The differential diagnosis of LMCAA includes single coronary artery, ALCAPA, and left coronary artery occlusion caused by other reasons (12). ① The anatomical change of LMCAA is that the aortic sinus has only one single right coronary artery opening, but its hemodynamics is different from that of single coronary artery. In the single coronary malformation, the blood supply direction is normal, branching from the main coronary artery to the small coronary arteries, while in the LMCAA, the blood from the right coronary artery flows back to the left coronary artery through one or more collateral branches. Generally, the collateral circulation from the right coronary to the left coronary cannot meet the metabolic needs of the heart, so almost all patients will suffer from myocardial ischemia (13). ② The clinical manifestations of ALCAPA are similar to those of LMCAA. The change of cardiac enlargement, decreased left ventricular ejection fraction, endocardial fibroelastosis, mitral insufficiency, and special electrocardiogram (ECG) changes are all caused by abnormal origin of LCA. Due to the abnormal left coronary artery originated from the pulmonary artery, the low pulmonary artery pressure results in the relatively serious right coronary artery steal, and the widening of the right coronary artery is more obvious. Yu et al. (14) summarized 30 children with infantile ALCAPA whose left ventricle was significantly enlarged and the RCA/AO ratio was >0.12. Different degrees of mitral regurgitation accounted for 60% of the patients. Different from ALCAPA patients, the widening of RCA was not obvious in our 12 children with LMCAA, and the RCA/AO ratio was 0.17–0.21 (0.19 ± 0.02). The Sign of coronary blood flow into pulmonary artery in CDFI of echocardiogram is helpful to distinguish the two diseases, and aortic root angiography or selective right coronary angiography can make a definite diagnosis. ③ LMCAA should be distinguished from complete occlusion of the left main coronary artery second to other diseases (such as Kawasaki

disease, Takayasu arteritis, and so on). In these cases, the main trunk is occluded but the anatomical morphology and inner diameter are normal.

We first reported this disease in China, and so far, it has been reported the most in a single center (12). The patients in our group were mainly treated with oral medicine to maintain cardiac function. The number of 1 patient died because of heart failure. Only 3 children underwent cardiac surgery mainly because of the difficulty in operation and parent's hesitation of risk of operation. Some researchers believed that surgical treatment was not needed on asymptomatic children with abundant collateral circulation and normal heart function. However, sudden death can occur at any age, and the severity of symptoms may be related to the development of collateral between right coronary artery and left coronary artery (2). Most researchers believed that due to the poor prognosis of the disease, the diagnosis itself of LMCAA was the surgical indication, and the purpose of the operation is to establish a normal dual coronary blood supply system.

Alsalehi et al. (2) reviewed 50 children diagnosed with LMCAA and strongly recommended immediate coronary revascularization due to its high incidence of heart failure and sudden death. Surgical procedures included coronary artery bypass grafting and coronary angioplasty. The choice of surgical procedure was mainly depended on the length from the orifice of the left coronary artery in the aortic sinus to the site of atresia. In the recent years, it was considered that coronary angioplasty was superior to coronary artery bypass grafting. Coronary angioplasty was referred to the reconstruction of the left main artery with autologous pericardial patch or arterial wall. After the successful operation, the left coronary artery was available to be redeveloped, which could provide more adequate blood flow for the blood supply area of the left coronary artery, while bypass grafting could only supply the area near the transplanted vessel. In 1972, Mullins et al. (15) reported the first case of great saphenous vein transplantation for the treatment of the disease. In 1992, Kitamura (16) reported that a 7-year-old girl was diagnosed as LMCAA complicated with severe mitral regurgitation and underwent coronary artery bypass grafting and mitral valve repair. Isotope myocardial perfusion scan after the surgery indicated significant improvement in myocardial blood supply and mild mitral valve regurgitation. In the follow-up of nearly 30 years after the operation, it was found that the patient's mitral regurgitation was aggravated, but no surgery is required. In 2017, Fujita et al. (17) reported that a 13-year-old child with syncope onset underwent bypass grafting and did not experience subsequent syncope. Albadi et al. (18) reported a case of left main coronary artery reconstruction with the autologous pericardium, which connects the anterior descending branch and circumflex branch with the aortic root. Then, 3 years after the surgery, CTA showed that the left main trunk was unobstructed and there was no calcification. In this group, three children underwent coronary angioplasty and mitral valvuloplasty. They all underwent coronary angioplasty using the anterior wall of the main pulmonary artery, and the surgical effect was good. At present, they were being followed up. After the operation, they continued to take oral diuretics and medicine to improve myocardial remodeling.

In conclusion, LMCAA was rare in clinic, but with the improvement of diagnostic experience and understanding of the disease, more and more coronary malformations would be found. Patients with cardiac insufficiency, a large amount of regurgitation in mitral valve, and pathological Q wave found by echocardiogram should be vigilant about the diagnosis of left coronary artery disease. Furthermore, cardiac CT and coronary angiography should be considered when necessary (19). Medical drug treatment could effectively improve and keep cardiac function, but surgery was the fundamental treatment for the disease.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

XJ led the overall study, contributed to the data collection and interpretation, and wrote the manuscript. YX contributed to the data collection, data analysis, and manuscript edits. WY contributed to the data interpretation and manuscript edits. All authors read, contributed to the research design, and approved the final manuscript.

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SYSTEMATIC REVIEW
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Exercise Capacity in Children and Adolescents With Congenital Heart Disease: A Systematic Review and Meta-Analysis

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Background: Congenital heart disease (CHD) entails structural defects in the morphogenesis of the heart or its main vessels. Analyzing exercise capacity of children and adolescents with CHD is important to improve their functional condition and quality of life, since it can allow timely intervention on poor prognostic factors associated with higher risk of morbidity and mortality.

Objective: To describe exercise capacity in children and adolescents with CHD compared with healthy controls.

Methods: A systematic review was carried out. Randomized clinical trials and observational studies were included assessing exercise capacity through direct and indirect methods in children and adolescents between 5 and 17 years-old. A sensitive analysis was performed including studies with CHD repaired participants. Additionally, it was sub-analyzed by age range (< and ≥ 12 years old). Two independent reviewers analyzed the studies, extracted the data, and assessed the quality of the evidence.

Results: 5619 articles were found and 21 were considered for the review. Eighteen articles used the direct exercise capacity measurement method by cardiopulmonary exercise test (CPET). The CHD group showed significant differences in peak oxygen consumption (VO_2peak) with a value of −7.9 ml/Kg/min (95% CI: −9.9, −5.9, p = 0.00001), maximum workload (Wmax) −41.5 (95% CI: −57.9, −25.1 watts, p = 0.00001), ventilatory equivalent (VE/VCO_2) *slope* 2.6 (95% CI: 0.3, 4.8), oxygen pulse (O_2 pulse)−2.4 ml/beat (95% CI: −3.7, −1.1, p = 0.0003), and maximum heart rate (HRmax) −15 bpm (95% CI: −18, −12 bpm, p = 0.00001), compared with healthy controls. Adolescents (≥ 12 yrs) with CHD had a greater reduction in VO_2peak (−10.0 ml/Kg/min (95% CI: −12.0, −5.3), p <0.00001), Wmax (−45.5 watts (95% CI: −54.4, −36.7), p < 0.00001) and HRmax (−21 bpm (95% CI: −28, −14), p<0.00001).

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Conclusion: Suffering CHD in childhood and adolescence is associated with lower exercise capacity as shown by worse VO_2peak, Wmax, VE/VCO_2 slope, O_2 pulse, and HRmax compared with matched healthy controls. The reduction in exercise capacity was greater in adolescents.

Systematic Review Registration: www.crd.york.ac.uk/prospero/display_record.php?RecordID=208963, identifier: CRD42020208963.

Keywords: pediatrics, heart defects, congenital malformations, cardiopulmonary exercise test, oxygen consumption, six-minute walking test

WHAT IS KNOWN

Exercise capacity is one of the main factors that affect health-related quality of life, prognosis, risk of morbidity, and early mortality from cardiovascular, metabolic, or respiratory disease.

Analyzing exercise capacity in children and adolescents with CHD is important to improve their functional condition and quality of life, since it can allow timely intervention on poor prognostic factors associated with higher risk of morbidity and mortality.

WHAT THE STUDY ADDS

VO_2peak, HRmax, Wmax, and O_2 pulse were significantly lower in children and adolescents with partially or fully repaired CHD compared with healthy controls.

INTRODUCTION

Congenital heart disease (CHD) entails structural defects in the morphogenesis of the heart or its main vessels (1). They are the most common congenital defect in children worldwide, with an average prevalence of 8.22 per 1000 live newly born, ranging from 2.4 to 13.7 (2, 3). According to intracardiac morphology and physiology, they are classified as acyanotic and cyanotic, and according to its severity as either simple, or complex (1).

For its treatment, there are both corrective and palliative surgeries (1). Due to medical advances, greater and better diagnostic, surgical and postoperative care technology, it is expected that more than 90% of children with CHD will currently survive to adulthood (4). However, despite the increase in the life expectancy of children with CHD, the residual defects that may remain after surgery can have a negative effect on both morbidity and mortality (5).

It has been reported that physical capacity in children with CHD is lower compared to healthy controls with limited exercise capacity and a shorter lifespan related to health (6). Limited exercise capacity favors a more sedentary lifestyle, a situation that can be maintained into adulthood (7). Accordingly, less physical activity increases the risk of overweight and obesity in children with CHD, which means an additional health burden (8).

Exercise capacity is one of the main factors when assessing health-related quality of life, prognosis, risk of morbidity, and early mortality from cardiovascular, metabolic, or respiratory disease (9). It can be evaluated by a standardized laboratory test such as cardiopulmonary exercise test (CPET) or standardized field tests such as the six-minute walking test (6MWT), shuttle walking test (SWT), time up and go (TUG), or similar tests (10). The CPET, which assesses the maximum oxygen consumption (VO_2max) or peak (VO_2peak) and measures ventilatory efficiency, has obtained a prognostic value in adults with acquired heart failure and CHD, by identifying subjects with limited cardiovascular reserve (11). Studies that consider the measurement of VO_2peak in subjects with cyanotic CHD and palliative surgery for complex CHD highlighted it as an independent predictor of death or hospitalization due to a cardiovascular event (12, 13). In children with chronic diseases, VO_2peak can predict adverse or unfavorable outcomes (6). The ventilatory equivalent for carbon dioxide production (V_E/VCO_2) has been shown to have high sensitivity as a predictor of mortality in subjects with various CHD (14).

Analyzing exercise capacity of children and adolescents with CHD is important to improve their functional condition and quality of life, since it can allow timely intervention on poor prognostic factors associated with higher risk of morbidity and mortality.

This review aims to systematically analyse studies to summarize exercise capacity, assessed with laboratory tests or standardized field tests, in children and adolescents with CHD compared with their healthy counterparts, using a meta-analysis of observational studies. Our purposes are to find out if the main exercise capacity variables such as VO_2peak or Wmax are reduced in children and adolescents with CHD, and to find out if the cardiac response to exercise is also influenced.

Abbreviations: 6MWT, Six-minute walking test; CHD, Congenital heart disease; CI, Cardiac index; CO, Cardiac output; CPET, Cardiopulmonary exercise test; HRmax, Maximum Heart rate; NHLBI, National Heart, Lung, and Blood Institute; PH, Pulmonary hypertension; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; PROSPERO, International prospective register of systematic reviews; RCTs, Randomized clinical trials; SV, Stroke volume; SWT, Shuttle walking test; TUG, Timed up and go test; V_E, Minute ventilation; V_E/VCO_2, Ventilatory equivalent for carbon dioxide; V_E/VCO_2 slope, Minute ventilation/carbon dioxide production slope; VO_2, Oxygen consumption; VO_2peak, Peak oxygen consumption; VO_2max, Maximum oxygen consumption; Wmax, Maximum workload.

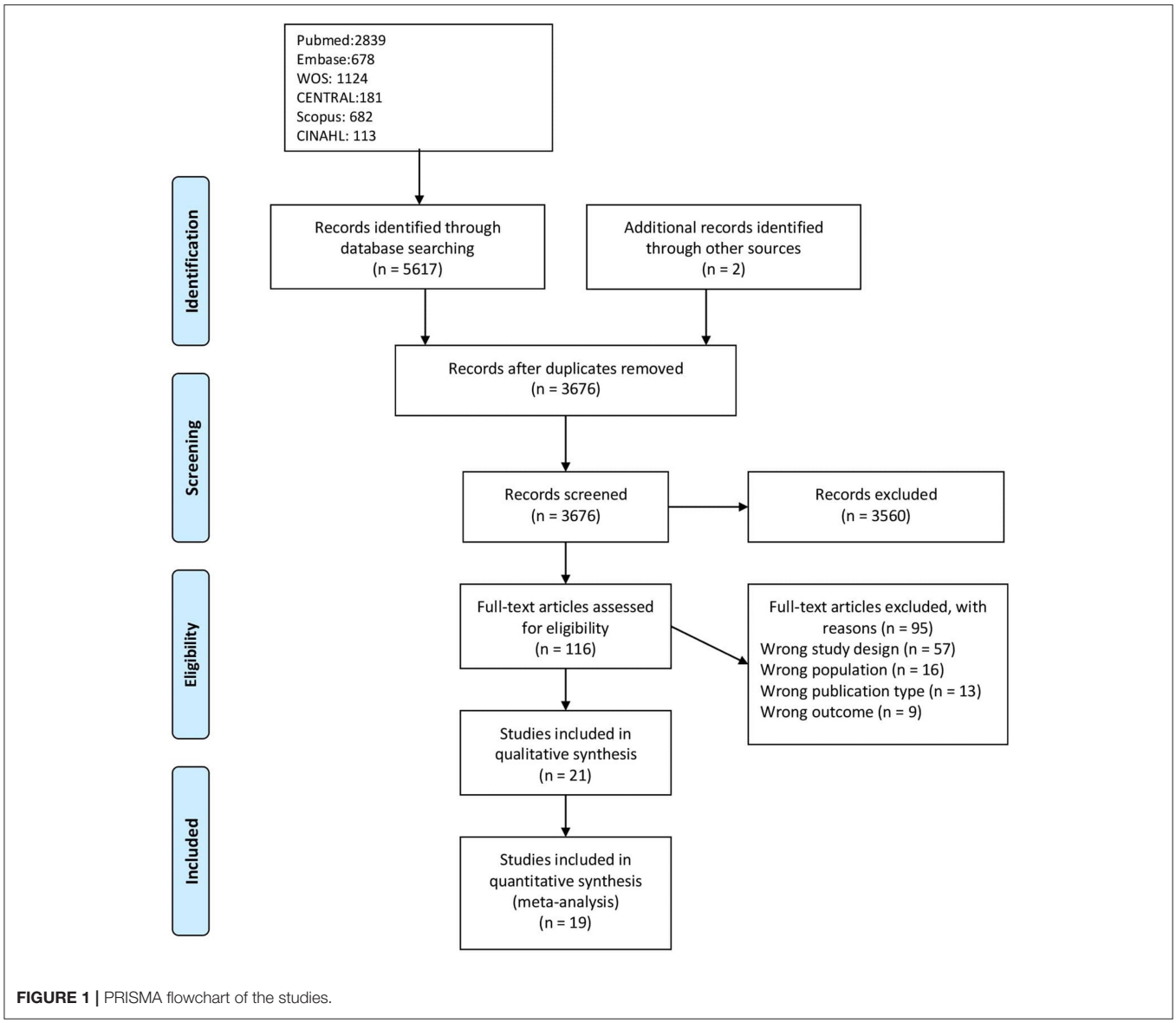

FIGURE 1 | PRISMA flowchart of the studies.

METHODS

Protocol and Registration

We performed a systematic review using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (15). The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) CRD42020208963.

Criteria for Considering the Studies in This Review

We included randomized clinical trials (RCTs) or observational studies (cross-sectional, longitudinal, case-control, and cohort) in children and adolescents with a diagnosis of CHD. The included studies aimed to determine the physical capacity in patients with CHD. Additionally, the studies should report VO_2peak, maximal workload (Wmax), distance walked in the 6MWT (6MWD), or similar measurements obtained from objective tests. All editorials, letters, conference publications, review articles, systematic reviews, meta-analyses, *in vivo* and *in vitro* studies were excluded.

Search Strategies and Data Resources

We reviewed seven databases: Embase, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Web of Science, PubMed/MEDLINE, Scopus, and SciELO, from their inception to 01 June, 2021 and conducted manual searches using the followings terms: a) [(Congenital heart disease) OR (Congenital heart defects) OR (Congenital heart surgery) OR (Fontan operation) OR (Fontan circulation) OR (Fontan patient) OR (Fontan physiology) OR (Fontan procedure) OR (Tetralogy of Fallot) OR (Interventricular communication) OR

(Atrial communication)] AND [(Exercise capacity) OR (Physical capacity) OR (Exercise tolerance) OR (Cardiopulmonary exercise test) OR (CPET) OR (Walking test) OR (Walk test) OR (6MWT) OR (Shuttle walking test) OR (SWT) OR (distance walked) OR (Oxygen uptake) OR (Oxygen consumption) OR (Wingate Anaerobic Test) OR (Timed Up and Go) OR (TUG) OR (Exercise Test) OR (sit to stand) OR (step test) OR (STS)] AND [(Children) OR (Adolescents) OR (Pediatrics) OR (Childhood) OR (Pediatric)].

The selected terms were combined using Boolean logical operators (OR, AND, NOT). Moreover, we performed a manual search of the references that were included in the selected articles. All the references were analyzed in Rayyan software, a web-based tool (16).

Reviewing Procedure and Study Selection

The review was performed independently by two investigators (YVR-JVM), who independently reviewed all articles titles and abstracts identified in the search strategy. The full text of potentially eligible studies was then read to verify their suitability for final inclusion. All studies that did not fulfill the predefined criteria were excluded, and their bibliographic details were listed with the specific reason for exclusion.

Data Extraction and Methodological Quality Assessment

Two investigators (YVR-JVM) independently extracted data from the selected articles and recorded them in an *ad hoc* spreadsheet of relevant data. This included author, country, year of publication, sample size, study design, age of subjects, diagnoses, evaluation instruments, evaluated variables, and results. Data from the first assessment were considered for randomized or non-randomized clinical trials. Differences obtained from data extraction were resolved by consensus. In the case of not reaching an agreement, a third investigator (RTC) resolved the differences. If some relevant data were not in the article, the author was contacted to request the information.

Assessment of the methodological quality of the primary articles was carried out using the quality assessment tools from the National Heart, Lung, and Blood Institute (NHLBI) (17). Each tool contains criteria based on which internal validity and risk of bias are evaluated. The criteria are evaluated as "yes" "no" or "other" (not reported, not applicable, or not determinable), and an overall rating is provided for each study based on the items rated with an affirmative answer ($> 75\%$ = good, 50–75% = fair, $< 50\%$ = poor).

Data Synthesis and Analysis

We reported summaries of the association between the outcomes for each study in terms of mean differences using Review Manager 5 (RevMan, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We obtained combined measurements of effect for each primary outcome through meta-analysis under a random-effect model, due to the expected heterogeneity between the studies. Statistical heterogeneity was measured through the I^2 statistic and classified as low (I^2 <25%), moderate (I^2 25–50%) or high (I^2 >50%). A sensitivity analysis was conducted including studies with only children and adolescents surgically repaired. Additionally, when possible, a subanalysis by age group ($<$ and $\geq$ 12 years) was performed in the group of patients with surgical correction.

RESULTS

Study Selection

The flow chart of the study selection process is shown in **Figure 1**. In the initial search of the selected databases, 5619 potential studies were identified. Of the 107 studies assessed as full text, we excluded 57 for wrong study designs, 16 for wrong population, 13 for wrong publication type, and nine due to a wrong outcome. In total, 21 studies fulfilled the criteria for eligibility and were included in the review.

Characteristics of the Included Studies

Fifteen studies were conducted in Europe (18–32), three in the United States (33–35), one in Brazil (36), one in Japan (37), and one was conducted in Egypt (38). Regarding the design, 20 were cross-sectional (18–23, 25–38), and only one was an RCT (24). The characteristics of the included studies are summarized in **Table 1**.

Participants

In total, 1540 participants with CHD and 1248 healthy controls were enrolled in the included studies. Among the studies, the CHD sample size ranged from 12 (30) to 496 (21). Age varied from 7.7 ± 1.7 (28) to 14 ± 2.72 (20). The majority of the studies included only complex CHD (18–20, 22, 25, 27, 31, 33–36, 38), and nine studies included both simple and complex CHD (21–24, 26, 28–30, 32, 37). Sixteen studies included only repaired CHD (18–20, 22, 24–27, 30, 31, 33–38); however, only ten studies reported the age of surgery, which was before 3 years old in the majority of the cases (19, 22, 26–28, 30, 33). A summary of patients' characteristics is presented in **Table 1**.

Type of Assessment

To assess exercise capacity, 18 studies used the direct CPET method: seven of them performed the CPET on a treadmill (18–20, 27, 36–38) and 13 in a cycle ergometer (21–26, 29–35). One study used the 6MWT (24). The results of the studies that used the CPET to evaluate exercise capacity are shown in **Table 2**. The quantitative variables (VO_2peak, Wmax, VE/CO_2 slope, O_2 Pulse, and HRmax) expressed as mean and SD were analyzed using a meta-analysis method. Results from Bowyer et al. (18) and Binkhorst et al. (29) were not included in the meta-analysis because they reported their results in other units.

Risk of Bias Assessment

Of the selected cross-sectional articles (n = 20), all were rated as "fair" (50–75% affirmative answers). The RCT study ($n = 1$) obtained a "fair" rating. The quality assessment results for the

TABLE 1 | Characteristics of the included studies.

Authors, year	Country	Group	Participants diagnosis	Severity/Repaired	Participants n (Female/Male)	Age (years)	Anthropometrics Weight (kgs) Height (cms) BMI (Kg·m^{-2})
Cross-sectional studies							
Bowyer et al., 1990 (18)	England	CHD	TGA post-surgery Mustard	Complex/repaired	20 (2F, 18M)	9 (6–12)*	Weight: 30 Height: 136
		Control	Healthy children		18 (3F, 15M)	9.5 (NR)	Weight: 31 Height: 137
Tomassoni et al., 1991 (33)	United States	CHD	TOF repaired	Complex/repaired	20 (9F, 11M)	9.93 ± 2.88 (SE)	Weight: 32.81 ± 12.35 (SE) Height: 136.07 ± 19.55 (SE)
		Control	Healthy children		20 (9 F, 11M)	10.22 ± 2.48 (SE)	Weight: 35.75 ± 11.47 (SE) Height: 139.98 ± 13.52 (SE)
Balderston et al., 1992 (34)	United States	CHD	CoA repaired	Complex/repaired	31 (9F, 22M)	11.2 (7–17)*	NR
		Control	Healthy children		22 (NR)	NR (7–17)*	NR
Takagi et al., 1994 (37)	Japan	CHD	CHD acyanotic and cyanotic post-surgery	Complex/simple/ repaired	Acyanotics: 15 Cyanotics: 21	Acyanotics: 10.7 ± 2.7 Cyanotics: 11.4 ± 3.9	NR
		Control	Healthy children		16 (NR)	10.9 ± 2.7	NR
Douard et al., 1997 (19)	France	CHD	TGA post Senning surgery	Complex/repaired	43 (11F, 32M)	12 ± 3.1	Weight: 38.2 ± 15.9 Height: 145 ± 17
		Control	Healthy children		43 (NR)	12.8 ± 3.4	Weight: 44.6 ± 15 Height: 154 ± 19
Buheitel et al., 2000 (25)	Germany	CHD	CHD complex post Fontan and TGA post Senning	Complex/repaired	Fontan: 21 (11F, 10M) TGA: 13 (8F, 5M)	Fontan: 11.1 ± 2.5 TGA: 11.8 ± 1.9	Fontan: Weight: 34.2 ± 10.3 Height: 144 ± 14 TGA: Weight: 38.0 ± 11.6 Height: 148 ± 12
		Control	Healthy children		21 (11F, 10M)	11.2 ± 2.3	Weight: 36.0 ± 10.9 Height: 143 ± 13
Pfammatter et al., 2002 (26)	Switzerland	CHD	ASD repaired	Simple/repaired	14 (9F, 5M)	11.4 (6.8-16.1)**	Weight: 40 (27–70)**
		Control	Healthy children		15 (9F, 6 M)	11 (7.8–15.8)**	Weight: 37 (28–53)**
Zajac et al., 2002 (27)	Poland	CHD	CHD post Fontan	Complex/repaired	14 (8F, 6 M)	8.1 (5.7–17)	NR
		Control	Healthy children		12 (6F, 6 M)	7.1 (6.1–16.8)*	NR
Norozi et al., 2005 (28)	Germany	CHD	TOF, PA, CoA, ASD/VSD	Simple/complex/ repaired	84 (40F, 47 M)	TOF: 8.2 ± 2.0 PA: 8.0 ± 2.5 CoA: 7.9 ± 2.2 ASD/VSD: 7.7 ± 1.7	TOF: Weight: 27.7 ± 9.4 Height: 130 ± 14 PA: Weight: 27.8 ± 9.5 Height: 130 ± 15 CoA: Weight: 26.1 ± 7 Height: 127 ± 13 ASV/VSD: Weight: 25 ± 5 Height: 127 ± 10
		Control	Healthy children		98 (49F, 49M)	7.8 ± 1.8	Weight: 27.3 ± 5.7 Height: 129 ± 11

(Continued)

TABLE 1 | Continued

Authors, year	Country	Group	Participants diagnosis	Severity/Repaired	Participants n (Female/Male)	Age (years)	Anthropometrics Weight (kgs) Height (cms) BMI (Kg·m^{-2})
Binkhorst et al., 2008 (29)	Netherlands	CHD	VSD repaired and VSD with conservative treatment	Simple/repaired/not repaired	27 (14F, 13M)	VSD repaired: 13 ± 2.5 VSD conservative: 12.5 ± 3	VSD repaired: Weight: 49 ± 15 Height: 158 ± 16 BMI: 19 ± 3 VSD conservative: Weight: 51 ± 18 Height: 159 ± 13 BMI: 20 ± 5
		Control	Healthy children		15 (8F, 7M)	12.5 ± 3	Weight: 49 ± 15 Height: 159 ± 17 BMI: 19 ± 2.5
Moalla et al., 2008 (30)	France	CHD	Complex CHDs repaired in NYHA Class II or III	Complex/repaired	12 (NR)	13.0 ± 1.2	Weight: 48.8 ± 5.2 Height: 159.4 ± 4.6 BMI 19.2 ± 1.9
		Control	Healthy children		12 (NR)	12.9 ± 1.1	Weight: 49.0 ± 10.2 Height: 156.5 ± 9.3 BMI: 19.9 ± 3.3
Van Beek et al., 2010 (31)	Netherlands	CHD	TGA post Arterial Switch	Complex/repaired	17 (5F, 12M)	12.1 ± 2.0	Weight: 47.3 ± 14.1 Height: 156.2 ± 14.6 BMI: 19.1 ± 2.4
		Control	Healthy children		20 (7F, 13M)	12.8 ± 2.4	Weight: 49.5 ± 10.6 Height: 159.9 ± 12.2 BMI: 19.2 ± 2.3
Kotby et al., 2012 (38)	Egypt	CHD	TOF repaired	Complex/repaired	21 (5F, 16M)	8 (5-13)	NR
		Control	Healthy children		15 (NR)	8 (5-13)	NR
Müller et al., 2013 (32)	Germany	CHD	CHD simple, moderate, and complex. NYHA I or II	Simple/complex/ repaired/no repaired	88 (36F, 52M)	12.7 (12-13.3)	BMI:18.5 (16.7–21.6)***
		Control	Healthy children		88 (36F, 52M)	12.5 (12.1-13.1)	BMI: 18.9 (17.1–21.8)***
Mazurek et al., 2016 (20)	Poland	CHD	TOF repaired, TGA repaired, CHD post Fontan NYHA I	Complex/repaired	42 (NR)	14 ± 2.72	NR
		Control	Healthy children		20 (NR)	14.90 ± 2.48	NR
Samos et al., 2016 (36)	Brazil	CHD	TGA post arterial switch	Complex/repaired	31 (12F, 19M)	10.2 ± 5.2	Weight: 17.0 ± 2.8 Height: 136 ± 17 BMI: 17.0 ± 2.8
		Control	Healthy children		29 (8F, 21M)	10.9 ± 4.3	Weight: 18.1 ± 3.5 Height: 147 ± 14 BMI: 18.1 ± 3.5
Amedro et al., 2018 (21)	France	CHD	Simple, moderate and complex CHD	Simple/complex/ repaired/ no repaired	496 (NR)	12.2 ± 3.3	Weight: 44.1 ± 15.8 Height: 150.9 ± 17.5 BMI: 18.7 ± 3.6
		Control	Healthy children		302 (NR)	11.1 ± 2.6	Weight: 42.2 ± 13.3 Height: 150.0 ± 16.0 BMI: 18.3 ± 2.9
Hock et al., 2018 (22)	Germany	CHD	CHD post Fontan	Complex/repaired	41 (NR)	12.0 ± 3.2	Weight: 39.1 ± 14.5 Height: 145.2 ± 18.7
		Control	Healthy children		121 (NR)	12.6 ± 2.4	Weight: 47.0 ± 14.2 Height: 155.0 ± 13.6

(Continued)

TABLE 1 | Continued

Authors, year	Country	Group	Participants diagnosis	Severity/Repaired	Participants n (Female/Male)	Age (years)	Anthropometrics Weight (kgs) Height (cms) BMI (Kg·m^{-2})
Coomans et al., 2020 (35)	United States	CHD	TOF repaired	Complex/repaired	45 (14F, 31M)	13.9 ± 2.9	Weight: 50.6 ± 18.3 Height: 157.2 ± 15.0
		Control	Healthy children		45 (14F, 31M)	13.9 ± 2.8	Weight: 4.8 ± 16.3 Height: 159.6 ± 18.0
Gavotto et al., 2020 (23)	France	CHD	Simple, moderate and complex CHD	Simple/complex/ repaired/no repaired	407 (179F, 228M)	12.2 ± 3.4	Weight: 44.3 ± 15.9 Height: 150.9 ± 17.6
		Control	Healthy children		302 (130F, 172M)	11.1 ± 2.6	Weight: 42.2 ± 13.3 Height: 150.0 ± 16.0
Controlled intervention studies							
Moalla et al., 2005 (24)	France	CHD	Complex CHD repaired. NYHA class II or III.	Complex/repaired	17 (NR)	13.5 ± 0.5 (SE)	Weight: 50.5 ± 3.3 Height: 161.1 ± 1.5 BMI: 19.6 ± 1 (SE)
		Control	Healthy children		14 (NR)	12.9 ± 0.3 (SE)	Weight: 49.1 ± 2.8 Height: 57.0 ± 2.5 BMI: 20.0 ± 0.9 (SE)

*Data are shown as mean ± SD, *mean range, **median (range), ***median (interquartile range).*
ASD, atrial septal defect; BMI, body mass index; CHD, congenital heart disease; CoA, coarctation of the aorta; F, female; M, male; NR, not reported; NYHA, new york heart association; PA, pulmonary atresia; SE, standard error; TGA, transposition of the great arteries; TOF, tetralogy of fallot; VSD, ventricular septal defect.

individual studies obtained using the NHBLI quality assessment tool are presented in the **Supplementary File 1**.

Main Findings

Peak Oxygen Consumption

Seventeen studies examined exercise capacity considering VO_2peak (19–27, 30–37). These studies compared 1388 participants with CHD vs. 1102 healthy controls. The heterogeneity of the comparison was high (I^2 = 91%). Participants with CHD averaged −7.9 ml/Kg/min (95% CI: −9.9, −5.9) of VO_2peak compared with controls ($p < 0.00001$) (**Figure 2**). When considering the analysis by subgroups according to the type of test, those who performed the test on treadmill included 166 subjects with CHD and 120 controls, while on cycle ergometer it was 1222 CHD and 982 controls. Those who performed CPET on a treadmill had on average −9.6 ml/Kg/min (95% CI: −14.0, −5.2) of VO_2peak compared with the control group ($p < 0.0001$) and those who performed test on cycle ergometer had an average of −7.1 ml/Kg/min (95% CI: −9.3, −5.0) of VO_2peak as compared with the control group ($p<0.00001$). If we analyze only studies with patients surgically repaired (19, 20, 22, 24–27, 30, 31, 33–37), the participants with CHD averaged −8.7 ml/Kg/min (95% CI: −12.0, −5.4) of VO_2peak compared with controls ($p < 0.00001$, I^2 = 92%) (**Supplementary File 2**, **Figure 1**). In addition, we sub-analyzed by age range and observed that the VO_2peak of the group under 12 years old had a decrease of −7.1 ml/Kg/min (95% CI: −11.7, −2.4) compared with the control group ($p < 0.00001$, I^2 = 89%), and the group ≥ 12 years old had a reduction of −10.0 ml/Kg/min (95% CI: −12.0, −5.3) compared with the control group ($p < 0.00001$, $I^2 = 82\%$) (**Figure 3**).

Maximum Workload

Ten studies reported the Wmax in watts (21–24, 27, 30–32, 34, 35). These studies compared 1168 participants with CHD vs. 938 healthy controls. The heterogeneity of the comparison was high (I^2 = 96%). Participants with CHD averaged −41.5 Wmax (95% CI: −57.9, −25.1 watts) compared with controls ($p < 0.00001$) (**Figure 4**). If we analyze only studies with patients surgically repaired (22, 24, 27, 30, 31, 34, 35) the participants with CHD averaged −49.9 watts (95% CI: −77.2, −22.6) of Wmax compared with controls ($p < 0.0003$, $I^2 = 95\%$) (**Supplementary File 2**, **Figure 2**). In addition, we sub-analyzed by age range and observed that the Wmax of the group under 12 years old was similar with the control group [−79.7 watts (95% CI: −229.2, 69.8), $p = 0.3$, $I^2 = 98\%$], and the group ≥ 12 years old had a reduction of −45.5 watts (95% CI: −54.4, −36.7) compared to the control group ($p < 0.00001$, $I^2 = 0\%$) (**Figure 5**).

VE/VCO_2 Slope

Five studies examined the VE/VCO_2 slope (19, 22, 32, 35, 36). These studies compared 248 participants with CHD vs. 326 healthy controls. The heterogeneity of the comparison was high (I^2 = 92%). Participants with CHD had on average 2.6 more VE/VCO_2 slope (95% CI: 0.3, 4.8) compared with controls ($p < 0.02$) (**Figure 6**). If we analyse only studies with patients surgically repaired (19, 22, 35, 36) the participants with CHD averaged 3.4 (95% CI: 1.7, 5.1) of VE/VCO_2 compared with controls ($p < 0.0001$, I^2 = 77%) (**Supplementary File 2**, **Figure 3**).

Oxygen Pulse

Four studies examined O_2 pulse in ml/beat (19, 27, 32, 36). These studies compared 176 participants with CHD vs 171 healthy

TABLE 2 | Results of the Cardiopulmonary Test of the included studies.

Authors, year	Group	Test Protocol	VO_2peak (ml·min^{-1} · kg^{-1})	VE/VCO_2 Slope	Maximum load (Wmax)	Pulse of O_2 (ml·beat^{-1})	HR máx (bpm)
Cross-sectional studies							
Bowyer et al., 1990 (18)	CHD	Treadmill Bruce Protocol	38	NR	NR	NR	175
	Control		52	NR	NR	NR	195
Tomassoni et al., 1991 (33)	CHD	Cycloergometer Bruce and modified Bruce protocol in children under 8 years	34.10 ± 2.98 (SE)	NR	NR	NR	173.8 ± 4.6 (SE)
	Control		37.53 ± 2.45 (SE)	NR	NR	NR	184.5 ± 2.9 (SE)
Balderston et al., 1992 (34)	CHD	Cycloergometer James Protocol	48.1 ± 1.4	NR	73 ± 4	NR	183 ± 21
	Control		49 ± 2.1	NR	78 ± 6	NR	189 ± 3
Takagi et al., 1994 (37)	CHD	Treadmill Bruce protocol	Acyanotics: 48.5 ± 11.0 Cyanotics: 36.1 ± 9.9	NR	NR	NR	Acyanotics: 183.4 ± 16.1 Cyanotics: 178.1 ± 16.0
	Control		52.7 ± 8.9	NR	NR	NR	189.8 ± 9.1
Douard et al., 1997 (19)	CHD	Treadmill Bruce protocol	32.6 ± 5.6	36.9 ± 1.5	NR	7.4 ± 2.9	166 ± 20
	Control		44.7 ± 6.1	31.4 ± 5.3	NR	10.7 ± 4.2	188 ± 16
Buheitel et al., 2000 (25)	CHD	Cycloergometer Ramp protocol	Fontan: 36.5 ± 5.7 Senning: 37.5 ± 7.1	NR	W/Kg Fontan: 2.0 ± 0.4 Senning: 2.2 ± 0.4	Fontan: 239 ± 48 Senning: 251 ±78 (by Kg)	Fontan: 156 ± 22 Senning: 155 ±27 (by Kg)
	Control		44.6 ± 6.0	NR	W/Kg 2.6 ± 0.4	O_2 pulse/ kg: 275 ± 49	165 ± 22
Pfammatter et al., 2002 (26)	CHD	Cycloergometer	37.8 (28.5-48.6)	NR	W/kg 3.2 (1.8-4.0)**	NR	180 (142-191)**
	Control		44.3 (30.9-52.3)	NR	W/kg 2.9 (2.0–4.0)**	NR	191 (152-202)**
Zajac et al., 2002 (27)	CHD	Treadmill Modified bruce protocol	14.4 ± 6.1	NR	80.8 ± 45.7	2.57 ± 1.23	142.2 ± 24.8
	Control		30.9 ± 7.6	NR	238.4 ± 63.5	6.14 ± 2.23	183.4 ± 23.6
Binkhorst et al., 2008 (29)	CHD	Cycloergometer Ramp protocol	VSD repaired: 45 ± 9 VSD Conservative: 46 ± 7	NR	VSD repaired: 3.4 ± 0.7 VSD Conservative: 3.4 ± 0.6 (W/Kg)	NR	VSD repaired: 179 ± 8 VSD Conservative: 188 ± 6
	Control		48 ± 8	NR	3.7 ± 0.9	NR	188 ± 8
Moalla et al., 2008 (30)	CHD	Cycloergometer Ramp protocol	30.2 ± 6.1	NR	107 ± 17	NR	170 ± 17
	Control		46.5 ± 6.7	NR	159.6 ± 26.7	NR	197 ± 10
Van Beek et al., 2010 (31)	CHD	Cycloergometer Ramp protocol	41.1 ± 6.6	NR	154.1 ± 61.6	NR	180 ± 14
	Control		47.4 ± 6.4	NR	179.3 ± 60.5	NR	189 ± 9
Müller et al., 2013 (32)	CHD	Cycloergometer	35.5 (31.3-41.0)***	27.7 (25.4-29.8)***	117 (94-133)***	ml/kg: 0.20 (0.18-0.24)***	175 (161-184)***
	Control		42.4 (36.1-47.3)***	27.8 (25.7-29.9)***	159 (143-193)***	ml/kg: 0.22 (0.19-0.26)***	187 (181-196)***
Mazurek et al., 2016 (20)	CHD	Treadmill Ramp protocol	34.6 ± 8.0*	NR	NR	NR	NR
	Control		38.4 ± 7.7	NR	NR	NR	NR
Samos et al., 2016 (36)	CHD	Treadmill Ramp protocol	40.52 ± 7.19	35.73 ± 4.94	NR	7.83 ± 2.8	162.97 ± 17.88
	Control		45.47 ± 8.05	34.75 ± 5.39	NR	9.68 ± 4.50	201 ± 78.32
Amedro et al., 2018 (21)	CHD	Cycloergometer Ramp protocol	38.1 ± 8.1	NR	105.2 ± 71.6	NR	174.7 ± 18.8
	Control		43.5 ± 7.5	NR	111.5 ± 73.9	NR	187.5 ± 11.1

(Continued)

TABLE 2 | Continued

Authors, year	Group	Test Protocol	VO_2peak (ml·min^{-1} · kg^{-1})	VE/VCO_2 Slope	Maximum load (Wmax)	Pulse of O_2 (ml·beat^{-1})	HR máx (bpm)
Hock et al., 2018 (22)	CHD	Cycloergometer Ramp protocol	34.8 ± 7.5	31.6 ± 3.3	125.2 ± 45.2	NR	NR
	Control		42.1 ± 8.4	27.5 ± 2.9	165.7 ± 41.3	NR	NR
Coomans et al., 2020 (35)	CHD	Cycloergometer Ramp protocol	34.46 ± 8.14	27.37 ± 3.88	112.2 ± 42.4	NR	174.0 ± 13.8
	Control		42.77 ± 8.14	25.09 ± 2.88	149.9 ± 65.7	NR	191.8 ± 9.4
Gavotto et al., 2020 (23)	CHD	Cycloergometer Ramp protocol	37.7 ± 6.9	NR	89.9 ± 44.3	NR	175.3 ± 15.8
	Control		42.6 ± 6.9	NR	121.8 ± 44.2	NR	187.6 ± 15.9
Controlled intervention studies							
Moalla et al., 2005 (24)	CHD	Cycloergometer Ramp protocol	28.9 ± 1.7 (SE)	NR	105.5 ± 5.8 (SE)	NR	163.5 ± 6 (SE)
	Control		46.5 ± 1.8 (SE)	NR	159.6 ± 7.1 (SE)	NR	197.2 ± 2.9 (SE)

*Data are shown as mean ± SD, **median (range), ***median (interquartile range).*
CHD, congenital heart disease; NR, not reported; SE, standard error; VSD, ventricular septal defect.

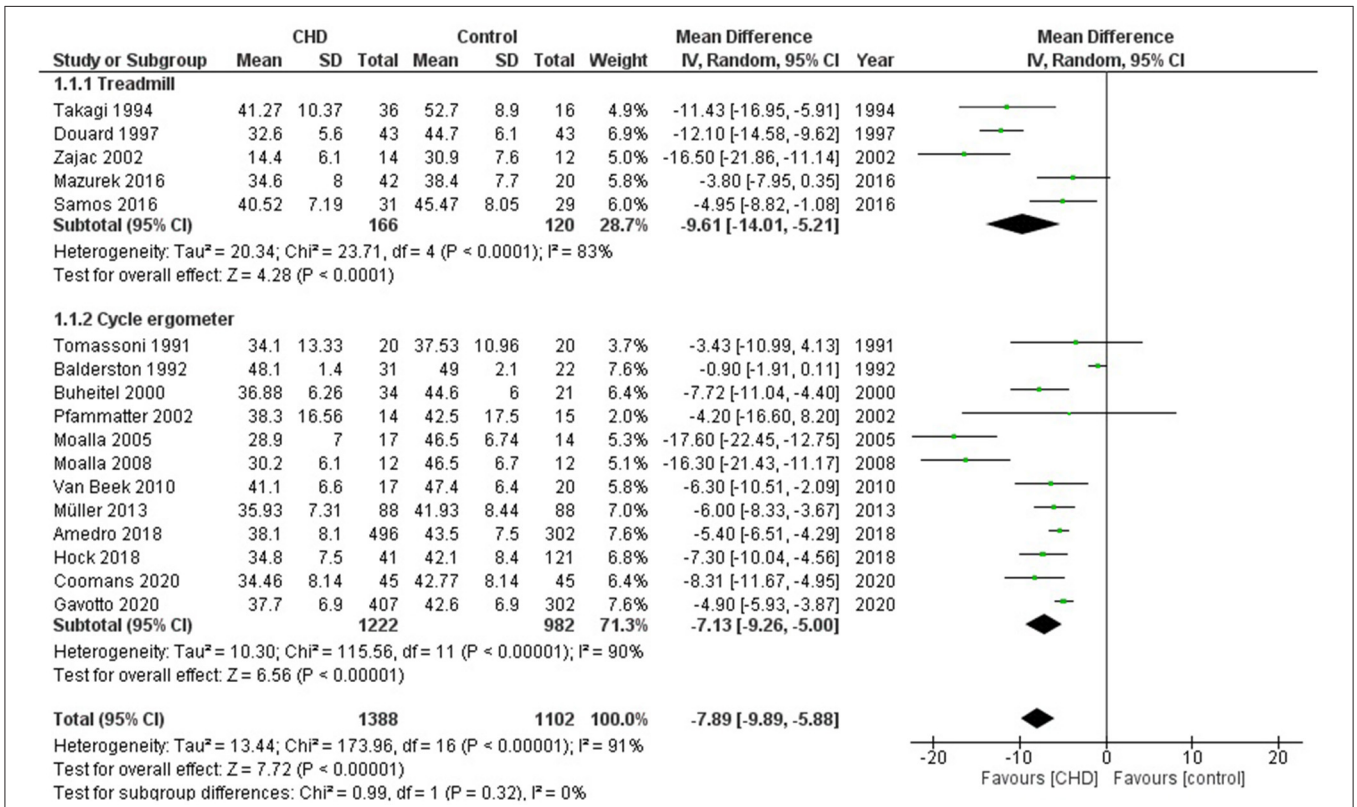

FIGURE 2 | Forest plot for mean peak oxygen consumption for CHD in children and adolescents and healthy controls.

controls. The heterogeneity of the comparison was high (I^2 = 73%). Participants with CHD had on average −2.4 ml/beat of O_2 pulse (95% CI: −3.7, −1.1 ml/beat) compared with controls ($p < 0.0003$) (**Figure 7**). If we analyse only studies with patients surgically repaired (19, 27, 36) the participants with CHD averaged−3.1 ml/beat (95% CI: −4.0, −2.1) of O_2 pulse compared with controls ($p < 0.00001$, I^2 = 6%) (**Supplementary File 2**, **Figure 4**).

Maximum Heart Rate

Fifteen studies reported working HRmax in beats per minute (bpm) during CPET (19, 21, 23–27, 30–37). These studies

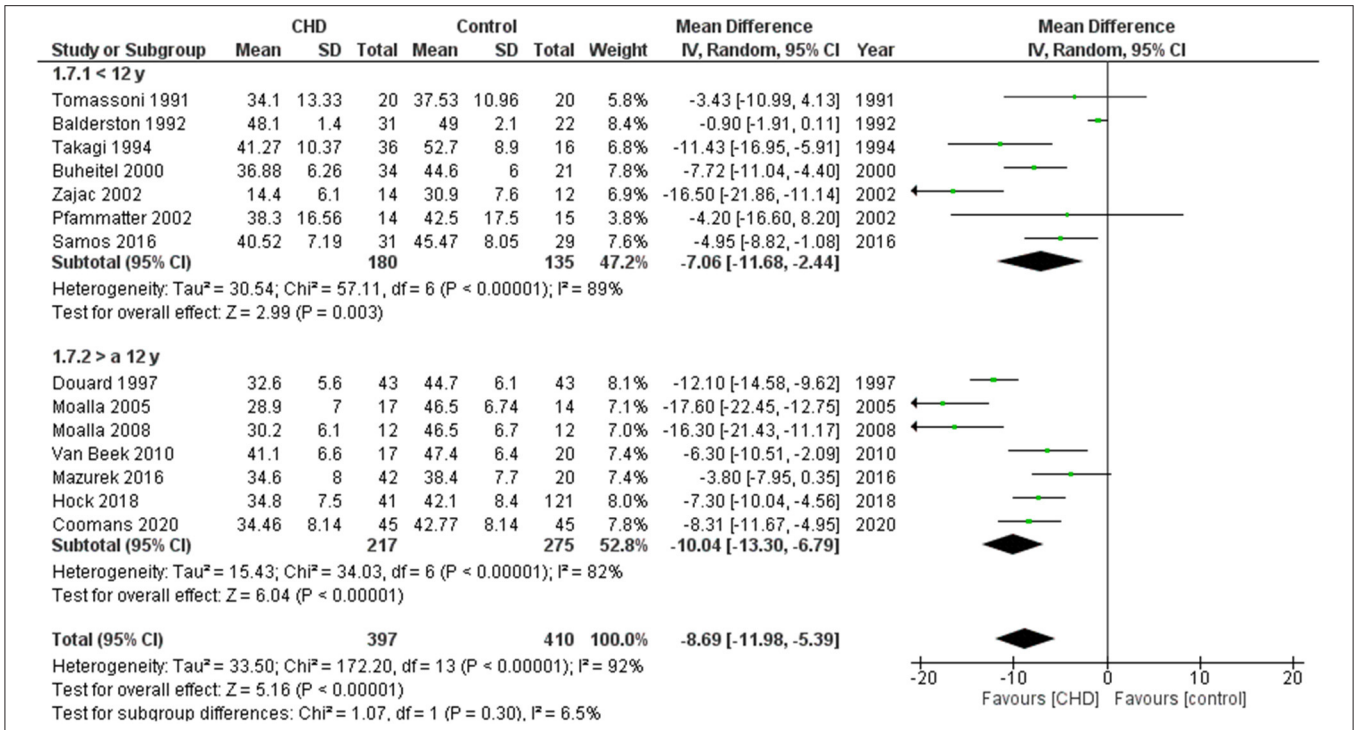

FIGURE 3 | Forest plot for mean peak oxygen consumption for CHD in children and adolescents and healthy controls. Subanalysis by age.

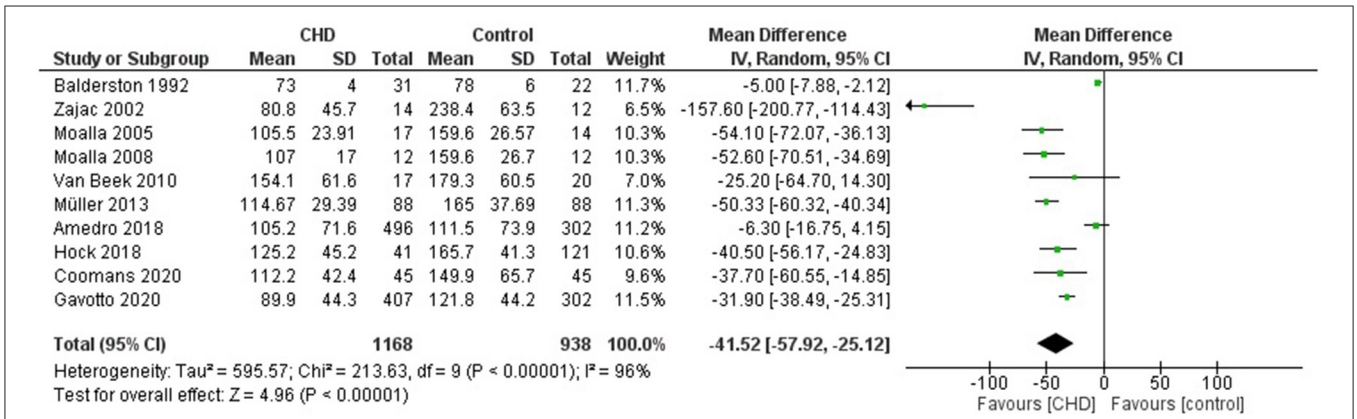

FIGURE 4 | Forest plot for mean maximum workload for CHD in children and adolescents and healthy controls.

compared 1305 participants with CHD vs. 961 healthy controls. The heterogeneity of the comparison was high (I^2 = 67%). Participants with CHD averaged −15 bpm (95% CI: −18, −12 bpm) of HRmax compared with controls ($p < 0.00001$) (**Figure 8**). When considering the analysis by subgroups according to the test type, those who performed the test on a treadmill included 124 subjects with CHD and 100 controls, while on the cycle ergometer it was 1181 CHD and 861 controls. Those who performed the test on a treadmill had an average of −24 bpm (95% CI: −37, −11) of HRmax compared with the control group; in contrast, those who performed the test on a cycle ergometer had an average of −14 bpm (95% CI: −17, −11) of HRmax compared with the control group ($p < 0.00001$). If we analyze only studies with patients surgically repaired (19, 24–27, 30, 31, 33–37) the participants with CHD averaged −17 bpm (95% CI: −23, −12) of HRmax compared with controls ($p < 0.0001$, I^2 = 71%) (**Supplementary File 2**, **Figure 5**). In addition, we sub-analyzed by age range and observed that the HRmax of the group under 12 years old had a decrease of −14 bpm (95% CI: −22, −6) compared with the control group ($p = 0.0004$, I^2 = 61%), and the group ≥ 12 years old had a reduction of −21 bpm (95% CI: −28, −14) compared with the control group ($p < 0.00001$, I^2 = 82%) (**Figure 9**).

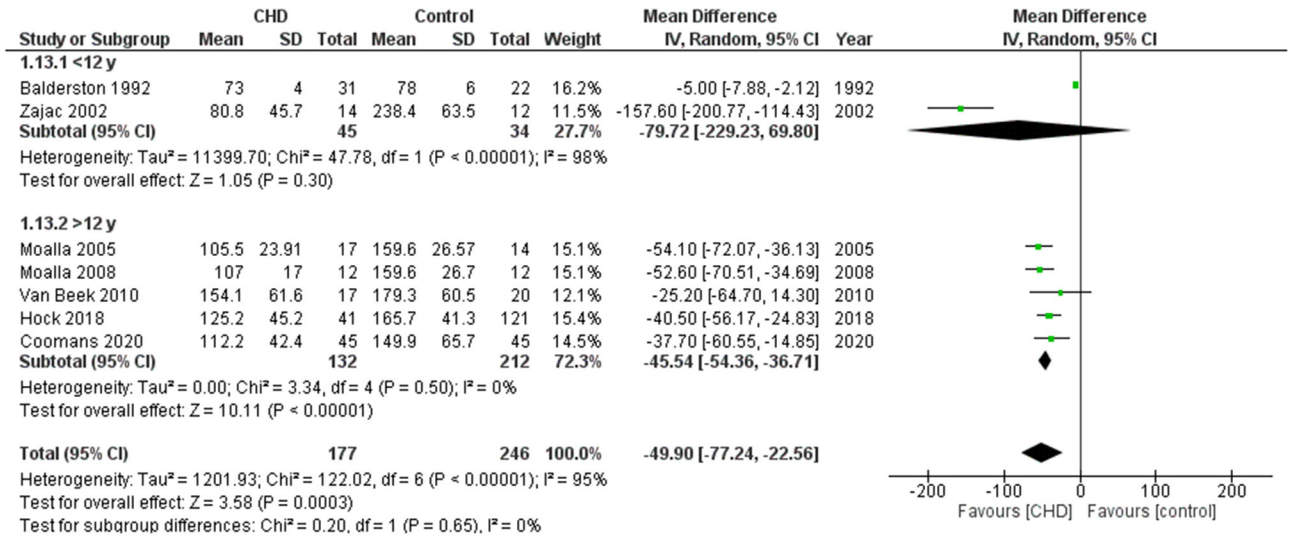

FIGURE 5 | Forest plot for mean maximum workload for CHD in children and adolescents and healthy controls. Subanalysis by age.

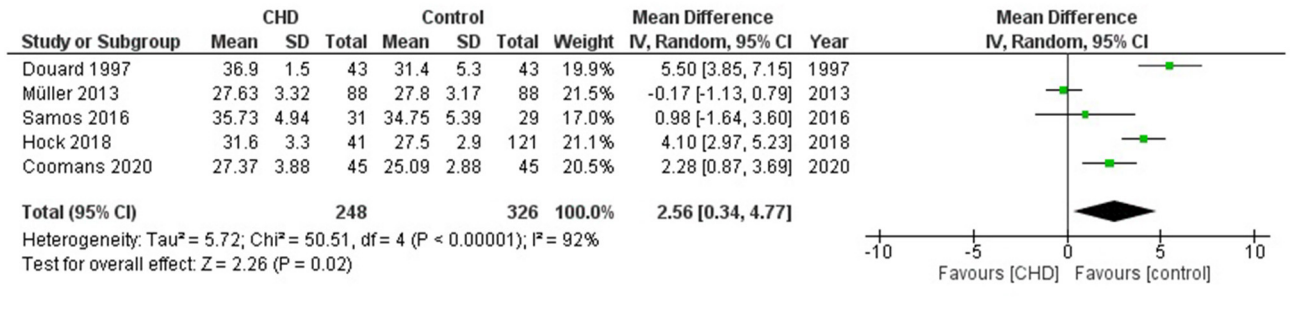

FIGURE 6 | Forest plot for mean ventilatory equivalent for carbon dioxide at anaerobic threshold for CHD in children and adolescents and healthy controls.

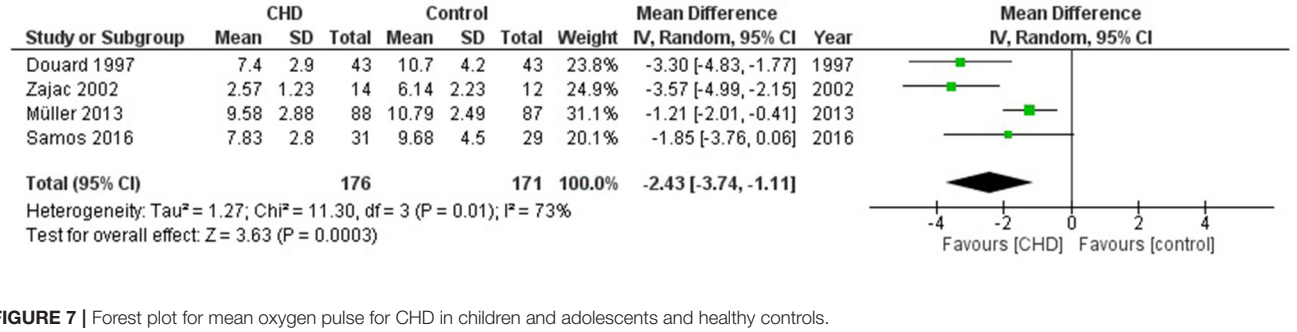

FIGURE 7 | Forest plot for mean oxygen pulse for CHD in children and adolescents and healthy controls.

DISCUSSION

This systematic review with meta-analysis of observational studies showed that children and adolescents with CHD have a significant decrease in the exercise capacity compared with healthy controls of similar age. VO_2peak, HRmax, Wmax, and O_2 Pulse were significantly lower in children and adolescents with partially or fully repaired CHD compared with healthy controls.

Our results showed that children and adolescents with CHD have a reduction close to 8 ml/Kg/min, although 76% of the selected articles exclusively evaluated patients with repaired CHD, which shows a considerable residual effect of CHD. The significant impairment of VO_2peak directly impacts on exercise

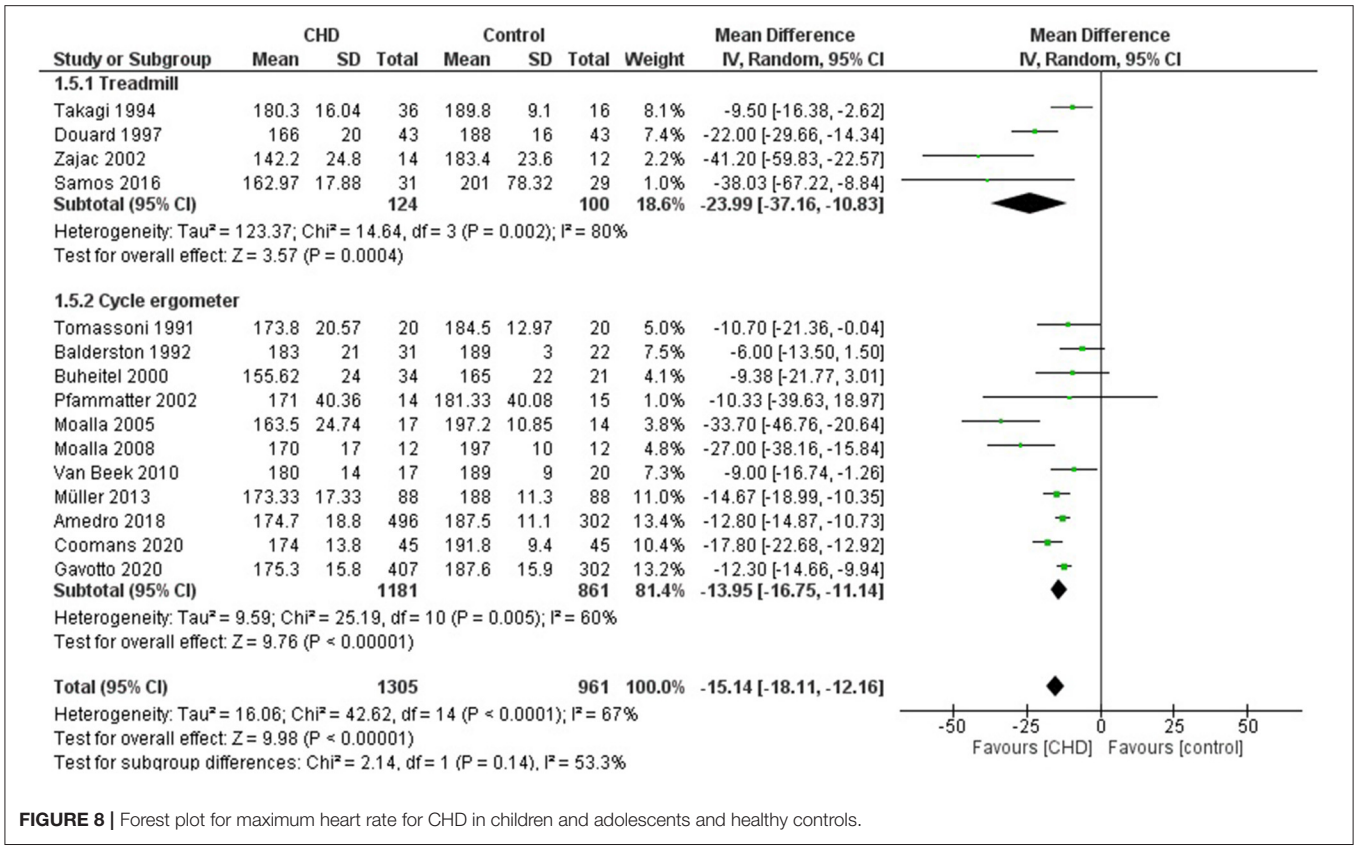

FIGURE 8 | Forest plot for maximum heart rate for CHD in children and adolescents and healthy controls.

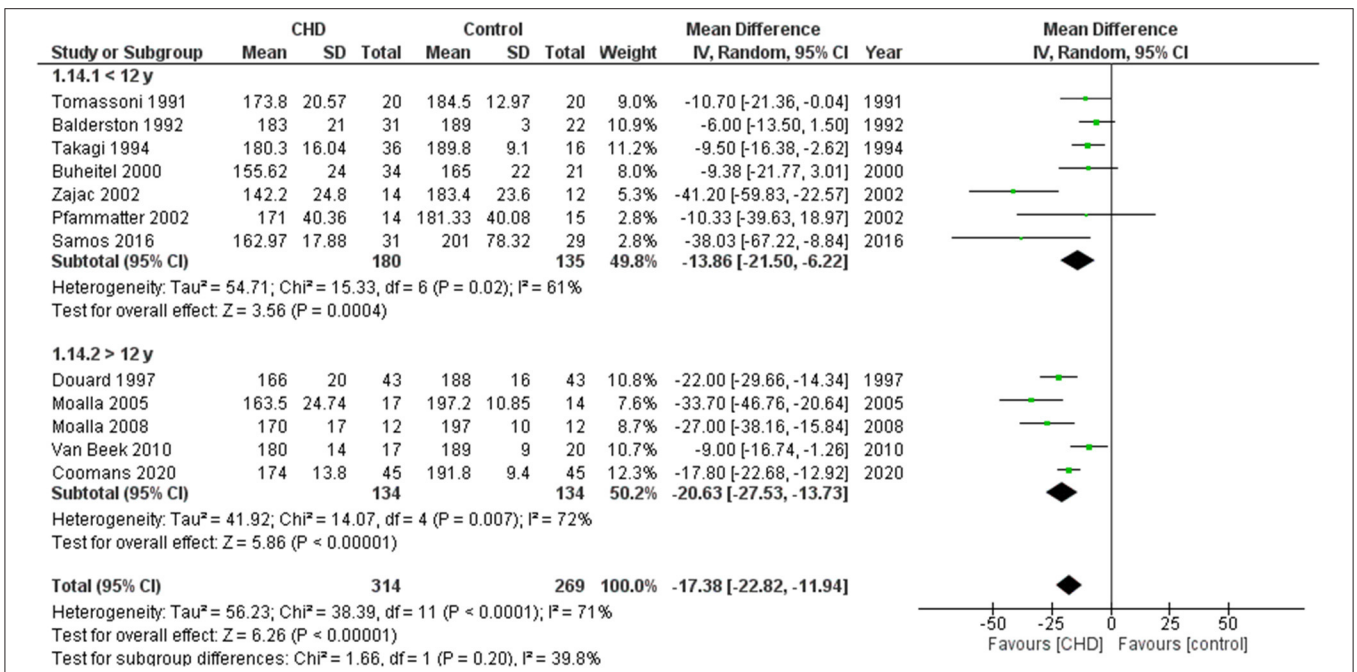

FIGURE 9 | Forest plot for maximum heart rate for CHD in children and adolescents and healthy controls. Subanalysis by age.

capacity, morbidity and mortality and is a prognostic factor in this population, reaching clinical and functional relevance. The presence of pulmonary hypertension (PH) is also a condition that could affect exercise capacity evaluated through VO_2peak;

however, it was not reported in most articles. On the other hand, one of the few manuscripts which reported it did find that the presence of PH was significantly associated with lower VO_2peak (21).

Coomans et al. (35) highlighted that, in patients with repaired Tetralogy of Fallot (TOF), VO_2peak and HRmax is lower as compared with controls, attributing, in part, the lower performance to chronotropic insufficiency due to a positive and significant correlation between HRmax and VO_2peak ($r = 0.418$; $p < 0.01$). Additionally, our results showed that patients with CHD, in the included studies, have a diminution close to 15 bpm compared with healthy peers. The decrease in HRmax is almost double in those who perform the test on a treadmill, which is in line with a greater decrease in VO_2peak in this evaluation device. These results highlight the importance of chronotropic insufficiency in maximum exercise performance, limiting the physical performance of individuals with even repaired TOF and being in line with other publications with similar results (35).

The lower HRmax in subjects with CHD was also related to factors affecting the correct function of the sympathetic and parasympathetic nervous system, among which is ischemia and / or denervation resulting from various cardiac surgical procedures or, in cases of cyanotic CHD, due to chronic hypoxemia (39).

Since most of the articles investigated exercise capacity in subjects with repaired heart disease, we decided to perform a subanalysis with only this group. Surprisingly, the surgically repaired subjects had lower VO_2peak, Wmax, O_2 pulse, and HRmax and higher VE/VCO_2. Several factors could influence this result.. On one hand, there could be a selection bias of the investigated subjects since the follow-up is stricter in those subjects who are more seriously sick. On the other hand, participants with surgical correction were more severe than those without surgery (23).

We also analyzed the influence of age on the reduced exercise capacity. Considering adolescents those subjects older than 12 years old, we showed a greater decrease in VO_2peak and HRmax compared with children under 12. A special case was Wmax, which was shown to be reduced only in the group older than 12 years. These results lead us to think that the differences increase over the years and are more pronounced during adolescence. Although our research does not include adult patients, there are already reports with decreased exercise capacity similar or even greater than what we found in those over 12 years old (40, 41).

Subjects with incomplete CHD repair have significant reductions in age-adjusted peak work rates and peak ventilation compared with their counterparts who had complete repair surgery (42). Amedro et al. observed that, in 496 children with CHD who underwent CPET compared with controls, VO_2peak alteration was more prevalent in most subjects with partial repair or complex CHD (single ventricles and complex anomalies of atrioventricular connections) (21). The lower VO_2peak in their study group was also associated with right ventricular systolic hypertension and tricuspid regurgitation, which are frequently common in many right heart complex CHD cases. The literature has also highlighted this situation, especially in patients with TOF, transposition of the great arteries, and univentricular heart with Fontan physiology (43).

Sequential CPET studies in young adult subjects with Fontan physiology have emphasized the prognostic value of this test regarding survival, mortality and the need for transplantation. There is often a decrease in VO_2peak that precedes these events (44). Cooney et al. postulate that a change in VO_2peak is an independent prognostic factor, which may allow early identification of subjects who could benefit from more intensive and preventive management (44). The change in VO_2peak between sequential CPETs predicts transplant-free survival during and above any risk predicted by a single VO_2peak measurement. Studies that have followed individuals with Fontan physiology from childhood to adulthood have documented a gradual decline in VO_2peak over the years (14, 45). The decrease in VO_2peak with age may be a factor to be identified and considered in subjects with CHD as a selection parameter for timely cardiac rehabilitation programmes starting even in the early stages of life (schooling).

The VE/VCO_2 slope is elevated in most subjects with heart failure as it is inversely related to CO at peak exercise and to pulmonary perfusion, a situation that could also be experienced in subjects with CHD (46). In addition, the elevation of this slope is commonly observed in pulmonary vascular anomalies such as PH (47), which can also be experienced in patients with partially repaired CHD due to greater physical exertion.

A decrease in the O_2 pulse during progressive exercise could indicate circulatory insufficiency or cardiovascular limitation (48). It is generally associated with the appearance of PH and impaired cardiac perfusion. In combination with a sudden decrease in the VO_2 / Wmax ratio, it could indicate myocardial ischemia (49). In addition, a low O_2 pulse is indicative of a reduced cardiac index (CI) or stroke volume, which implies a greater dependence on HR to increase CO (48, 50), a situation that may be common to certain CHD considered in the different subgroups that constitute the total of subjects with CHD of this revision.

Although our objective was to measure exercise capacity and not physical activity, it is important to note that some articles reported it (31, 32). This is important because a previous investigation of our group has shown that the moderate-to-vigorous physical activity of 46% of children with CHD is less than what is recommended by WHO (51). However, Van Beek et al. and Müller et al. found that exercise capacity is decreased in children with CHD, but physical activity showed no differences between groups (31, 32). Even in Müller's study, both groups performed more physical activity than recommended by clinical guidelines (32).

Finally, although the search period was long, our results consider only studies from the last three decades that explored exercise capacity in a large cohort of children and adolescents with CHD worldwide, which gives high value to our main message.

Limitations

Our study has some limitations. Most of the studies included subjects with different types of CHD, which may limit the extrapolation of the results and recommendations to the entire spectrum of children and adolescents with CHD; even though

our results were statistically significant. The heterogeneous nature of CHD implies that many lesions have different pathophysiological behaviors and conditions, a wide spectrum of severity, as well as the implication or impact that suffering from associated comorbidities may influence the congenital health condition they may have. Another important limitation is that most studies do not report whether patients presented PH. This point is key since it is well known that PH determines lower exercise capacity. In this context, it is important to systematically review associations in order to establish in more detail the factors that can condition a certain result.

Additionally, there was heterogeneity in the control participants since some of them performed the CPET to get the authorization to play sports (22) and others who presented any symptoms although the CPET showed no disease (21, 23, 35). On the other hand, physical activity analysis was not included, which could have provided us information on how sedentary the population was, and were not evaluated respiratory exchange ratio (RER) that indirectly shows the muscle's oxidative capacity to get energy. Sedentarism, exercise and physically active lifestyles modify it.

Concerning the possible bias occurred in VO_2peak and other CPET variables due to variability in different countries (with different daily levels of physical activity, for example, due to different cultural habits) it is important to remark that the comparisons of these parameters, both for the studies and the meta-analysis, were performed comparing patients to controls (adjusted for sex and age in each article) and not regarding their percentages of the predicted values. Therefore, using a control population was essential to avoid these biases.

CONCLUSION

In conclusion, suffering from CHD in childhood and adolescence is associated with a lower exercise capacity as shown by worse VO_2peak, Wmax, VE/VCO_2 slope, O_2 pulse, HRmax compared with healthy controls, not only in CPET but also in other variables as shown in indirect exercise capacity tests. These findings highlight the importance of carrying out a continuous evaluation and early determination of the factors associated with a potential decrease in exercise capacity. In this way, it would be possible to intervene in time by planning rehabilitation programmes and promoting an active lifestyle, since a lower exercise capacity can lead to a greater risk of morbidity, mortality, and deterioration of functionality.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YV-R: conceptualization, formal analysis, methodology, reviewing procedure and data extraction, writing—original draft, and writing—review & editing. JV-M: conceptualization, formal analysis, methodology, writing—original draft, and writing—review & editing. RT-C: conceptualization, formal analysis, methodology, supervision, writing—original draft, and writing—review & editing. LV-C: reviewing procedure and data extraction, writing—original draft, and writing—review & editing. GM: supervision and writing—review & editing. JV and IB: writing —original draft and writing—review & editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Pulmonary Valve Replacement in Repaired Tetralogy of Fallot: Midterm Impact on Biventricular Response and Adverse Clinical Outcomes

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Background: Pulmonary regurgitation (PR), though well tolerated for short term in patients with repaired tetralogy of Fallot (rTOF), could lead to right ventricular (RV) dysfunction, arrhythmias, and sudden cardiac death. Pulmonary valve replacement (PVR), considered as the gold-standard treatment for PR, is performed to mitigate these late effects. In this study, we aimed to evaluate the midterm outcomes and predictors of adverse clinical outcomes (ACO).

Methods: From May 2014 to December 2017, 42 patients with rTOF undergoing surgical or transcatheter PVR in our department were retrospectively included. Cardiovascular magnetic resonance was performed before PVR (pre-PVR), early after PVR (early post-PVR), and midterm after PVR (midterm post-PVR). Medical history and individual data were collected from medical records. ACO included all-cause death, new-onset arrhythmia, prosthetic valve failure, and repeat PVR.

Results: The median follow-up duration was 4.7 years. PVR was performed at a median age of 21.6 years. There was no early or late death. Freedom from ACO at 3 and 5 years was 88.1 ± 5% and 58.2 ± 9%, respectively. RV end-diastolic volume index (RVEDVI) and end-systolic volume index (RVESVI) significantly reduced early after PVR and further decreased by midterm follow-up (pre-PVR vs. early post-PVR vs. midterm post-PVR: RVEDVI, 155.2 ± 34.7 vs. 103.8 ± 31.2 vs. 95.1 ± 28.6 ml/m^2, $p < 0.001$; RVESVI, 102.9 ± 28.5 vs. 65.4 ± 28.2 vs. 57.7 ± 23.4 ml/m^2, $p < 0.001$). Multivariable analysis revealed that the occurrence of ACO was significantly increased in patients with lower left ventricular end-systolic volume index.

Conclusions: A significant reduction of RV volume occurred early after PVR, followed by a further improvement of biventricular function by midterm follow-up. The midterm freedom from ACO was favorable.

Keywords: pulmonary valve replacement, repaired tetralogy of fallot, pulmonary regurgitation, cardiovascular magnetic resonance, right ventricular reverse remodeling

INTRODUCTION

Pulmonary regurgitation (PR), largely attributed to the classic surgical repair with the use of a transannular patch, is generally considered well-tolerated in patients with repaired Tetralogy of Fallot (rTOF) for the short term (1). This ongoing valve insufficiency, however, frequently leads to progressive right ventricular (RV) enlargement, adverse clinical outcomes (ACO), and even sudden cardiac death (2–5). As the gold-standard treatment for PR to eliminate these late effects, pulmonary valve replacement (PVR) has been already proven to be associated with reversible RV remodeling, RV normalization, and notable symptomatic benefits (6–8). Nevertheless, many current studies placed great emphasis on the optimal timing and indications for PVR in patients with rTOF. The prior results reporting the improvement of RV function in response to PVR are conflicting (6, 9–12). It is unknown whether the reverse RV remodeling and normalization after PVR will present an ongoing improvement over time, or simply will stabilize after the reduction of RV volume load (13, 14). Following the favorable outcomes previously published by our prospective case-control study (15), this cohort continued to evaluate the midterm results of PVR and investigate potential risk factors for ACO.

MATERIALS AND METHODS

Study Design and Patients Inclusion

This retrospective single-center study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Fuwai Hospital. All patients were provided with written informed consent for examination protocol and medical record review. For the initial inclusion in the study, patients had to fulfill the following criteria: (1) rTOF; (2) PVR performed in our hospital between May 1, 2014, and December 31, 2017; (3) the latest post-PVR cardiovascular magnetic resonance (CMR) performed no more than 5 years following PVR, and no contraindications to CMR; (4) follow-up $\geq$3 years. CMR was performed at 3 time points: pre-PVR, early post-PVR (minimum, 6 months), and midterm post-PVR (minimum, 36 months) during the entire follow-up. Only patients with a complete CMR imaging data set at all three assessment points were incorporated and analyzed. Of the 45 subjects screened for enrollment, 42 patients met the inclusion criteria described above and formed the study cohort. Demographic and surgical characteristics before exclusion are listed in **Supplementary Tables**. Medical history and individual data were collected from medical records. Clinical status was obtained through outpatient visits or telephone follow-up with patients or family members, as appropriate. CMR was performed on a 1.5 Tesla magnetic resonance scanner (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany). Our protocols for image acquisition and analysis in patients with rTOF have been previously reported (15). The CMR data were analyzed using commercially available software packages (Philips Intellispace Portal).

PVR Strategy

In the current study, those same indications for asymptomatic patient's referral to surgical or transcatheter PVR were moderate or severe PR with one of the following: (1) right ventricular end-diastolic volume index (RVEDVI) $\geq$150 ml/m^2, or (2) right ventricular end-systolic volume index (RVESVI) $\geq$120 ml/m^2, or (3) right ventricular ejection fraction (RVEF) $<$ 47%. Favorable anatomy and patient's weight, however, need to be considered for transcatheter PVR: (1) pulmonary valve annulus $\leq$30 mm by cardiac computerized tomography, (2) no significant right ventricular outflow tract or main pulmonary artery narrowing, (3) no significant obstruction of the proximal branches of pulmonary artery, and (4) patent central veins (16).

Endpoints

ACO was defined as the composite of all-cause death, new-onset arrhythmia, prosthetic valve failure, and repeat PVR. Time zero was defined as the date of PVR and the time to clinical outcomes was determined to be the first occurrence of ACO or the date of the last follow-up for those patients without an outcome. Early death was defined as death occurring $\leq$30 days after the initial operation or during the same hospitalization. Conversely, late death was defined as death occurring $>$30 days after the initial operation or after discharge. According to Khaled Alfakih's study (17), regardless of gender, normal RV volume was defined as RVEDVI $\leq$114 ml/m^2, and RV normalization was defined as both RVEDVI $\leq$114 ml/m^2 and RVEF $\geq$ 48%, by steady-state free precession imaging sequences. Cardiomegaly was defined as the cardiothoracic ratio $\geq$ 0.50 on posteroanterior chest X-ray.

Statistical Analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were presented as means $\pm$ standard deviation (SD) or medians with interquartile range (IQR). Comparisons between paired groups were performed using paired Student t-tests or the Wilcoxon signed-rank test as appropriate. Categorical variables were compared by χ^2 and McNemar tests as appropriate. Bonferroni correction was applied when multiple comparisons were undertaken by dividing the original value of 0.05 by the number of analyses on the dependent variable (k). Survival estimates and the time to ACO were determined by the Kaplan–Meier analysis. Risk factors associated with ACO after PVR were identified by the Cox proportional hazards regression model. Linear regression analysis was performed to evaluate the association between two continuous variables. Statistical analysis was completed by SPSS Statistics Version 25 (IBM 16 Corporation, Armonk, New York) and R (version 3.1.2). A two-sided value of p $<$0.05 was considered statistically significant.

RESULTS

Patient Characteristics and Clinical Outcomes

The demographic characteristics of 42 patients are listed in **Tables 1**, **2**. Surgical PVR was performed in 24 patients, and transcatheter PVR in 18 patients. Concomitant procedures

TABLE 1 | Demographics.

Variables	Values
Male	20 (48)
Age at TOF repair, years	2.0 (0.8-5.5)
Weight at TOF repair, kgs	9.3 (8.0-11.2)
Previous palliative shunts	
Blalock-Taussig shunt	2 (5)
Modified Blalock-Taussig shunt	8 (19)
Type of initial repair	
Transannular patch	32 (76)
Non-transannular patch	6 (14)
RV-to-PA conduit	4 (10)
Age at PVR, years	21.6 (15.4–24.8)
Time interval between TOF repair and PVR, years	16.4 (11.0–19.9)
Follow-up time, years	4.7 (4.2–5.0)
NYHA functional class	
I	13 (31)
II	18 (43)
III	11 (26)
IV	0
TR grade	
None	11 (26)
Trivial	4 (10)
Mild	18 (42)
Moderate	5 (12)
Severe	4 (10)

Data are presented as n (%) or median (IQR). NYHA, New York Heart Association; PA, pulmonary artery; PVR, pulmonary valve replacement; RV, right ventricle; TR, tricuspid regurgitation; TOF, tetralogy of Fallot.

TABLE 2 | Perioperative characteristics and post-PVR outcomes.

Variables	Values
Types of prosthetic pulmonary valve	
Surgical bioprosthetic	10 (24)
Homograft	14 (33)
Transcatheter bioprosthetic	18 (43)
Prosthetic pulmonary valve size, mm	26 (24–32)
Concomitant procedures	
Tricuspid valve surgery	9 (21)
RVOT muscle resection	3 (7)
Residual VSD closure	1 (2)
PDA closure	1 (2)
MAPCA occlusion	1 (2)
CPB time, minutes	190.9 ± 69.3
ACC time, minutes	93.3 ± 34.6
Hospital stay, days	17 ± 8
Post-PVR outcomes	
Re-intervention	4 (10)
New-onset arrhythmias	12 (29)
Prosthetic valve failure and dysfunction	4 (10)
Adverse clinical outcomes	16 (38)

Data are presented as n (%), mean ± SD or median (IQR). ACC, aortic cross-clamp; CPB, cardiopulmonary bypass; MAPCA, major aortopulmonary collateral arteries; PDA, patent ductus arteriosus; PVR, pulmonary valve replacement; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

during PVR included: tricuspid valvuloplasty in eight patients, right ventricular outflow tract muscle resection in three, residual ventricular septal defect closure in one patient, patent ductus arteriosus ligation in one patient, and major aortopulmonary collateral arteries occlusion in one patient. The mean cardiopulmonary bypass time was 190.9 ± 69.3 min, and the mean aortic cross-clamp time was 93.3 ± 34.6 min. The mean duration of hospital stay was 17 ± 8 days (**Table 2**).

The median duration of follow-up was 4.7 years (IQR, 4.2–5.0 years). About 74% of patients presented heart function in New York Heart Association Class I or II at baseline, and 95% maintained in New York Heart Association Class I or II by midterm follow-up after PVR ($p < 0.001$) (**Table 3**). Baseline QRS duration of 140 ± 31 ms on electrocardiogram (ECG) decreased with marginal statistical significance by midterm follow-up (140 ± 31ms vs. 111 ± 20 ms, $p < 0.001$). Cardiomegaly was documented in 40 (95%) patients preoperatively and reduced significantly by midterm follow-up after PVR (0.58 ± 0.05 vs. 0.49 ± 0.02, $p < 0.001$) (**Table 3**).

There was no early or late death in this study. ACO occurred in 16 (38%) patients: prosthetic valve failure in four patients, and new-onset arrhythmia in 12 (**Figure 1**). Freedom from ACO at 3 and 5 years was 88.1 ± 5% and 58.2 ± 9%, respectively (**Figure 2A**). One of four patients with developed prosthetic valve failure accepted a repeat PVR in the third year after the initial PVR. Freedom from repeat PVR and prosthetic valve failure at 3 and 5 years was 97.6 ± 2% and 92.5 ± 4%, respectively (**Figure 2B**). For patients with new-onset arrhythmia (ventricular arrhythmia in four patients, and sustained atrial arrhythmia in eight patients), three patients with atrial flutter were indicated to necessary radiofrequency catheter ablation treatment, and four patients developed non-sustained ventricular tachycardia but without requiring intervention. Freedom from new-onset ventricular arrhythmia at 3 and 5 years was 97.6 ± 2.4% and 88.3 ± 5.7%, respectively (**Figure 2C**).

Cardiovascular Magnetic Resonance

The early postoperative CMR was performed at a median time of 1.0 year (IQR, 0.5–1.7 years) and the midterm postoperative CMR at a median time of 4.2 years (IQR, 3.5–4.8 years) after PVR. Massive RV dilation (RVEDVI ≥ 200 ml/m^2) was only detected in five patients on preoperative CMR. Compared with the baseline, there was a 33% reduction in RVEDVI by the early post-PVR period (155.2 ± 34.7 vs. 103.8 ± 31.2 ml/m^2, $p < 0.001$), which decreased further to 39% by the midterm follow-up (103.8 ± 31.2 vs. 95.1 ± 28.6 ml/m^2, $p < 0.001$). RVESVI promptly decreased by early post-PVR period to 36% (102.9 ± 28.5 vs. 65.4 ± 28.2 mL/m^2, $p < 0.001$) and decreased further by the midterm follow-up to 44% lower than the baseline (102.9 ± 28.5 vs. 57.7 ± 23.4 ml/m^2, $p < 0.001$) (**Table 3**). Compared with the baseline, RVEF increased by 17% at midterm follow-up (35.1 ± 8.8 vs. 41.2 ± 8.7 %, $p < 0.001$). Normal RV volume was noted in 35

TABLE 3 | Pre-PVR, early post-PVR, and midterm post-PVR variables of patients with rTOF.

Variables	Pre-PVR	Early post-PVR	Midterm post-PVR	P value		
				Pre-PVR vs. Early post-PVR	Early post-PVR vs. Midterm post-PVR	Pre-PVR vs. Midterm post-PVR
CMR						
RVEDVI, mL/m^2	155.2±34.7	103.8±31.2	95.1±28.6	<0.001	<0.001	<0.001
RVESVI, mL/m^2	102.9±28.5	65.4±28.2	57.7±23.4	<0.001	<0.001	<0.001
RVEF, %	35.1±8.8	37.9±10.1	41.2±8.7	0.06	<0.001	<0.001
PR fraction, %	38.1±8.2	5.1±3.6	4.7±3.7	<0.001	0.74	<0.001
LVEDVI, mL/m^2	69.2±14.1	77.6±18.1	77.5±14.9	<0.001	0.52	0.001
LVESVI, mL/m^2	36.2±9.9	36.2±11.3	37.8±11.1	0.93	0.30	0.99
LVEF, %	48.1±7.8	53.8±6.6	56.1±6.4	<0.001	<0.001	<0.001
Echocardiography						
RVAPD, mm	33.8±8.3	29.1±7.7	28.5±6.0	<0.001	0.42	<0.001
RVSP, mmHg	17.5±14.1	14.6±8.2	13.0±6.7	0.41	0.14	0.17
QRS duration, ms	140±31	134±30	111±20	0.039	<0.001	<0.001
Cardiothoracic ratio	0.58±0.05	0.51±0.05	0.49±0.02	<0.001	0.037	<0.001
NYHA functional class I/II/III/IV	13/18/11/0	32/9/1/0	39/2/1/0			<0.001
Grade of TR, *n* (%)						
None/trivial/mild	33 (79)		40 (95)			
Moderate/severe	9 (21)		2 (5)			0.021

Data are presented as n (%) or mean ± SD. CMR, cardiac magnetic resonance; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVR, pulmonary valve replacement; PR, pulmonary regurgitation; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; RVAPD, right ventricular anteroposterior diameter; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.

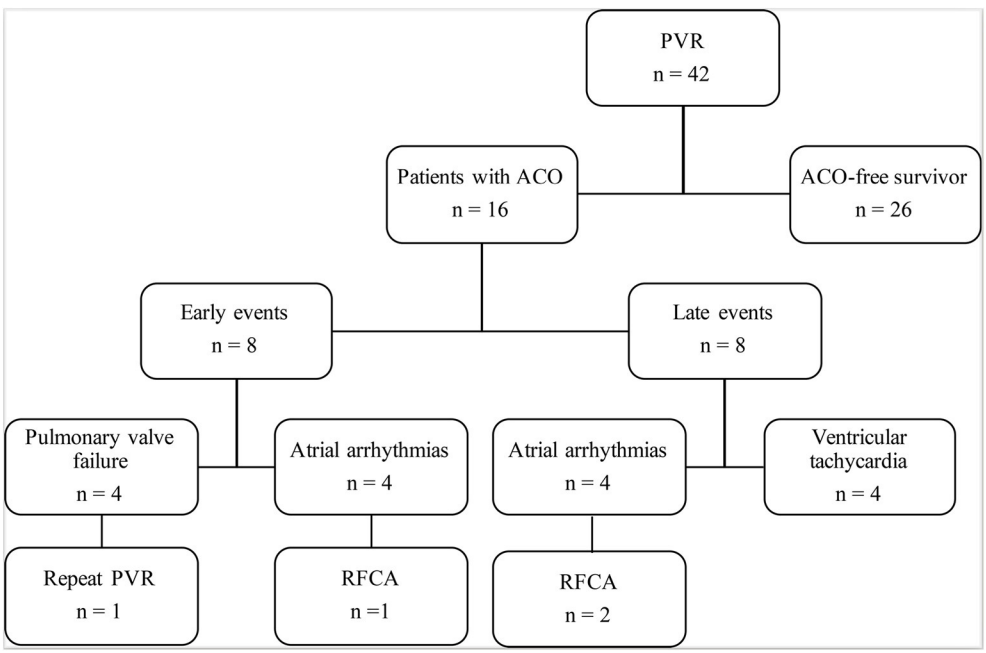

FIGURE 1 | Follow-up and outcomes after PVR. ACO, adverse clinical outcomes; PVR, pulmonary valve replacement; RHCA, radiofrequency catheter ablation.

patients, and RV normalization occurred in 21 (50%) patients by midterm follow-up. Left ventricular end-diastolic volume index increased by 12% early after PVR (69.2 ± 14.1 vs. 77.6 ± 18.1 ml/m^2, $p < 0.001$) and sustained at midterm follow-up. Left ventricular end-systolic volume index (LVESVI) only increased by 4% at midterm follow-up (36.2 ± 9.9 vs. 37.8 ± 11.1 ml/m^2,

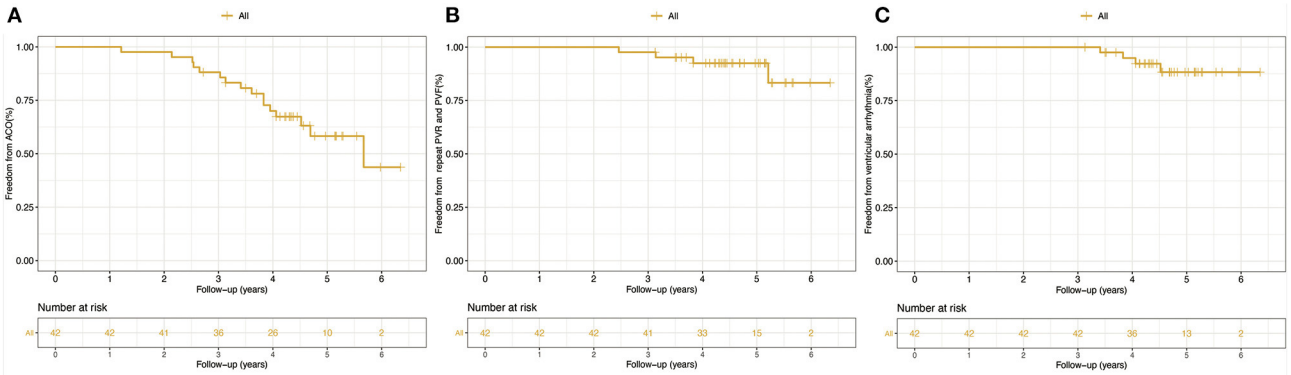

FIGURE 2 | Kaplan-Meier analysis for clinical outcomes. **(A)** Freedom from ACO. **(B)** Freedom from repeat PVR and PVF. **(C)** Freedom from new-onset arrhythmia. ACO, adverse clinical outcomes; PVR, pulmonary valve replacement; PVF, pulmonary valve failure.

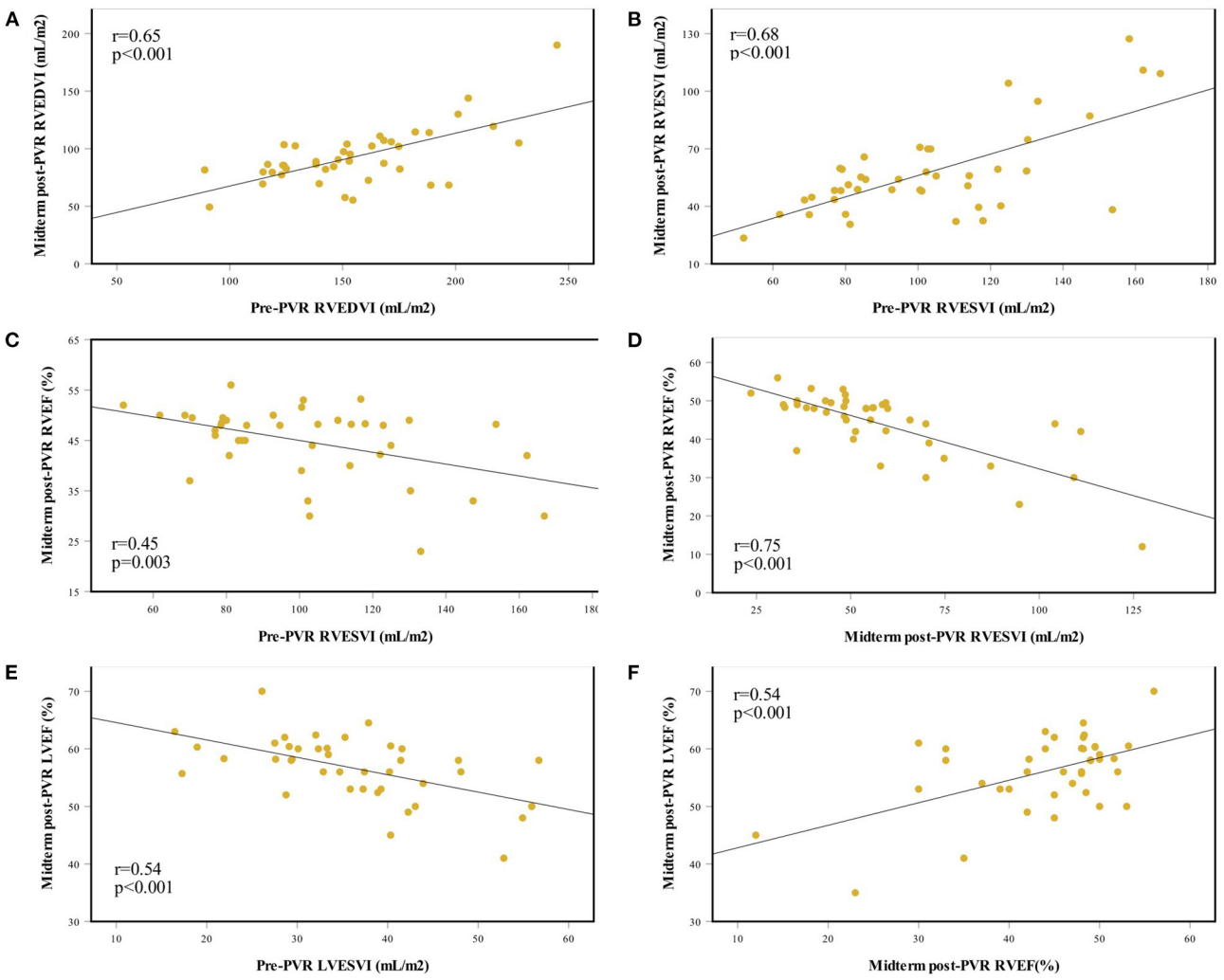

FIGURE 3 | Associations between pre-PVR and midterm post-PVR CMR parameters. **(A)** Association between pre-PVR and midterm post-PVR RVEDVI. **(B)** Association between pre-PVR and midterm post-PVR RVESVI. **(C)** Association between pre-PVR RVESVI and midterm post-PVR RVEF. **(D)** Association between midterm post-PVR RVESVI and RVEF. **(E)** Association between pre-PVR LVESVI and midterm post-PVR LVEF. **(F)** Association between midterm post-PVR RVEF and LVEF. CMR, cardiac magnetic resonance; LVESVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; PVR, pulmonary valve replacement; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction.

TABLE 4 | Risk factors associated with adverse clinical outcomes after PVR.

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Patient and surgical characteristics						
Age at TOF repair, years	0.95	0.89–1.02	0.18			
Age at PVR, years	0.98	0.94–1.03	0.51			
Transannular repair	0.36	0.09–1.40	0.14			
NYHA functional class III or IV	1.69	0.84-3.39	0.13			
Moderate or severe TR	1.36	0.95–1.96	0.08			
CPB time, minutes	1.01	0.99–1.02	0.22			
ACC time, minutes	1.01	0.99–1.04	0.19			
Pre-PVR examination parameters						
RVEDVI, mL/m^2	1.02	1.00–1.03	0.038			
RVESVI, mL/m^2	1.02	1.00–1.04	0.035			
RVEF, %	1.03	1.01–1.12	0.042	0.99	0.95–1.01	0.32
PR fraction, %	0.97	0.91–1.04	0.49			
LVEDVI, mL/m^2	1.02	0.99–1.05	0.14			
LVESVI, mL/m^2	1.05	1.00–1.10	0.030	1.05	1.00–1.10	0.034
LVEF, %	1.02	1.00–1.14	0.026			
QRS duration, ms	1.01	0.99–1.03	0.18			

ACC, aortic cross-clamp; CPB, cardiopulmonary bypass; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVR, pulmonary valve replacement; PR, pulmonary regurgitation; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; TOF, tetralogy of Fallot; TR, tricuspid regurgitation.

p=0.99). Left ventricular ejection fraction (LVEF) increased by 12% early after PVR (48.1 ± 7.8 vs. 53.8 ± 6.6 %, $p < 0.001$) and continued the improvement of 4% at midterm follow-up (53.8 ± 6.6 vs. 56.1 ± 6.4 %, $p < 0.001$).

Figure 3 demonstrates the correlations between pre- and midterm post-PVR CMR parameters. Pre-PVR RV volumes were associated with midterm post-PVR RV volumes (RVEDVI, $r = 0.65$, $p < 0.001$; RVESVI, $r = 0.68$, $p < 0.001$). Lower midterm post-PVR RVEF was associated with increasing pre-PVR and midterm post-PVR RVESVI. Lower midterm post-PVR LVEF was associated with lower midterm post-PVR RVEF ($r = 0.54$, $p < 0.001$).

Factors Associated With ACO After PVR

Age at TOF repair, age at PVR, transannular repair, New York Heart Association (NYHA) function class III or IV, moderate or severe TR, CPB time, ACC time, and pre-PVR examination parameter were included in the univariable analysis. Among parameters of pre-PVR examination, larger RVEDVI [hazard ratio (HR) = 1.02, 95% confidence interval (CI) 1.00–1.03; $p = 0.038$], larger RVESVI (HR = 1.02, 95% CI 1.00–1.04; $p = 0.035$), lower RVEF (HR = 1.03, 95% CI 1.01–1.12; $p = 0.042$), lower LVESVI (HR = 1.05, 95% CI 1.00–1.10; $p = 0.030$), and lower LVEF (HR = 1.02, 95% CI 1.00–1.14; $p = 0.026$) were associated with ACO in the univariable analysis. In the multivariable analysis, however, lower preoperative LVESVI was identified as a sole independent risk factor for ACO (**Table 4**).

DISCUSSION

Our study demonstrated an acceptable midterm outcome of PVR with reversible RV remodeling in patients with rTOF. Freedom from ACO at 3 and 5 years was 88 and 58%, respectively. Notably, we observed a remarkable reduction of RV volumes on CMR through a follow-up of 4.7 years, accompanied by a significant improvement in RV and LV function.

Midterm Outcomes of PVR

With the increasing emphasis on cut-off values of preoperative RV volume in determining the optimal timing of PVR, a proactive approach is predominating the surgical strategy for patients with rTOF (18–21). Therein, the improved event-free survival rate was encouraging. Cheung et al. (7) reported low operative mortality of 1% to 4% for PVR, and our study has confirmed this finding. Also consistent with previous studies (2, 10, 22–25), we showed a favorable midterm ACO-free survival of 88.1% at 3 years. Impaired LV function (LVEF < 50%) and large RV volumes (RVEDVI > 150 ml/m^2) were documented in those four patients with sustained ventricular tachycardia before PVR. Our results might correspond with the finding of earlier studies showing that PVR did not reduce the occurrence of ventricular arrhythmias, particularly for those with high preoperative RV volumes and LV impairment (12, 26). Nevertheless, careful surveillance and routine ECGs examinations during follow-up are warranted for adult patients with rTOF.

RV and LV Reverse Remodeling

On CMR, we demonstrated the marked reduction of RV volumes and improvement of biventricular function during the follow-up time of 4.7 years. Hallbergson et al. (27) reported similar results of early reduction in RVEDVI and RVESVI. In accordance with their findings, a subsequent decline of RV volume might not occur after PVR, and even a gradual rebound of RV volume toward preoperative values would take place, for which the late deterioration of implanted pulmonary valve could be to blame. On the contrary, the continued improvements of RV size and function were found by midterm follow-ups in this series. These different changes might correlate with the decreased occurrence of late prosthetic valve failure, given favorable freedom from repeat PVR and pulmonary valve failure and dysfunction at 3 and 5 years (97.6 and 92.5%, respectively). Meanwhile, Heng et al. (14) revealed that rapid reduction of RV volumes after PVR might be followed by time-dependent biological remodeling by midterm follow-up. Our data supported this finding. As the ongoing improvement of RV function, however, seemed to appear a "slow-down" reduction of both RVEDVI and RVESVI from the early post-PVR period to midterm follow-up. Considering the close correlation between lower RVEF and higher RVESVI, our findings indicated that post-PVR RV normalization might occur in a time-dependent sequence from ventricular dilation to remodeling.

Of note, although the majority (83%) of patients regained normal RV volume, RV normalization merely occurred in half of the study population. This might imply that too much emphasis on preoperatively RVEDVI would be insufficient for predicting RV normalization after PVR. After all, achieving RV normalization is important for the improvement of long-term outcomes (4, 23). Meanwhile, we observed a close correlation between the progressive reduction of RVESVI and continued improvement of RVEF, justifying the potential use of RVESVI in predicting the intrinsic RV normalization. Additionally, larger RVESVI and lower RVEF were identified to be associated with ACO in the univariable analysis. In summary, our findings verified the diagnostic combination of preoperative RVESVI and RVEF in determining the optimal timing of PVR, which calls into question the current focus on CMR-based pre-PVR threshold values of RVEDVI that predicts RV normalization.

Previous studies have suggested the association between reverse RV remodeling and improvement of LV function (9, 28, 29). In our study, we also found that higher LVEF was associated with increasing RVEF by midterm follow-up. With pulmonary valve competency restored by PVR, normalized RV cardiac output leads to increased LV filling and volumes, and resultant increased LVEF?that is, the positive interaction between RV and LV. This might explain the symptomatic benefits of our patients, wherein the majority (95%) of them had regained normal exertion capacity in NYHA class I or II by midterm follow-up.

Predictors of ACO After PVR

In this study, predictors of ACO including larger preoperative RV volume, depressed RV function, and lower LV function were identified in the univariate analysis, which was consistent with reported findings of previous studies (13, 18, 30, 31). Interestingly, age at PVR for predicting adverse outcomes is still sparking debate. Jang et al. (32) found that early PVR might decrease the durability of implanted valves. Conversely, Lee et al. (30) reported that patients with older age at TOF repair and older age at PVR were at increased risk for ACO. These two factors, however, were not found to be associated with ACO in our study. The median time interval between TOF repair and PVR in this cohort was 16.4 years, which was in line with the previously suggested time interval of 20 years after TOF repair (33). Similar to previous studies describing the prognostic value of LV function in rTOF (14, 31), lower LVESVI was identified as an independent risk factor for ACO.

LIMITATIONS

By design, this cohort is restricted to patients who had undergone three complete CMR. Patients with incomplete CMR or contraindications to CMR were excluded, which certainly reduce the population size. Additionally, since the majority of variables were time-dependent, the time interval between PVR and postoperative CMR study is another significant limitation of our study. A long-term follow-up on the continuous benefits of PVR is warranted.

CONCLUSIONS

The midterm outcome of PVR in patients with repaired TOF was favorable with the improvement of biventricular function. Preoperative LVESVI on CMR was the independent predictor for adverse clinical outcomes after PVR.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FH, ZF, and SL conceived and designed the research. JY, KM, and SZ performed the research. KY and SL performed the surgery. ML analyzed the cardiovascular magnetic resonance data. FH and ZF analyzed the data and wrote the article. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.864455/full#supplementary-material

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Prevalence of Congenital Heart Disease in Chinese Children With Different Birth Weights and Its Relationship to the Neonatal Birth Weight

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Objective: This study aimed to examine the prevalence and the related risk factors of congenital heart disease (CHD) in children with different birth weights in China and the relationship between the subtypes of CHD and birth weight (BW).

Methods: This study conducted a cross-sectional survey on the data collected in the children's congenital heart disease database (CHDD) established in China. This database contained data from one Grade A, Level III Children's Public Hospital in Zhengzhou, Henan. The study included all the children and their parents in the database from 2014 to 2020 as the study subjects, and the missing data were processed by means of imputation. Diagnoses of CHD were coded using the International Classification of Diseases version 10 (ICD-10), and subtypes were classified by the codes Q20 to Q26. We reported the prevalence of CHD based on birth weight and gestational age and analyzed the related risk factors for children with CHD in different birth weight groups and factors for children of the same birth weight groups between the CHD groups and the non-CHD groups. The generalized linear model was used to assess the association between the subtypes of CHD and BW by establishing three adjusting models, and the data were stratified for further analysis by urban-rural and infant gender.

Results: A total of 42,814 children were identified as having CHD among 5,071,799 live children; the overall prevalence of CHD was 8.44 per 1,000 live births during 2014–2020; and the three subtypes with the highest prevalence of CHD were atrial septal defect (ASD) (2.75‰), ventricular septal defect (VSD) (2.57‰), and patent foramen ovale (PFO) (1.12‰). The prevalence of CHD was 18.87‰ in the group with BW <1,500 g, 12.84‰ in the group with BW 1,500–2,500 g, 8.24‰ in the group with BW 2,500–4,000 g, and 4.80‰ in the group with BW ≥4,000 g. The prevalence of CHD was 16.62‰ in the small for gestational age (SGA) group, 6.99‰ in the appropriate for gestational age (AGA) group, and 6.40‰ in the larger for gestational age (LGA) group.

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Parental factors such as drinking, smoking, viral infections, peri-pregnancy exposure to radioactive substances, low family monthly expenditure, and low Apgar scores at 1 and 5 min were related to the increased risk of CHD in the offspring. Parental supplementation of folic acid and exercise during the peri-pregnancy period could reduce the risk of CHD in the offspring. The results of Model 3 adjusting for confounding variables showed that infants with ASD had a birth weight 461 g lower (95% CI: −1,085, −128), infants with VSD had a birth weight 426 g lower (95% CI: –932, –120), infants with tetralogy of Fallot (TOF) had a birth weight 532 g lower (95% CI: –987, –168), and without classification, infants with CHD had a birth weight 973 g lower (95% CI: –1,502, –204).

Conclusion: In very low birth weight (VLBW) and low birth weight (LBW) infants, CHDs are more prevalent than in the general live-born population. Moreover, some peri-pregnancy factors of parents are closely related to the occurrence of CHD in offspring; different types of heart defects can lead to LBW. Therefore, if the fetus is found to have a heart defect during the prenatal examination, the mother should pay more attention to maintaining weight and ensuring that the fetus is within the normal weight range, thereby increasing the postpartum survival rate, reducing complications, and promoting children's health.

Keywords: congenital heart disease, birth weight, prevalence, special disease database, children

INTRODUCTION

Congenital heart disease (CHD) is one of the most common congenital malformations. It refers to the abnormal anatomy caused by the formation of the heart and large blood vessels during the development of the embryo, or abnormal development, or channel that should be closed but failed to shut down after birth (1). It was reported that the global average prevalence of CHD at birth was 5–9 per 1,000 births; however, CHD frequencies were as high as 20–40/1,000 in very low birth weight (VLBW) babies weighing less than 1,500 g (2). The etiology of most CHD is not fully understood, but it is likely to involve complex interactions between environmental and genetic factors (3, 4). Similarly, the etiology for low birth weight (LBW) is also exceedingly broad and wide-ranging.

Some studies have shown that there is an association between CHD and LBW, which is a known comorbidity of CHD. A study based on the population of Sudan shows that infants with CHD are 2.6 times more likely to develop LBW than the general Sudanese population (5). CHDs that caused a decrement in birth weight in a descending order of severity are atrial septal defect (721 g/23%), patent ductus arteriosus (669 g/21%), ventricular septal defect (610 g/19%), pulmonary stenosis (548 g/13%), and tetralogy of Fallot (248 g/8%) (5). In addition, the prevalence of CHD in very premature/VLBW infants is higher than that of general live births, and it is independent of other risk factors and causes death and serious complications (6–8).

In China, the prevalence of CHD varies from 7 to 22.9 per 1,000 live births or perinatal infants (9–13), causing serious disease and economic burden to society and families. However, there are few reports on the prevalence of CHD in infants with birth weights less than 2,500 g and more than 4,000 g, and there is a lack of relevant research on the relationship between CHD and LBW. Therefore, it is necessary to conduct a detailed epidemiological investigation of CHD in children with different birth weights in China. This study aimed to determine the prevalence of CHD in very low birth weight infants, low birth weight infants, and giant infants by using the congenital heart disease database (CHDD) established in China containing detailed clinical data. Related risk factors and possible confounding factors were adjusted to further explore the relationship between CHD and birth weight.

MATERIALS AND METHODS

Sources and Subjects

This study conducted a cross-sectional survey on the data collected from the children's CHDD established in China. The database center was established by a university-affiliated children's hospital in Henan Province, China (Grade A, Level III Children's Public Hospital in Zhengzhou, Henan). The CHDD contained childbirth information, such as date of birth, birth weight, feeding method, congenital abnormalities, apgar score of newborn, current health status, and medical history data, and parental sociodemographic information, such as maternal perinatal information (parity, gestational week, and mode of delivery), parents' socioeconomic factors (age, household registration, occupation, education level, and family monthly expenditure), parents' lifestyle factors (folic acid supplementation, smoking, drinking, and exercise habits during pregnancy), parents' exposure to virus, toxic, and harmful

substances, and radioactive substances during the perinatal period. The CHDD was connected to the doctor's medical record system, which could simultaneously obtain the child's birth information, medical treatment, and record data. The sociodemographic information of the parents was obtained by the investigator through questionnaires and imported into the database in real-time. Data had been collected since 2014; all data were collected prospectively by the hospital data management center, which was equipped with 10 data management specialists for real-time data quality inspections; and then the supervisor completed the review before the data were locked every year.

The study included all the children and their parents in the database from 2014 to 2020 as the study subjects, excluding those with insufficient medical records, transfers after birth, and those who did not want to participate in the study. The study was reviewed and approved by the Ethics Committee of Zhengzhou University, and all respondents signed informed consent. The whole process and all methods of the study were performed in accordance with the relevant guidelines and regulations for the construction of clinical diagnosis and treatment and clinical research ethics review committees.

Newborn Birth Weight (g) and Diagnosis of Congenital Heart Disease

The birth weight of the newborn was collected by the birth certificate, or the weight was directly measured: after birth, the body was dried, the package was removed, the naked body was placed on the electronic scale, and the stable data were read. The accuracy of the scale was 1 g. When the newborn weighed <1,500 g, it was defined as very low birth weight (VLBW) infant; when the newborn weighed 1,500–2,500 g, it was defined as low birth weight (LBW) infant; when the newborn birth weighed 2,500–4,000 g, it was defined as normal weight infant (NBW); and when the newborn weighed ≥4,000 g, it was defined as macrosomia (14). Referring to the revised report on the birth weight of newborns of different gestational ages in China, the newborns were divided into three categories according to the relationship between birth weight and gestational age: infants were defined as small for gestational age (SGA) when birth weight was below the 10th percentile (P_{10}) of the average gestational age; infants with birth weight above the 90th percentile (P_{90}) of the same gestational age were defined as larger for gestational age (LGA); and between P_{10} and P_{90} of the same gestational age was appropriate for gestational age (AGA) (15).

In this study, those with positive records of prenatal echocardiography or with abnormal findings in CHD screening were offered neonatal ultrasound screening for CHD. The final diagnosis was based on neonatal echocardiographic findings from a scan and confirmed by the pediatrician. Diagnoses of CHD were coded using the International Classification of Diseases version 10 (ICD-10), and subtypes were classified by the codes Q20–Q26 (16). We defined 13 types of CHD, including atrial septal defect (ASD, Q21.102); ventricular septal defect (VSD, Q21.001); patent foramen ovale (PFO, Q21.103); patent ductus arteriosus (PDA, Q25.001); tetralogy of Fallot (TOF, Q21.300); atrioventricular septal defect (AVSD, Q21.200); pulmonary valve stenosis (PS, Q22.101); tricuspid regurgitation (TR, Q22.801); pulmonary hypertension (PHT, Q25.751); coarctation of the aorta (COA, Q25.300); mitral regurgitation (MR, Q23.300); aortic valve stenosis (AOS, Q23.001); transposition of great vessels (TGA, Q20.302), and other classification was not clear. In the case of multiple diagnoses in one patient, a prespecified hierarchical scheme founded on a consensus-based classification of defect severity was used, by means of which the diagnosis with the worst prognosis was established as the main diagnosis.

Statistical Analysis

Data were electronically registered. The prevalence of CHD in children with different birth weights was shown as the number of cases per 1,000 births, and any type of CHD was calculated as the total prevalence of CHD per 1,000 births. The continuous variables were statistically described by mean ($\bar{X}$) and standard deviation (*SD*) and median (*M*) and quartile (Q_1~Q_3); categorical variables were described by composition ratio and rate. For missing values, we used the mean padding method for processing. The X^2 test or, when appropriate, Fisher's exact test was used to compare the prevalence of various types of congenital heart disease in different birth weight groups and characteristics of children with CHD at different birth weight groups and characteristics of children of the same birth weight groups between CHD and non-CHD groups. Chi-square trend analysis was used to track changes in the prevalence of CHD over time. The means were compared by one-way ANOVA; medians were compared with the Wilcoxon Mann–Whitney rank-sum test. The generalized linear model was used to analyze the relationship between BW and each subtype of CHD, taking BW as the dependent variable, whether each subtype of CHD was diseased as an independent variable, and adjusting possible confounding factors. The research model was as follows: $g(\mu i) = \beta_0 + \beta_1 x$ (whether each subtype of CHD was diseased) + $\beta_2 x$ (adjusted variable) + εi. Three models were mainly established as follows: Model 1: no variable was adjusted; Model 2: adjusting fetal sex, gestational age, gravidity, parity, and apgar score at 1 min and 5 min; Model 3: on the basis of Model 2, continuing to adjust the parents' age, residence (urban and rural), education level, occupation, folic acid supplementation, whether drink, smoke, viral infection, radioactive material exposure, doing physical exercise or not, and family monthly expenditure. And the data were stratified for further analysis by urban-rural and infant gender in the gender-specific model; the baby's gender was no longer adjusted. These analyses were performed using SAS.9.4 and SPSS25.0; the drawing process was carried out using Microsoft Office 2010 Excel and GraphPad Prism software. *P* values < 0.05 (two-sided) were considered statistically significant, unless indicated otherwise.

RESULTS

Patients' Characteristics and Time Trends of Congenital Heart Disease With Different Birth Weights

From January 2014 to December 2020, a total of 42,814 children were identified as having CHD among 5,071,799 live children.

The mean age of children was 6.4 ± 2.2 months. The overall prevalence of CHD was 8.44 per 1,000 live births. The total number of live births with VLBW was 112,560, the number of patients with CHD was 2,124, and the prevalence of CHD was 18.87 per 1,000 live births. The number of LBW newborns was 160,047, the number of patients with CHD was 2,055, and the prevalence of CHD was 12.84 per 1,000 live births. The number of NBW newborns was 4,541,238, the total number of patients with CHD was 37,405, and the prevalence of CHD was 8.24 per 1,000 live births. A total of 256,250 newborns with birth weight ≥4,000 g, the number of children with CHD was 1,230, and the prevalence of CHD was 4.80 per 1,000 live births. The total number of SGA was 786,129, the number of children with CHD was 13,062, and the prevalence of CHD was 16.62 per 1,000 live births. The total number of AGA was 3,950,931, the number of children with CHD was 27,608, and the prevalence of CHD was 6.99 per 1,000 live births. The total number of LGA was 331,875, the number of children with CHD was 2,142, and the prevalence of CHD was 6.40 per 1,000 live births (**Table 1**).

The prevalence of CHD in the group with birth weight <1,500 g increased from 12.81 per 1,000 births in 2014 to 20.65 per 1,000 births in 2020 (X^2 trend = 125.62, $P < 0.001$). The prevalence of CHD in the group with birth weight 1,500–2,500 g increased from 5.22 per 1,000 births in 2014 to 18.33 per 1,000 births in 2020 (X^2 trend = 98.37, $P < 0.001$). The prevalence of CHD in the group with birth weight 2,500–4,000 g increased from 3.92 per 1,000 births in 2014 to 10.91 per 1,000 births in 2020 (X^2 trend = 85.23, $P < 0.001$). The prevalence of CHD in the group with birth weight ≥4,000 g increased from 1.82 per 1,000 births in 2014 to 6.41 per 1,000 births in 2020 (X^2 trend = 80.19, $P < 0.001$). It was worth noting that the prevalence of CHD in each birth weight group had a peak in 2017 (**Figure 1**).

Prevalence of Different Subtypes of Congenital Heart Disease by Birth Weight

Overall, the three subtypes with the highest prevalence of CHD were ASD (2.75‰), VSD (2.57‰), and PFO (1.12‰). In the VLBW group, the three subtypes with the highest prevalence of CHD were TOF (5.73‰), VSD (4.23‰), and ASD (3.55‰). In the LBW group, the three subtypes with the highest prevalence of CHD were PFO (2.84‰), TOF (2.05‰), and PHT (2.05‰). In the NBW group, the three subtypes with the highest prevalence of CHD were ASD (2.52‰), VSD (2.28‰), and PFO (1.26‰). In the macrosomia group, the three subtypes with the highest prevalence of CHD were PFO (1.33‰), VSD (0.98‰), and ASD (0.87‰). Comparing the prevalence of various types of congenital heart disease within different birth weight groups, there were differences in the prevalence of ASD, VSD, PFO, PDA, TOF, AVSD, and PHT among different weight groups. In the group of SGA, the three subtypes with the highest prevalence of CHD were TOF (3.36‰), ASD (2.57‰), and VSD (2.19‰). In the group AGA, the three subtypes with the highest prevalence of CHD were ASD (2.11‰), VSD (1.92‰), and PFO (1.00‰). In the group of LGA, the three subtypes with the highest prevalence of CHD were PFO (1.84‰), VSD (1.30‰), and ASD (1.09‰). Comparing the prevalence of different types of congenital heart disease in different gestational age groups of birth weights, it was found that there were differences in the prevalence among SGA, AGA, and LGA groups (**Table 1**).

Risk Factors Related to Congenital Heart Disease

Table 2 shows that the influencing factors of children with CHD in different birth weight groups included maternal characteristics (gestational age, mother's place of residence, educational levels, folic acid supplementation status, and doing physical exercise during pregnancy and 3 months before pregnancy), paternal characteristics (father's place of residence, drinking status, smoking status, folic acid supplementation status before pregnancy, and doing physical exercise 3 months before pregnancy), family monthly expenditure, and child factors (apgar score at 1 and 5 min). Mothers tended to be full-term when they gave birth, and the higher the proportion of urban residents and taking folic acid supplements and doing exercise, the higher the education level; the higher the proportion of fathers living in cities and taking folic acid supplements and doing exercise, the lower the proportion of alcohol drinkers and smokers were lower; the higher the monthly family expenditure, the higher the apgar scores of 1 min and 5 min; and the more children with CHD tended to have a normal birth weight.

Further analysis showed that factors that differed between those with and without CHD in the VLBW group included parents' characteristics (maternal and paternal viral infection, drinking status, radioactive material exposure, folic acid supplementation status, and maternal smokes status), family monthly expenditure, and child factors (apgar score at 1 min). The factors that differed between those with and without CHD in the LBW group included parents' characteristics (maternal and paternal drinking status, smoking status, radioactive material exposure, folic acid supplementation status, and maternal viral infection), family monthly expenditure, and child factors (apgar score at 1 min and 5 min). The factors that differed between those with and without CHD in the NBW and macrosomia group were identical, including parents' characteristics (maternal and paternal viral infection, drinking status, smoking status, radioactive material exposure, folic acid supplementation status, and maternal educational levels) and child factors (apgar score at 5 min) (**Table 3**).

The Relationship Between Different Subtypes of Congenital Heart Disease and Birth Weight

In the absence of stratified analysis, the ASD, VSD, TOF, and total CHD status had a statistically significant detrimental effect on birth weight in Model 1; after adjusting for some confounding factors (Model 2), similar results were still obtained; and after further adjusting for other confounding factors (Model 3), the results had not changed. On average, infants with ASD had a birth weight 461 g lower (95% CI: –1,085, –128), infants with VSD had a birth weight 426 g lower (95% CI: –932, –120), infants with TOF had a birth weight 532 g lower (95% CI: –987, –168),

TABLE 1 | Prevalence of different subtypes of congenital heart disease by birth weight (average prevalence from 2014 to 2020).

Subgroup	Total		Grouped by birth weight									Grouped by birth weight and gestational age						
			<1500 g		1500~2500 g		2500~4000 g		≥4000 g		*P* value	SGA		AGA		LGA		*P* value
	n	‰	*n*	‰	*n*	‰	*n*	‰	*n*	‰		*n*	‰	*n*	‰	*n*	‰	
ASD/Q21.102	1994	2.75	57	3.55^{a,c}	39	1.70^{a,e}	1635	2.52^{f}	32	0.87^{c,e,f}	**<0.001**	289	2.57^{①,②}	1191	2.11^{①,③}	52	1.09^{②,③}	**<0.001**
VSD/Q21.001	1865	2.57	68	4.23^{a,b,c}	38	1.66^{a}	1480	2.28^{b,f}	36	0.98^{c,f}	**<0.001**	246	2.19^{②}	1085	1.92^{③}	62	1.30^{②,③}	**0.001**
PFO/Q21.103	813	1.12	17	1.06^{a}	65	2.84^{a,d,e}	818	1.26^{d}	49	1.33^{e}	**<0.001**	188	1.67^{①}	564	1.00^{①,③}	88	1.84^{③}	**<0.001**
PDA/Q25.001	587	0.81	13	0.81^{c}	22	0.96^{e}	460	0.71^{f}	5	0.14^{c,e,f}	**<0.001**	162	1.44^{①,②}	300	0.53^{①,③}	9	0.19^{②,③}	**<0.001**
TOF/Q21.300	379	0.52	92	5.73^{a,b,c}	47	2.05^{a,d,e}	278	0.43^{b,d}	26	0.71^{c,e}	**<0.001**	377	3.36^{①,②}	162	0.29^{①,③}	46	0.96^{②,③}	**<0.001**
AVSD/Q21.200	294	0.41	35	2.18^{a,b,c}	17	0.74^{a}	257	0.40^{b}	12	0.33^{c}	**<0.001**	174	1.55^{①,②}	347	0.61^{①,③}	10	0.21^{②,③}	**<0.001**
PS/Q22.101	73	0.10	6	0.37	6	0.26	123	0.19	2	0.05	0.069	80	0.71^{①,②}	122	0.22^{①}	3	0.06^{③}	**<0.001**
TR/Q22.801	43	0.06	6	0.37	4	0.17	91	0.14	8	0.22	0.074	80	0.71^{①,②}	79	0.14^{①}	13	0.27^{③}	**<0.001**
PHT/Q25.751	18	0.02	3	0.19^{a}	47	2.05^{a,d,e}	69	0.11^{d}	2	0.05^{e}	**<0.001**	82	0.73^{①,②}	39	0.07^{①}	3	0.06^{③}	**<0.001**
COA/Q25.300	15	0.02	2	0.12	3	0.13	37	0.06	0	0.00	0.140	19	0.17^{①}	0	0^{①,③}	2	0.04^{③}	**<0.001**
MR/Q23.300	12	0.02	2	0.12	2	0.09	32	0.05	0	0.00	0.231	41	0.37^{①,②}	28	0.05^{①}	1	0.02^{②}	**<0.001**
AOS/Q23.001	9	0.01	1	0.06	1	0.04	27	0.04	4	0.11	0.316	71	0.63^{①,②}	20	0.04^{①,③}	15	0.31^{②,③}	**<0.001**
TGA/Q20.302	7	0.01	1	0.06	1	0.04	21	0.03	0	0.00	0.626	37	0.33^{①,②}	0	0^{①,③}	1	0.02^{②,③}	**<0.001**
Other	7	0.01	0	0.00	2	0.09	16	0.02	1	0.03	0.291	6	0.05^{①}	7	0.01^{①}	1	0.02	**0.017**
Total	6116	8.44	303	18.87^{a,b,c}	294	12.84^{a,d,e}	5344	8.24^{b,d,f}	177	4.80^{c,e,f}	**<0.001**	1866	16.62^{①,②}	3944	6.99^{①}	306	6.40^{②}	**<0.001**

ASD, atrial septal defect; VSD, ventricular septal defect; PFO, patent foramen ovale; PDA, patent ductus arteriosus; TOF, tetralogy of Fallot; AVSD, atrioventricular septal defect; PS, pulmonary valve stenosis; TR, tricuspid regurgitation; PHT, pulmonary hypertension; COA, coarctation of the aorta; MR, mitral regurgitation; AOS, aortic valve stenosis; TGA, transposition of great vessels; Other, classification is not clear. [a]A difference between the <1,500 g group and the 1,500–2,500 g group; [b]A difference between the <1,500 g group and the 2,500–4,000 g group; [c]A difference between the <1,500 g group and the ≥4,000 g group; [d]A difference between the 1,500–2,500 g group and the 2,500–4,000 g group; [e]A difference between the 1,500–2,500 g group and the ≥4,000 g group; [f]A difference between the 2,500–4,000 g group and the ≥4,000 g group; [①]A difference between the SGA group and the AGA group; [②]A difference between the SGA group and the LGA group; [③]A difference between the AGA group and the LGA group. The bold values in the tables represent statistically significant differences.

and without classification, infants with CHD had a birth weight 973 g lower (95% CI: −1,502, −204). After stratifying by gender of children, among boys, multiple models showed that VSD and TOF had significant adverse effects on birth weight. Infants with VSD were associated with a mean loss of birth weight of 467 g (95% CI: −1,052, −117), and infants with TOF were associated with a mean loss of birth weight of 1,056 g (95% CI: −1,424, −537) in Model 3. Among girls, multiple models showed that ASD, TOF, and total CHD had significant adverse effects on birth weight. Infants with ASD were associated with a mean loss of birth weight of 738 g (95% CI: −1,519, −295), infants with TOF were associated with a mean loss of birth weight of 544 g (95% CI: −906, −194), and infants with CHD were associated with a mean loss of birth weight of 812 g (95% CI: −1,359, −285) in Model 3. In addition, infants with PDA were associated with a mean loss of birth weight of 283 g (95% CI: −511, −55) only in Model 3 (**Table 4**).

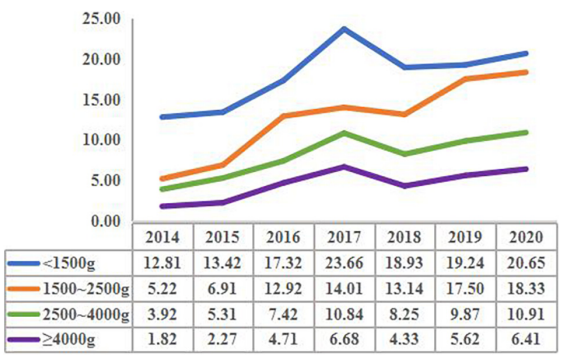

FIGURE 1 | The prevalence of congenital heart disease in children with different birth weights in different years (per 1,000 births).

After stratified by residence, children with urban households showed that TOF and total CHD had a significant adverse effect on birth weight under multiple models. On average, infants with TOF had a birth weight 875 g lower (95% CI: −1,406, −293), and infants with CHD had a birth weight 649 g lower (95% CI: −1,125, −160) in Model 3. In addition, infants with ASD had a birth weight 507 g lower (95% CI: 1,033, −147), and infants with VSD had a birth weight 345 g lower (95% CI: −764, −96) only in Model 3. For rural children, the ASD, VSD, TOF, and total CHD status had a statistically significant detrimental effect on birth weight in multiple models. Infants with ASD would cause an average reduction in birth weight of 688 g (95% CI: −1,241, −133), infants with VSD would cause an average weight loss of 392 g (95% CI: −677, −123), infants with TOF would cause an average weight loss of 631 g (95% CI: −1,181, −193), and infants with CHD would cause an average weight loss of 879 g (95% CI: −1,367, −234) in Model 3 (**Figure 2**).

DISCUSSION

At present, there have been some reports on the prevalence of CHD in LBW infants and premature infants, and some

TABLE 2 | Characteristics of children with congenital heart disease at different birth weight groups (*N* = 42,814).*

Characteristics	VLBW with CHD (*n* = 2124)	LBW with CHD (*n* = 2055)	NBW with CHD (*n* = 37405)	Macrosomia with CHD (*n* = 1230)	*P* value
Gestational age (week, $\bar{x} \pm s$)	28.5 ± 2.3	33.4 ± 1.5	39.5 ± 1.0	39.8 ± 1.2	**<0.001**
Maternal place of residence (n(%))					
Urban	266 (12.5)	399 (19.4)	11334 (30.3)	305 (24.8)	**0.018**
Rural	1858 (87.5)	1656 (80.6)	26071 (69.7)	925 (75.2)	
Maternal educational levels (n(%))					
Elementary school and below	601 (28.3)	567 (27.6)	6134 (16.4)	312 (25.4)	**0.035**
Junior high school	1266 (59.6)	1198 (58.3)	6883 (18.4)	426 (34.6)	
High school and secondary school	193 (9.1)	214 (10.4)	18777 (50.2)	387 (31.5)	
University degree and above	64 (3.0)	76 (3.7)	5611 (15.0)	105 (8.5)	
Maternal folic acid supplementation or not (n(%))#					
Yes	652 (30.7)	783 (38.1)	27867 (74.5)	694 (56.4)	**<0.001**
No	1472 (69.3)	1272 (61.9)	9538 (25.5)	536 (43.6)	
Mother doing physical exercise during pregnancy (n(%))					
Yes	280 (13.2)	341 (16.6)	14401 (38.5)	119 (9.7)	**0.037**
No	1844 (86.8)	1714 (83.4)	23004 (61.5)	1111 (90.3)	
Mother doing physical exercise 3 months before pregnancy (n(%))					
Yes	335 (15.8)	403 (19.6)	17019 (45.5)	140 (11.4)	**0.030**
No	1789 (84.2)	1652 (80.4)	20386 (54.5)	1090 (88.6)	
Paternal place of residence (n(%))					
Urban	316 (14.9)	477 (23.2)	11410 (30.5)	308 (25.0)	**0.018**
Rural	1808 (85.1)	1578 (76.8)	25995 (69.5)	922 (75.0)	
Father drinks or not (n(%))					
Yes	1703 (80.2)	1510 (73.5)	15500 (41.4)	657 (53.4)	**0.005**
No	421 (19.8)	545 (26.5)	21905 (58.6)	573 (46.6)	
Father smokes or not (n(%))					
Yes	1769 (83.3)	1654 (80.5)	25735 (68.8)	940 (76.4)	**0.038**
No	355 (16.7)	401 (19.5)	11670 (31.2)	290 (23.6)	
Paternal folic acid supplementation or not before pregnancy (n(%))					
Yes	406 (19.1)	462 (22.5)	19300 (51.6)	503 (40.9)	**0.016**
No	1718 (80.9)	1593 (77.5)	18105 (48.4)	727 (59.1)	
Father doing physical exercise 3 months before pregnancy (n(%))					
Yes	542 (25.5)	748 (36.4)	21620 (57.8)	248 (20.2)	**0.035**
No	1582 (74.5)	1307 (63.6)	15785 (42.2)	982 (79.8)	
Family monthly expenditure (¥, $\bar{x} \pm s$)	2378.5 ± 362.3	2431.2 ± 276.4	2998.6 ± 430.7	2556.3 ± 379.2	**0.023**
Apgar score at 1 min (M, P_{25}–P_{75})	5 (3–6)	5 (4–7)	6 (4–8)	6 (3–8)	**0.002**
Apgar score at 5 min (M, P_{25}–P_{75})	7 (5–8)	7 (6–8)	8 (7–9)	8 (6–9)	**0.001**

**Only statistically significant variables are shown; #replenish folic acid for at least 3 months before or during pregnancy. The bold values in the tables represent statistically significant differences.*

TABLE 3 | Characteristics of children of the same birth weight between CHD and non-CHD groups.*

A

Characteristics	VLBW with CHD (*n* = 2124)	VLBW with Non-CHD (*n* = 110279)	*P* value	LBW with CHD (*n* = 2055)	LBW with Non-CHD (*n* = 158265)	*P* value
Maternal viral infection (n(%))						
Yes	266 (12.5)	18196 (16.5)	**0.043**	399 (19.4)	37984 (24.0)	**0.015**
No	1858 (87.5)	92083 (83.5)		1656 (80.6)	120281 (76.0)	
Mother drinking or not (n(%))						
Yes	200 (9.4)	3419 (3.1)	**<0.001**	154 (7.5)	3640 (2.3)	**<0.001**
No	1924 (90.6)	106860 (96.9)		1901 (92.5)	154625 (97.7)	
Mother smoking or not (n(%))						
Yes	164 (7.7)	2757 (2.5)	**<0.001**	115 (5.6)	3165 (2.0)	**0.001**
No	1960 (92.3)	107522 (97.5)		1940 (94.4)	155100 (98.0)	
Maternal radiation material exposure (n(%))						
Yes	134 (6.3)	2095 (1.9)	**<0.001**	105 (5.1)	2849 (1.8)	**0.005**
No	1990 (93.7)	108184 (98.1)		1950 (94.9)	155416 (98.2)	
Maternal folic acid supplementation or not (n(%))#						
Yes	652 (30.7)	61205 (55.5)	**0.016**	783 (38.1)	95750 (60.5)	**0.011**
No	1472 (69.3)	49074 (44.5)		1272 (61.9)	62515 (39.5)	
Paternal viral infection (n(%))						
Yes	316 (14.9)	19519 (17.7)	**0.047**	477 (23.2)	40199 (25.4)	0.058
No	1808 (85.1)	90760 (82.3)		1578 (76.8)	118066 (74.6)	
Father drinking or not (n(%))						
Yes	1703 (80.2)	74218 (67.3)	**0.038**	1510 (73.5)	95909 (60.6)	**0.027**
No	421 (19.8)	36061 (32.7)		545 (26.5)	62356 (39.4)	
Father smoking or not (n(%))						
Yes	1769 (83.3)	88333 (80.1)	0.079	1654 (80.5)	110786 (70.0)	**0.031**
No	355 (16.7)	21946 (19.9)		401 (19.5)	47479 (30.0)	
Paternal radiation material exposure (n(%))						
Yes	89 (4.2)	1434 (1.3)	**0.007**	68 (3.3)	1583 (1.0)	**0.018**
No	2035 (95.8)	108845 (98.7)		1987 (96.7)	156682 (90.0)	
Paternal folic acid supplementation or not before pregnancy (n(%))						
Yes	406 (19.1)	31430 (28.5)	**0.031**	462 (22.5)	56501 (35.7)	**0.037**
No	1718 (80.9)	78849 (71.5)		1593 (77.5)	101764 (64.3)	
Family monthly expenditure (¥, $\bar{x}\pm s$)	2378.5 ± 362.3	2597.6 ± 303.1	**0.013**	2431.2 ± 276.4	2771.3 ± 315.9	**0.005**
Apgar score at 1 min (M, P_{25}–P_{75})	5 (3–6)	6 (3–8)	**0.027**	5 (4–7)	6 (4–8)	**0.018**
Apgar score at 5 min (M, P_{25}–P_{75})	7 (5–8)	7 (4–9)	0.058	7 (6–8)	8 (7–9)	**0.003**

B

Characteristics	NBW with CHD (*n* = 37405)	NBW with Non-CHD (*n* = 4503833)	*P* value	Macrosomia with CHD (*n* = 1230)	Macrosomia with Non-CHD (*n* = 256608)	*P* value
Maternal viral infection (n(%))						
Yes	11334 (30.3)	1747487 (38.8)	**0.024**	305 (24.8)	76726 (29.9)	**0.033**
No	26071 (69.7)	2756346 (61.2)		925 (75.2)	179882 (70.1)	

(Continued)

TABLE 3 | (Continued)

B

Characteristics	NBW with CHD (*n* = 37405)	NBW with Non-CHD (*n* = 4503833)	*P* value	Macrosomia with CHD (*n* = 1230)	Macrosomia with Non-CHD (*n* = 256608)	*P* value
Maternal educational levels (n(%))						
Elementary school and below	6134 (16.4)	409849 (9.1)	**<0.001**	312 (25.4)	36182 (14.1)	**<0.001**
Junior high school	6883 (18.4)	463895 (10.3)		426 (34.6)	48499 (18.9)	
High school and secondary school	18777 (50.2)	1819549 (40.4)		387 (31.5)	94432 (36.8)	
University degree and above	5611 (15.0)	1810540 (40.2)		105 (8.5)	77495 (30.2)	
Mother drinking or not (n(%))						
Yes	1608 (4.3)	54046 (1.2)	**0.001**	71 (5.8)	5389 (2.1)	**0.005**
No	35797 (95.7)	4449787 (98.8)		1159 (94.2)	251219 (97.9)	
Mother smoking or not (n(%))						
Yes	1347 (3.6)	36031 (0.8)	**<0.001**	47 (3.8)	2566 (1.0)	**<0.001**
No	36058 (96.4)	4467802 (99.2)		1183 (96.2)	254042 (90.0)	
Maternal radiation material exposure (n(%))						
Yes	1534 (4.1)	40534 (0.9)	**<0.001**	58 (4.7)	3849 (1.5)	**<0.001**
No	35871 (95.9)	4463299 (99.1)		1172 (95.3)	252759 (98.5)	
Maternal folic acid supplementation or not (n(%))[#]						
Yes	27867 (74.5)	4062457 (90.2)	**<0.001**	694 (56.4)	183475 (71.5)	**0.001**
No	9538 (25.5)	441376 (9.8)		536 (43.6)	73133 (28.5)	
Paternal viral infection (n(%))						
Yes	11410 (30.5)	1801533 (40.0)	**0.021**	308 (25.0)	77752 (30.3)	**0.027**
No	25995 (69.5)	2702300 (60.0)		922 (75.0)	178856 (69.7)	
Father drinking or not (n(%))						
Yes	15500 (41.4)	1378173 (30.6)	**0.005**	657 (53.4)	118553 (46.2)	**0.010**
No	21905 (58.6)	3125660 (69.4)		573 (46.6)	138055 (53.8)	
Father smoking or not (n(%))						
Yes	25735 (68.8)	2098786 (46.6)	**<0.001**	940 (76.4)	169105 (65.9)	**0.017**
No	11670 (31.2)	2405047 (53.4)		290 (23.6)	87503 (34.1)	
Paternal radiation material exposure (n(%))						
Yes	1047 (2.8)	13511 (0.3)	**<0.001**	39 (3.2)	2309 (0.9)	**0.006**
No	36358 (97.2)	4490322 (99.7)		1191 (96.8)	254299 (99.1)	
Paternal folic acid supplementation or not before pregnancy (n(%))						
Yes	19300 (51.6)	3121156 (69.3)	**0.013**	503 (40.9)	125225 (48.8)	**0.031**
No	18105 (48.4)	1382677 (30.7)		727 (59.1)	131383 (51.2)	
Apgar score at 5 min (M, P_{25}–P_{75})	8 (7–9)	9 (8–10)	**0.001**	8 (7–9)	9 (7–10)	**0.001**

**Only statistically significant variables are shown; [#]replenish folic acid for at least 3 months before or during pregnancy. The bold values in the tables represent statistically significant differences.*

studies have revealed that there is a certain correlation between CHD and birth weight in the world. However, in China, there are few reports on the prevalence of CHD in VLBW and macrosomia, and there is also a lack of relevant research on the relationship between CHD and birth weight. This study with a large sample size described the epidemiology of CHD in Central Plains of China and could accurately reflect the occurrence of CHD, including the prevalence of some rare subtypes. And we explored the relationship between the subtypes of CHD and birth weight and provided theoretical and practical references

TABLE 4 | Generalized linear model results of the relationship between different subtypes of congenital heart disease and birth weight in children.*

	ASD		VSD		PDA		TOF		Total CHD	
	β *(95%CI)*	*P* value	β *(95%CI)*	*P* value	β *(95%CI)*	*P* value	β *(95%CI)*	*P* value	β *(95%CI)*	*P* value
The boy										
Model 1	−120 (−201, 392)	0.818	−252 (−827, −30)	**0.005**	−285 (−449, 276)	0.668	−838 (−1321, −397)	**0.038**	237 (−112, 552)	0.394
Model 2	−95 (−152, 278)	0.912	−398 (−990, −85)	**0.010**	−175 (−448, 299)	0.795	−934 (−1406, −407)	**0.025**	202 (−243, 577)	0.515
Model 3	−86 (−165, 293)	0.907	−467 (−1052, −117)	**0.016**	−124 (−423, 275)	0.541	−1056 (−1424, −537)	**0.007**	170 (−220, 460)	0.278
The Girl										
Model 1	−502 (−1004, −199)	**0.032**	−180 (−540, 419)	0.584	−152 (−441, 320)	0.738	−372 (−663, −99)	**0.019**	−530 (−983, −125)	**<0.001**
Model 2	−680 (−1343, −103)	**0.017**	−149 (−598, 537)	0.721	−168 (−483, 354)	0.761	−527 (−845, −199)	**0.016**	−648 (−1069, −128)	**<0.001**
Model 3	−738 (−1519, −295)	**0.009**	−193 (−502, 484)	0.422	−283 (−511, −55)	**0.035**	−544 (−906, −194)	**0.012**	−812 (−1359, −285)	**<0.001**
Total										
Model 1	−247 (−762, −56)	**0.036**	−270 (−509, −31)	**0.012**	−306 (−891, 391)	0.217	−358 (−778, −93)	**0.034**	−473 (−902, −43)	**<0.001**
Model 2	−357 (−965, −107)	**0.033**	−329 (−661, −97)	**0.005**	−274 (−749, 302)	0.233	−459 (−895, −112)	**0.023**	−629 (−1018, −128)	**0.005**
Model 3	−461 (−1085, −128)	**0.025**	−426 (−932, −120)	**0.009**	−231 (−628, 393)	0.206	−532 (−987, −168)	**0.018**	−973 (−1502, −204)	**0.001**

**A generalized linear model was used, the dependent variable was birth weight, the independent variable was the type of CHD (ASD, VAD, PDA, and TOF), adjusting for related confounding factors, and β was the model regression coefficient, 95% CI was 95% confidence interval. Model 1: no variable was adjusted; Model 2: adjusting fetal sex, gestational age, gravidity, parity, and apgar score at 1 and 5 min; Model 3: on the basis of Model 2, continuing to adjust the parents' age, residence (urban and rural), education level, occupation, folic acid supplementation, whether drink, smoke, viral infection, radioactive material exposure, doing physical exercise or not, and family monthly expenditure. In the gender-specific model, the baby's gender was no longer adjusted. The bold values in the tables represent statistically significant differences.*

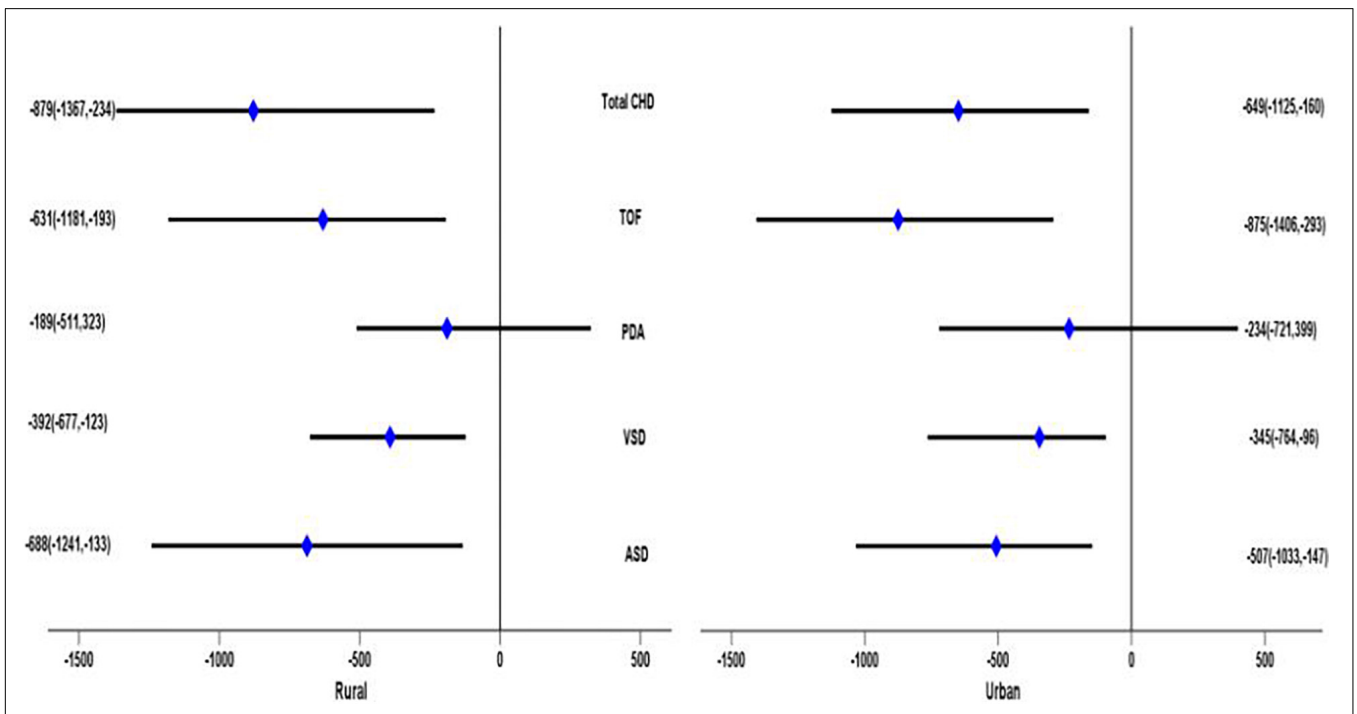

FIGURE 2 | Adjusted β value and 95% CI of the relationship between different subtypes of congenital heart disease and birth weight in children of different places of residence (results of Model 3).

for Chinese children to reduce the occurrence of CHD and abnormal birth weight.

We observed that the overall prevalence of CHD was 8.44 per 1,000 live births, and the three subtypes with the highest prevalence of CHD were ASD, VSD, and PFO, which was similar to most of the previous studies (8–10 per 1,000 births at global and local levels) (17–21). The prevalence of CHD in VLBW, LBW, and SGA infants was higher than in other birth weight groups, which was consistent with previous studies (2, 6–8), but the prevalence varied slightly in different regions; the reasons why heterogeneity of CHD prevalence might be differences in study populations, prenatal detection capability, and ascertainment of criteria. The reasons for the increased frequency of CHD in VLBW and SGA infants are still a matter of speculation (22), small septal defects may close spontaneously in utero, and therefore fewer may be apparent in term infants (7). CHD may impair intrauterine growth (23), which justifies the higher frequency of CHD in the VLBW and SGA groups documented by our study. Our research results had observed that, in each birth body reorganization, the prevalence of CHD also increased as the years grew; the increase in the prevalence of CHD in our study might reflect a true increase. The global prevalence of CHD increased from 4.6 per 1,000 live births in 1970–1974 to 9.4 per 1,000 live births in 2010–2017 (17). Increasing trends had also been observed for some specific forms of CHD, such as ASD in the United States and SV, ASD, and TOF in Europe (24, 25). Our results presented that the prevalence of CHD in each birth weight group had a peak in 2017. It might be related to China's change in the birth policy that opened up the second child in 2016. The parents who gave birth to the second child were generally older, which might lead to an increase in the prevalence of CHD in their offspring.

Our results showed the influencing factors of children with CHD in different birth weight groups, among them, the factors that could be changed included folic acid supplementation before and during pregnancy, more exercise, drinking, and smoking. Folic acid is a water-soluble vitamin, which is indispensable in human metabolism as a coenzyme. Folic acid promotes the development of the fetal nervous system, and the lack of folic acid in the first trimester can lead to neural tube defects in infants (26). Due to the rapid growth and development of the fetus in the second and third trimesters, the demand for folic acid increases sharply; it will be extremely unfavorable to the growth and development of the fetus if the supplement of folic acid is ignored (27). Some studies had suggested that the nutritional status of folic acid during pregnancy was closely related to the growth and development of the fetal (27, 28). One meta-analysis also found that folic acid supplementation during pregnancy was associated with a reduced risk of low birth weight, although only at high doses (29). European and American scholars believed that if pregnant women received adequate nutrition during the development of the fetal nervous system, the heavier the baby's weight, and the higher the baby's IQ (28). In addition, good living habits such as physical exercise before and during pregnancy and not drinking or smoking can keep the parents in good health and cultivate healthy fertilized eggs, thereby avoiding the adverse outcome of low birth weight in the offspring (30).

Previous researches had proved that CHD was a multifactorial disease. Our study found that several maternal and paternal factors during pregnancy were associated with an increased risk of their children's CHD in each birth weight group. These factors included pregnancy viral infection, smoking and drinking, exposure to radioactive substances, folic acid supplementation, exercise, family monthly expenditure, and apgar score. It has been suggested that the key period of heart embryonic development is the second to eighth weeks of pregnancy. Some studies indicated that maternal factors, including viral infection, smoking and drinking, exposure to radioactive substances, or treatment of such infections during the first trimester of pregnancy might precipitate CHD in the children (30, 31). There have been some studies on the relationship between folic acid supplementation during pregnancy and CHD in offspring (32, 33). Our study found that folic acid supplementation could reduce the risk of CHD. Folic acid participates in one-carbon unit metabolism and plays an important role in the process of nucleotide synthesis, amino acid conversion, and methylation (34). Cell proliferation and differentiation during early embryonic development are active, so folic acid metabolism disorders are closely related to early embryonic development abnormalities and birth defects (35). Epidemiological evidence shows that peri-pregnancy supplementation of folic acid or folic acid-containing multivitamins can effectively reduce the risk of CHD, and the key enzyme gene polymorphisms of its metabolic pathways are closely related to CHD (34–37). Folic acid metabolism disorders can lead to the occurrence of hyperhomocysteinemia, which is an independent risk factor for the onset of CHD (38); however, the mechanism of folate metabolism disorders in CHD is still unclear. Some studies have shown that it might cause CHD by affecting the formation and migration of cardiac neural crest cells, hindering DNA synthesis, and interfering with cell proliferation and apoptosis (37–39). Previous studies focused on the influence of maternal perinatal factors on CHD, and our research found that some of the father's prepregnancy factors also had an impact on the occurrence of CHD. Deng K et al. had showed that fathers who smoked during peri-pregnancy increased the risk of CHD in their offspring, which might be related to the increased probability of sperm chromosome abnormalities and DNA mutations caused by toxic and harmful substances in tobacco, or it might also be related to the increased passive smoking of mothers caused by their fathers' smoking (40). However, the association between paternal smoking and CHD in offspring needs to be further explored in a large population study. Besides, a father's alcohol usage and radioactive material intake can increase the risk of CHD in the offspring, which may be largely due to the influence of alcohol and radioactive substances on sperm quality (41, 42).

Our findings clearly demonstrated that infants with CHDs were more likely to be of low birth weight than the general China children. And infants with ASD had a birth weight 461 g lower (95% CI: −1,085, −128), infants with VSD had a birth weight 426 g lower (95% CI: −932, −120), infants with TOF had a birth weight 532 g lower (95% CI: −987, −168), and without classification, infants with CHD had a birth weight 973 g lower (95% CI: −1,502, −204). It closely mirrored previous research

done on this topic. Kramer et al. pointed out that the CHD group had significantly lower birth weights, and the decrease in birth weight was distinct only in children with TOF and ASD (43). Other studies showed that the mean birth weight of pure VSD and ASD case subjects was 2.52 and 2.41 kg, which was correspondingly 23% (deficit of 612 g) and 28.6% (deficit of 722 g) less than the control, and the comorbidity of congenital cardiovascular malformations was low birth weight, but the reasons for this association remained obscure (44). It is well established that ventricular and atrial septum are associated with a significant decrease in birth weight (5, 45). Different types of CHD may lead to LBW due to hemodynamics changes, and the specific mechanisms need to be further explored. The types of CHD that causes LBW are not the same in boys and girls, and the specific mechanisms are still unclear.

The advantage of this research is that the survey has been strictly scientifically designed, the data management personnel are of high quality, the data collection work is organized and planned, and the data collected is relatively accurate. This study is with large sample size, and the possible confounding factors are controlled as much as possible during the analysis to increase the reliability of the conclusion. However, there are still some limitations to our study. First of all, we mainly adopt the cross-sectional research method, which cannot verify the causal relationship. Second, we cannot fully monitor all factors that affect birth weight. Peri-pregnancy factors of parents are acquired through recall, which has a certain recall bias. Eventually, some potential confounding factors may not be controlled during the analysis process. This study is an ongoing project, and we will obtain more data on children with continuous improvement of our database system. In this study, we used a database with a large sample size to describe the prevalence of CHD in different birth weights of children in central China from 2014 to 2020, analyzed the parental peri-pregnancy risk factors related to CHD, and explored the relationship between different types of CHD and birth weights. It fills up the gaps in related research in China, and the research results have important reference significance for parents' peri-pregnancy healthcare, the reduction of CHD, and the improvement of birth weight.

CONCLUSION

This study confirms that the prevalence of CHD in VLBW and LBW infants is higher than that of NBW infants in China. Moreover, some peri-pregnancy factors of the parents are closely related to the occurrence of CHD in the offspring; ASD, VSD, and TOF are the main types of CHD that cause LBW in infants. Therefore, prenatal care and other public health efforts such as folic acid supplementation and exercise by parents are expected to reduce the occurrence of CHD and improve the birth weight of the children. And if the fetus is found to have a heart defect during the prenatal examination, the mother should pay more attention to maintaining weight and ensuring that the fetus is within the normal weight range, so as to improve the survival rate after birth, reduce complications, and promote the children's health.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Zhengzhou University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HY contributed to conceptualization, methodology, software, statistical analysis of data, writing—original draft preparation, review and editing, investigation, and data curation. BZ contributed to management and coordination responsibility for the research activity planning and execution, data curation, resources, project administration, and validation. RF contributed to formal analysis, data collection and curation, supervision, investigation, and validation. PW contributed to oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team, and investigation. YZha contributed to conducting a research and investigation process, specifically performing the data/evidence collection, and investigation and validation. YW contributed to data collection, scrub data, and maintain research data. YH contributed to data collection and data quality control. YZho contributed to visualization, investigation, data curation, supervision, project administration, resources, article revision, and project financial support. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Normalization of Four Different Types of Pulmonary Hypertension After Atrial Septal Defect Closure

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Pulmonary hypertension (PH) is an established risk factor in patients with atrial septal defect (ASD), and its persistence after ASD closure is associated with increased mortality. Therefore, predictors for PH normalization after defect closure are needed. Multiple hemodynamic types of PH exist, but little is known about their prevalence and prognostic value for PH normalization after ASD closure. We carried out a retrospective study on 97 patients (76% female, median age at ASD closure 58 years) with four types of PH determined predominantly by right heart catheterization: hyperkinetic, pulmonary arterial hypertension, isolated post-capillary, and combined pre- and post-capillary. We investigated the frequency of the PH types and their prognostic significance for PH normalization after ASD closure. Frequency of PH types before ASD closure in our study was: hyperkinetic 55%, pulmonary arterial hypertension 10%, isolated post-capillary PH 24%, and combined PH 11%. Hyperkinetic PH type was positively associated with PH normalization after ASD closure (78% patients normalized), remaining a significant independent predictor when adjusted for age at closure, sex, heart failure, and NYHA. Hyperkinetic PH patients also had significantly better survival prognosis versus patients with other PH types ($p = 0.04$). Combined PH was negatively associated with PH normalization, with no patients normalizing. Pulmonary arterial hypertension and isolated post-capillary PH had intermediate rates of normalization (60 and 52%, respectively). In summary, all four hemodynamic types of PH are found in adult patients with ASD, and they can be used to stratify patients by their likelihood of PH normalization and survival after ASD closure.

Keywords: pulmonary hypertension, atrial septal defect, hemodynamic type of pulmonary hypertension, normalization, reversibility, mortality

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INTRODUCTION

Pulmonary hypertension (PH) represents an important risk factor associated with reduced functional capacity and increased mortality in patients with atrial septal defect (ASD) (1–6). Moreover, persistence of PH after ASD closure is strongly associated with increased mortality (4, 7, 8). On the other hand, patients with normalization of PH after ASD closure have similar outcome as patients without PH (7). The decision of whether to close ASD in patients with PH

presents a complex clinical dilemma (9, 10). Therefore, it is highly important to predict in which patients with ASD and PH the defect closure will lead to PH normalization and in which patients the closure may be detrimental with right heart failure and persistence or even progression of PH.

The guidelines give limits for safe defect closure for pulmonary vascular resistance (PVR) < 3 Wood Units (WU) or 4 WU × m^2 and contraindication of defect closure for PVR more than 5 WU or 8 WU × m^2 (2, 11, 12). However, the guidelines do not specify the probability of PH normalization after defect closure, an important factor for survival (4, 7, 8). Moreover, many studies (including guidelines) deal only with pulmonary arterial hypertension (PAH) in congenital shunt lesions (2, 3, 13, 14), although it is just one of four hemodynamic types of PH in adults with ASD (9, 15). We hypothesized that the hemodynamic types of PH may be predictive of normalization of PH following ASD closure.

Existing ESC/ERS guidelines for the diagnosis and treatment of PH recognize pre-capillary PH, isolated post-capillary PH (IpcPH), and combined pre- and post-capillary PH (CpcPH) (2, 15). Pre-capillary PH involves pulmonary arterial hypertension (PAH), defined by elevated pulmonary vascular resistance (PVR ≥ 3 WU). One of the causes of PAH can be congenital heart disease (CHD) with shunt (2). Although most studies on ASD with PH focus just on PAH (3, 14, 16), hyperkinetic PH (H-PH), characterized by normal or only modestly increased PVR (<3 WU) and normal pulmonary capillary wedge pressure (PCW ≤15 mmHg), is another type of PH described in ASD (9, 17, 18). Interestingly, hyperkinetic PH is currently not discussed in ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension (2, 15). IpcPH is characterized by increased left atrial pressure or PCW (>15 mmHg), which can in some cases worsen after defect closure (10, 19). Little is known about CpcPH in patients with ASD.

The objective of this study was to characterize the frequency of the four types of PH (H-PH, PAH, IpcPH, and CpcPH) as determined predominantly by right heart catheterization (RHC) in adults with ASD, to assess their prognostic value for predicting PH normalization after defect closure, and to evaluate patient mortality in the four PH types.

METHODS

Patients

Following institutional ethics committee approval (Na Homolce Hospital), we performed a retrospective observational study including all the adult patients in our database with the diagnosis of ASD (type secundum, sinus venosus or coronary sinus defect) with PH who underwent defect closure, with known PH type before defect closure. Patients with incomplete atrioventricular septal defects (ASD type primum) or ASD combined with other hemodynamically important CHD were excluded. PH was defined for the purpose of this study as mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg (2). The contraindications for ASD closure were: PVR > 5 WU not responding to advanced therapy or (previously) to acute vasodilation testing which is not recommended any more (11, 12). Another contraindication for ASD closure was increase in left atrial mean pressure during temporary balloon occlusion > 10 mmHg compared to baseline in patients with postcapillary PH (19). Mortality data were obtained from the national mortality register. Processing of human data was carried out in accordance with institutional guidelines.

Catheterization

During right heart catheterization (RHC) the right atrial pressure, sPAP, mPAP, pulmonary capillary wedge pressure (PCW), and left atrial pressure were measured. Cardiac output (pulmonary flow) was measured by Fick method preferentially with measured oxygen consumption, but also with estimated oxygen consumption or dye-dilution or thermodilution, according to the cath-lab facilities. PVR was calculated, and the shunt was quantified by oximetry. Left heart catheterization with coronary angiography was performed according to the usual criteria. Re-catheterization after defect closure was performed in the case of suspected moderate or severe PH from echocardiography.

For the purpose of this study, the four investigated hemodynamic types of PH were defined as specified in **Table 1** (2, 15, 17, 18). IpcPH and CpcPH were distinguished by PVR, not by diastolic pressure gradient (15).

Echocardiography

The size of the ASD was assessed by transesophageal echocardiography. In addition to RHC-determined hemodynamic types of PH, 19 out of the 97 patients (all 19 with H-PH) were diagnosed by echocardiography (20–22). These patients had only mild PH (mPAP 25–30 mHg), with no signs of left heart disease, high pulmonary flow and near-normal PVR (assessed by echocardiographic method which has good correlation with invasive PVR) (21). Therefore, we consider the diagnosis of H-PH in these patients as reliable. All other 78 patients had diagnosis of the type of PH assessed by RHC.

PH normalization was assessed by echocardiography using the method of mPAP assessment described by Aduen et al. (22). Mean PAP = mean pressure difference between right ventricle and right atrium, which is derived from the velocity-time integral (VTI) of the tricuspid regurgitation and the estimated right atrial pressure (RAP) is added. This method correlates closely with invasive measurements (22). Only in the rare case of absence of tricuspid regurgitation we used the alternative method of peak Doppler velocity of the pulmonary regurgitation, mPAP = $4V^2$ + RAP. Both methods are recommended in a review article by Parasurman (20). When PH was suspected after defect closure, RHC was used for the diagnostics. PH was considered normalized when mPAP was < 25 mmHg (2).

Statistical Methods

Kruskal-Wallis ANOVA was used to compare clinical features between PH types (**Table 2**). Cox proportional-hazards ratio was used to study the association between clinical features and PH normalization (**Table 3**). One exception within **Table 3** is the CpcPH, where the zero rate of normalization

TABLE 1 | Definition of hemodynamic types of PH in ASD.

	mPAP (mmHg)	PCW (mmHg)	PVR (WU)
Hyperkinetic (H-PH)	≥ 25	≤15	<3
Pulmonary arterial hypertension (PAH)	≥ 25	≤15	≥3
Isolated post-capillary PH (IpcPH)	≥ 25	>15	<3
Combined pre- and post-capillary PH (CpcPH)	≥ 25	>15	≥3

mPAP, mean pulmonary arterial pressure; PCW, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

TABLE 2 | Cohort summary.

Clinical variable	H-PH ($n = 53$)	PAH ($n = 10$)	IpcPH ($n = 23$)	CpcPH ($n = 11$)	All ($n = 97$)	p-value
PH normalization	78% (35/45)	60% (6/10)	52% (12/23)	0% (0/11)	60% (53/89)	$4.8{\cdot}10^{-5}$
Sex (female)	77% (41/53)	90% (9/10)	57% (13/23)	100% (11/11)	76% (74/97)	0.025
Age at diagnosis (years)	47.0 [34.0–59.0] ($n = 53$)	59.0 [37.0–60.0] ($n = 10$)	50.0 [10.0–65.0] ($n = 23$)	66.0 [52.8–72.0] ($n = 11$)	50.0 [28.0–61.0] ($n = 97$)	0.18
Age at closure (years)	52.0 [42.0–61.3] (n =53)	59.0 [51.0–65.0] (n =10)	60.0 [51.0–70.8] (n =23)	69.0 [58.0–74.0] (n =11)	58.0 [46.8–65.0] (n =97)	0.009
NYHA before closure	2.0 [2.0–3.0] (n =53)	3.0 [2.0–3.5] (n =10)	3.0 [2.6–3.0] (n =23)	3.0 [2.6–3.0] (n =11)	2.5 [2.0–3.0] (n =97)	$2.4{\cdot}10^{-5}$
ASD size (mm)	20.0 [16.5–25.5] (n =48)	28.0 [20.0–39.3] (n =7)	15.5 [11.0–21.0] (n =20)	19.5 [14.0–22.5] (n =8)	20.0 [15.0–24.8] (n =83)	0.06
Qp/Qs	2.4 [1.8–3.0] (n =48)	2.0 [1.7–2.5] (n =9)	2.2 [1.6–2.6] (n =18)	2.5 [2.2–2.7] (n =6)	2.3 [1.8–3.0] (n =81)	0.63
HF before closure	13% (7/53)	40% (4/10)	35% (8/23)	55% (6/11)	26% (25/97)	0.011
mPAP before closure (mmHg)	30.0 [27.0–33.8] (n =51)	32.0 [28.0–40.0] (n =10)	33.5 [28.0–44.0] (n =22)	37.5 [35.0–45.0] (n =10)	32.0 [28.0–36.3] (n =93)	0.009
sPAP before closure (mmHg)	44.0 [39.8–50.0] (n =53)	47.5 [45.0–63.0] (n =10)	50.0 [42.0–59.8] (n =23)	55.0 [52.0–69.5] (n =11)	47.0 [41.0–55.0] (n =97)	0.0006
Surgical closure	77% (41/53)	100% (10/10)	100% (23/23)	64% (7/11)	84% (81/97)	0.012
PH follow-up length (months)	14.5 [9.0–48.5] (n =44)	14.0 [10.0–40.0] (n =10)	31.0 [12.0–60.8] (n =23)	13.0 [4.0–84.3] (n =11)	16.0 [10.0–51.0] (n =88)	0.74

Binary variables are given as percentage (positive/all cases in the PH type). Numerical variables are given as median [interquartile range] (n), where n is the number of patients in the PH group with available data. Qp/Qs, pulmonary-to-systemic flow; HF, heart failure; sPAP, systolic PAP; mPAP, mean PAP; H-PH, hyperkinetic PH; PAH, pulmonary arterial hypertension; IpcPH, Isolated post-capillary PH; CpcPH, combined pre- and post-capillary PH. "Surgical closure" corresponds to sternotomy, minithoracotomy, or robotic thoracoscopy (in the other cases, transcatheter closure was used).

precludes the use of the Cox proportional-hazards ratio, and a Fisher test was used instead on the underlying contingency table to obtain the p-value. We verified that all covariates in the Cox model fulfill the proportional hazards assumption, using the MATLAB fitcox function, which is based on the scaled Schoenfeld residuals, as derived by Grambsch and Therneau (23). The variables significant in univariable Cox proportional hazard ratio model and sex and age at closure and the NYHA class were then included in a multivariable model. Kaplan-Meier survival analysis was used to compare survival rates in the four PH types (**Figure 1**). Wilcoxon rank-sum test was used to assess the difference in NYHA in PH-normalized vs. PH-persisting patients. Only patients with data available on normalization were included in the Cox proportional-hazards and Kaplan-Meier analyses. Hypothesis testing was two-sided and $p < 0.05$ was considered statistically significant. Data were analyzed using MATLAB (R2021b).

RESULTS

A total of 97 adult patients after ASD closure (70% *via* sternotomy, 8% *via* minithoracotomy, 5% *via* robotic thoracoscopy, 17% *via* transcatheter) were included in the study. The median age at the ASD closure was 58 years [47–65 IQR] and 76% of the patients were female. Before defect closure, 53 (55%) patients had H-PH, 10 (10%) PAH, 23 (24%) IpcPH, and 11 (11%) CpcPH. During long-term follow-up for PH normalization after ASD closure (median 16 months, IQR 10–51), PH normalized in 53 patients out of 89 (60%) for whom the data on normalization were available.

PH normalization differed significantly between the hemodynamic types ($p = 4.8{\cdot}10^{-5}$, **Table 2**). Patients with H-PH manifested the greatest rate of normalization (78%), while normalization was lowest in patients with CpcPH (0%). Other features significantly different between

TABLE 3 | Univariable and multivariable Cox proportional-hazards analysis for association of PH normalization and clinical features.

Univariable Cox proportional-hazards models				
Feature	**PH normalized ($n = 53$)**	**PH persisting ($n = 36$)**	**Hazard ratio [CI]**	***p*-value**
Sex (female)	81% (43/53)	69% (25/36)	1.633 [0.819–3.258]	0.16
Age at diagnosis (years)	49.0 [33.5–60.0] (n =53)	57.5 [18.0–66.0] (n =36)	1.008 [0.996–1.021]	0.19
Age at closure (years)	53.0 [42.0–62.3] (n =53)	60.5 [54.5–69.5] (n =36)	1.003 [0.984–1.022]	0.74
NYHA before closure	2.0 [2.0–3.0] (n =53)	3.0 [2.0–3.0] (n =36)	0.685 [0.449–1.047]	0.08
ASD size	20.0 [14.3–24.8] (n =47)	20.0 [16.3–23.3] (n =29)	1.003 [0.969–1.038]	0.86
Qp/Qs	2.2 [1.8–3.0] (n =44)	2.3 [1.9–3.5] (n =29)	0.895 [0.637–1.255]	0.52
HF before closure	17% (9/53)	42% (15/36)	0.456 [0.221–0.942]	0.034
H-PH	66% (35/53)	28% (10/36)	2.414 [1.344–4.338]	0.003
PAH	11% (6/53)	11% (4/36)	1.236 [0.526–2.904]	0.63
IpcPH	23% (12/53)	31% (11/36)	0.610 [0.313–1.188]	0.15
CpcPH	0% (0/53)	31% (11/36)	N/A	$1.6{\cdot}10^{-5}$
mPAP before closure (mm Hg)	30.0 [27.0–33.8] (n =51)	35.0 [29.0–40.0] (n =34)	0.991 [0.955–1.029]	0.65
sPAP before closure (mm Hg)	45.0 [40.0–52.3] (n =53)	50.0 [45.0–61.5] (n =36)	0.995 [0.971–1.019]	0.67
Surgical closure	85% (45/53)	78% (28/36)	1.230 [0.576–2.628]	0.5924

Multivariable Cox proportional-hazards model			
Model	**Feature**	**Hazard ratio [CI]**	**p-value**
H- PH adjusted for age at closure, sex, HF, and NYHA	Hyperkinetic PH	2.37 [1.22–4.6]	0.01
	Age at closure (years)	1.0 [0.99–1.03]	0.56
	Sex	1.43 [0.7–2.94]	0.33
	HF before closure	0.53 [0.23–1.22]	0.13
	NYHA before closure	1.12 [0.64–1.96]	0.68

Binary variables are given as percentage (positive/all cases). Numerical variables are given as median [interquartile range] (n). Distinct PH types were represented as four separate binary variables (1=presence of the PH type). Hazard ratios (HR) are expressed with regards to PH normalization, i.e., hazard ratio > 1 means a positive association between the feature and PH normalization. Qp/Qs, pulmonary-to-systemic flow; HF, heart failure; sPAP, systolic PAP; mPAP, mean PAP; H-PH, hyperkinetic PH; PAH, pulmonary arterial hypertension; IpcPH, Isolated post-capillary PH; CpcPH, combined pre- and post-capillary PH. In the case of CpcHP, the Cox proportional-hazards analysis cannot be applied given the zero normalization rate; the Fisher-test was used to calculate the p-value from the underlying contingency table instead.

hemodynamic types were: sex, age at closure, NYHA class before closure, presence of heart failure (HF) before closure, the measurements of sPAP (systolic PAP) and mPAP (mean PAP) before closure, and the proportion of surgical closure (as opposed to transcatheter closure) (**Table 2**).

Three clinical variables were significantly predictive of PH normalization (**Table 3**, top). While H-PH type was positively predictive of PH normalization ($p = 0.003$, HR = 2.4 [1.34–4.34]), CpcPH type was negatively predictive ($p = 1.6{\cdot}10^{-5}$). Presence of HF before closure was negatively predictive of normalization [$p = 0.034$, HR = 0.46 (0.22–0.94)]. In addition, the NYHA class was borderline nonsignificantly negatively predictive of PH normalization [$p = 0.08$; HR = 0.69 (0.45–1.05)].

Next, we used a multivariable Cox proportional-hazards model for the H-PH, further accounting for age at closure, sex, heart failure, and the NYHA class. H-PH remained a significant independent predictor of PH normalization ($p = 0.01$) (**Table 3**, bottom). Given the zero normalization rate in the CpcPH group, a similar analysis could not be carried out for this hemodynamic type.

In addition, we compared the improvement in NYHA class after ASD closure between PH-normalized and PH-persisting patients. The PH-normalized patients showed a significantly increased improvement in NYHA class compared to PH-persisting patients (mean improvement of 0.85 vs. 0.28; $p = 0.007$).

Finally, we compared survival of patients in the four hemodynamic types using Kaplan-Meier survival analysis (**Figure 1A**). H-PH type showed the best survival ($p = 0.04$; logrank test compared to other PH types) with a 10-year survival of 92% (**Figure 1B**). PAH and IpcPH types had intermediate 10-year survival (77 and 66%, respectively). The survival was lowest in CpcPH type with a 10-year survival of 61%.

Due to the exclusion criterion PVR > 5 WU in our study, advanced therapy (bosentan and sildenafil) was used in 7 (7%) of our ASD patients only (6 after defect closure, one before and after closure). Majority of patients with advanced therapy (5 out of 7) did not normalize PH (3x CpcPH, 1x PAH, 1x H-PH). The patient with H-PH had PVR 2.7 WU before closure and developed CpcPH after ASD closure with PVR 5 WU and died due to heart failure with severe left ventricular dysfunction 12 years after ASD closure.

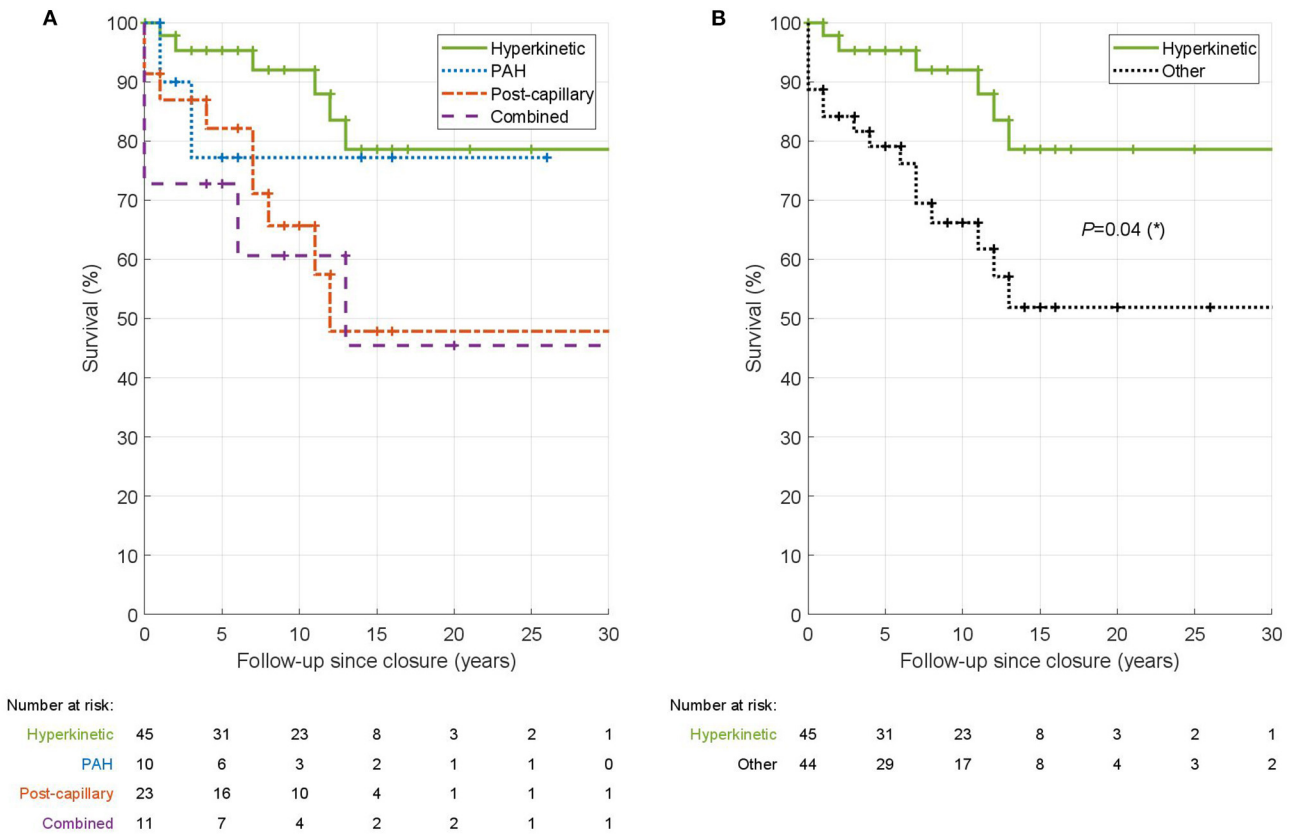

FIGURE 1 | Kaplan-Meier survival analysis of hemodynamic types of PH in ASD. In the left panel **(A)** is shown the comparison of survival among the four hemodynamic types. In the right panel **(B)** is the comparison of H-PH patients vs. patients with other PH types pooled together. The tables underneath the Kaplan-Meier curves give the number of patients who were alive and followed at the given time point. The log-rank test was used to test the significance of survival difference between hyperkinetic patients and all other patients.

DISCUSSION

This study is the first to evaluate the frequency of the four different types of PH in ASD patients, as well as their predictive value for PH normalization and mortality. We observed that the PH types are highly predictive of PH normalization after ASD closure, with H-PH being a significant positive predictor, even after adjusting for age, sex, NYHA class, and presence of heart failure. Conversely, CpcPH was a significant negative predictor of PH normalization. Moreover, we observed a substantially higher improvement in NYHA class after ASD closure in PH-normalized patients compared to PH-persisting patients. Our study therefore shows the importance of assessing the hemodynamic PH type for the risk stratification and design of treatment strategy of ASD patients. The RHC is recommended for PH type diagnosis; the echocardiography-based studies cannot usually conclusively determine the hemodynamic type of PH, particularly in more severe PH.

The reversibility of PH is known to be affected by the severity of pulmonary vascular disease (PVD) and the extent of remodeling of the pulmonary vasculature (14). In the past, the prediction of PH normalization was assessed by histology from open lung biopsies; however, it was abandoned for risk of the procedure and non-uniform distribution of histological changes. More recently, non-invasive predictors of PH normalization have been suggested, reporting age at closure, NYHA class, degree of tricuspid regurgitation, and baseline PAP as significant predictors (4, 16, 24).

Interestingly, women comprised the vast majority of patients with PVR $\geq$ 3 WU (PAH and CpcPH, **Table 2**) in our study, although there was no significant difference in the rate of PH normalization between men and women. On the contrary, the hazard ratio for PH normalization was non-significantly better for women (HR = 1.6; $p = 0.16$), (**Table 3**).

Hyperkinetic PH

Hyperkinetic PH (H-PH) in ASD is a consequence of increased pulmonary blood flow due to the left-to-right shunt on the atrial level. Volume overload of the highly distensible pulmonary vascular bed in young patients may or may not lead to increased PAP. If the increased pulmonary pressure is proportional to the increased pulmonary flow, the PVR is low with no pulmonary vascular disease (PVD). With time, excess pulmonary blood flow can lead to early PVD changes with marked remodeling of the

distal pulmonary vasculature and loss of the elastic properties and stiffening of the large proximal pulmonary arteries. High pulmonary flow leads to upregulation of flow-sensitive genes with endothelial cell dysfunction and neomuscularization, which is reversible when the high pulmonary flow is normalized (13). In the case of progression of pulmonary vascular bed remodeling, PVR increases. If PVR exceeds 3 WU, the H-PH turns to PAH, suggesting the presence of a significant PVD. It is worth mentioning that the cut-off of 3 WU is relatively arbitrary, and PVR > 2 WU could be also considered abnormal (15). The impact of mildly increased PVR (2.5–3 WU) on patient prognosis in H-PH remains to be assessed.

In our study, H-PH was the most frequent PH type (55% patients). It was an independent positive predictor of PH normalization after ASD closure, manifesting the greatest normalization rate of 78%. Patients with H-PH had also significantly better long-term survival after defect closure compared to other types of PH, with a 10-year survival of 92%. This is in line with the mild PVD in H-PH, as well as high pulmonary pressure proportional to high pulmonary flow, resulting in normal or mildly increased PVR.

More attention therefore needs to be paid to the hyperkinetic type of PH in ASD. Some patients with high PAP due to H-PH may be erroneously considered inoperable by inexperienced cardiologists, even though their prognosis after ASD closure might have been very good with PH normalization. In addition, hyperkinetic PH patients misdiagnosed as having PAH may be prescribed expensive advanced therapy with no evidence of its utility for hyperkinetic PH. Therefore, consultation in specialized expert centers including RHC is important for patients with signs of moderate or severe PH according to echocardiography.

Pulmonary Arterial Hypertension

While being the most studied PH type in connection with shunt CHD, PAH was the least frequent type in our study (present in 10% patients with ASD). It showed 60% PH normalization rate and 77% 10-year survival rate after ASD closure. PAH is characterized by increased PVR (≥ 3 WU) and more severe PVD (2, 15). This includes not only the medial hypertrophy and intimal hyperplasia but also resistance to apoptosis, neointimal fibrosis with vascular lumen occlusion, and plexiform lesions (13). While high likelihood of irreversible changes in pulmonary vascular bed can be expected in patients with PVR above 5 WU (2, 11, 12, 25), such patients are contraindicated for ASD closure and therefore not a part of this study. However, more precise prediction of PH normalization in PAH patients with PVR of 3–5 WU is needed. The role of new methods such as nuclear imaging, circulating biomarkers, or specific genetic mutations should be evaluated in the future (13). Advanced pulmonary vasodilator therapy, before and/or after ASD closure, may be helpful in stabilization of the clinical state with NYHA improvement and lowering of PAP and PVR, even if not leading to complete PH normalization. Advanced therapy may lower PVR below 5 WU in some patients and thus allow ASD closure, usually with fenestration (treat-and-repair strategy) if significant left-to right shunt is still present (Qp:Qs > 1.5) (12).

Isolated Post-capillary PH

IpcPH was the second most frequent PH type (24% patients) with 52% normalization rate and 66% 10-year survival rate since ASD closure. IpcPH is a consequence of left heart failure with increased filling pressures and PCW ≥ 15 mmHg. The reason may be the co-incidence of ASD with mitral regurgitation or stenosis or with left ventricular (LV) systolic dysfunction. IpcPH may be also a consequence of LV diastolic dysfunction resulting from altered geometry of the LV due to severely dilated right ventricle. In post-capillary PH, the defect serves as a pop-off valve alleviating the risk of pulmonary edema in the case of high left atrial pressure. It is therefore important to exclude further increase of filling pressures after defect closure. Based on literature and our experience, temporary occlusion testing, fenestrated closure, heart failure treatment before defect closure and correction of valvular heart disease and arrhythmias are important and recommended (7, 19, 26).

Combined Pre- and Post-capillary PH

Little is known about clinical and physiological characteristics of CpcPH generally (27) and in connection with ASD. In our study, CpcPH was present in 11% patients with ASD. It was a significant negative predictor of PH normalization in our study (no patients normalized) and resulted in the lowest 10-year survival of 61%. Patients with this PH type also had the highest mPAP and sPAP and the highest rate of heart failure before ASD closure (55%). Patients with ASD and CpcPH were the oldest (median age of 66 and 69 years at diagnosis and defect closure, respectively). Patients with CpcPH develop more severe PVD than patients with IpcPH and resemble PAH in hemodynamic and genetic characteristics (27). Design of an optimal treatment strategy in these patients needs further research. In our experience, measures should be applied beyond ASD closure (if PVR is below 5 WU), such as heart failure treatment, concomitant valvular or antiarrhythmic surgery, fenestrated closure or pulmonary vasodilator treatment in individual cases and individual dosage before and/or after defect closure (27).

Patients with ASD and IpcPH or CpcPH due to left heart disease (mitral valve disease, left ventricular dysfunction, etc.) are sometimes excluded from research studies concerning ASD (14, 16). Consequently, information on their prognosis and treatment strategies is lacking. Our results demonstrate substantial differences between normalization rates and prognosis in IpcPH (52% normalized) vs. CpcPH (0% normalized), highlighting these as two functionally highly distinct types.

Summary

In conclusion, we investigated four different hemodynamic types of PH based on RHC, which may accompany ASD in adulthood. They differed in frequency within the studied cohort, likelihood of normalization following ASD closure, and in mortality. The high frequency and strong prognostic value of hyperkinetic PH suggests that this PH type is worth including and discussing in future ESC/ERS guidelines (2, 15). The knowledge of the PH type in ASD can help to guide a tailored treatment strategy.

LIMITATIONS OF THE STUDY

We used an older cut-off value for the diagnosis of PH with mPAP $\geq$ 25 mmHg in our study, based on the guidelines from the time of data collection and study design (2). According to our experience, inclusion of patients with mPAP 20–24 mmHg would only increase the number of patients with mild hyperkinetic PH who did not have RHC.

Given the retrospective nature of the study, certain clinical variables are missing in some of the patients. However, **Tables 2**, **3** contain the patient counts for each comparison so that the number of available measurements is clear.

Due to the exclusion criterion PVR > 5 WU in this study, advanced therapy was used only in 7 of our ASD patients with PH, which does not allow detailed analysis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Na Homolce hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JR conceived the study, collected the patient data, and is the guarantor of the study. RŽ contributed to data collection. JT and MT carried out data analysis. JT and JR wrote the initial draft, with all authors subsequently carrying out critical revisions. All authors contributed to the article and approved the submitted version.

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Health and Well-Being in Surviving Congenital Heart Disease Patients: An Umbrella Review With Synthesis of Best Evidence

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Background: Advances in the management of congenital heart disease (CHD) patients have enabled improvement in long-term survival even for those with serious defects. Research priorities (for patients, families and clinicians) have shifted from a focus on how to improve survival to exploring long-term outcomes in patients with CHD. A comprehensive appraisal of available evidence could inform best practice to maximize health and well-being, and identify research gaps to direct further research toward patient and clinical need. We aimed to critically appraise all available published systematic reviews of health and well-being outcomes in adult patients with CHD.

Methods: We conducted an umbrella review, including any systematic reviews that assessed the association of having vs. not having CHD with any long-term health (physical or mental), social (e.g., education, occupation) or well-being [e.g., quality of life (QoL)] outcome in adulthood (≥18-years).

Results: Out of 1330 articles screened, we identified five systematic reviews of associations of CHD with adult outcomes. All but one (which studied QoL) explored health outcomes: one cardiovascular, two mental, and one mortality after transplant. CHD patients had a higher risk of stroke, coronary heart disease and heart failure, with the pooled relative risk (RR) for any outcome of 3.12 (95% CI: 3.01 to 3.24), with substantial heterogeneity (I^2 = 99%) explained by the outcome being studied (stronger association for heart failure) and geography (stronger in Europe compared with other regions). CHD patients had a higher risk of anxiety (OR = 2.58 (1.45 to 4.59)], and higher mean scores for depression/anxiety symptoms (difference in means = −0.11 SD (–0.28 to 0.06), I^2 = 94%)]. Compared with patients having a cardiac transplant for other (non-CHD) diseases, CHD patients had higher short-term mortality (RR at 30-days post-transplant = 2.18 [1.62 to 2.93)], with moderate heterogeneity (I^2 = 41%) explained by previous surgery (higher mortality with prior Fontan/Glenn operation). All domains of QoL were lower in patients with Fontan's circulation than non-CHD adults.

Conclusion: Adults with CHD have poorer cardiovascular, mental health and QoL outcomes, and higher short-term mortality after transplant. The paucity of systematic

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reviews, in particular for outcomes such as education, occupation and lifestyles, highlights the need for this to be made a priority by funders and researchers.

Systematic Review Registration: [www.crd.york.ac.uk/prospero], identifier [CRD42020175034].

Keywords: congenital heart disease, long term, umbrella review, adult, health and well-being

INTRODUCTION

Congenital heart diseases (CHD) are among the most common types of congenital anomalies, affecting between 6 and 8 individuals per 1000 live births (1). Historically, CHDs have been considered solely a pediatric disorder, given that only a minority of patients with moderate and severe CHD reached adulthood. However, advances in the management of this high-risk subgroup have enabled substantial improvement in long-term survival even for those with serious cardiac defects, with more than 90% of patients with CHD reaching adult life (2). As more CHD patients live longer, research priorities need to shift from a primary focus on how to improve survival to include research on the health and well-being of those surviving through childhood and into adulthood. Patients, their families and charities who support them have identified the need for research that assesses the extent to which CHD patients can expect to live healthy, productive lives in comparison to those without CHD, including differences in health, reproductive capacity, behaviors such as physical activity and in educational attainment and career prospects (3, 4). Further ongoing initiatives (e.g., The James Lind Alliance, a United Kingdom non-profit initiative that includes patients with CHD, their carers and clinicians) are expected to identify research priorities for children and adults with CHD by bringing together patients, carers and clinicians (5). Consequently, research around long-term outcomes in patients with CHD has become increasingly important.

It is difficult to get an overall picture of what the key risks to future health and well-being are. A comprehensive appraisal of available evidence could provide information for patients, their families and clinicians on important aspects of their adult life and areas where targeted interventions, such as additional educational support, or earlier monitoring to prevent diseases, might be valuable. An up-to-date review of current evidence can also provide guidance on future research needs around the long-term consequences of CHDs.

Umbrella reviews are systematic reviews of existing systematic reviews that can produce holistic evidence and identify important gaps in the literature (6). As systematic reviews are only recently emerging for long-term outcomes in CHDs, an umbrella review could be important in identifying outcomes where there is sufficient robust evidence to reassure patients (e.g., of no or little risk) or provide guidance (such as additional educational support or clinical monitoring) and identify research gaps.

To our knowledge, an umbrella review of long-term outcomes beyond survival in adults with CHD has not been undertaken to date. We therefore aimed to critically appraise available systematic reviews of health and well-being of adult patients with CHD. We aimed to include a broad range of outcomes and therefore did not pre-specify specific outcomes. Our hope was that we would identify systematic reviews covering educational achievement, quality of life (QoL), psychological functioning, neurodevelopment, reproduction/pregnancy, social and behavioral outcomes (e.g., physical activity, occupation) as well as outcomes reflecting cardiovascular health. Ultimately, we aimed to use findings from an umbrella review to develop recommendations for future research and clinical practice.

METHODS

The present work was developed according to current recommendations for umbrella reviews (6). The protocol was registered in PROSPERO (registration Number CRD42020175034).

Inclusion Criteria

Study Design

Systematic reviews with or without meta-analyses were included. Studies were considered a systematic review if they met the following criteria: (i) the research question was clearly stated; (ii) a reproducible search strategy was presented (e.g., naming of databases, platforms/engines, search date and complete search strategy); (iii) inclusion and exclusion criteria were stated; (iv) selection (screening) methods were well defined; (v) study quality/risk of bias was critically appraised; (vi) information about data analysis and synthesis were provided (7).

Population

The target population was adults, defined as anyone aged 18 years or above. If reviews defined themselves as exploring outcomes in adults but used a lower age threshold (e.g., 16 years) we included those studies and tried to seek results for those only 18 years or older. The exposure was having a CHD vs. not. This was defined as born with any type of CHD, whether diagnosed antenatally, at birth or later in life. We included reviews of studies with any type of non-CHD comparison group and, in summarizing findings, considered the different sources of bias in relation to different comparison groups (see Risk of bias below).

Outcomes

In accordance with recommendations for umbrella reviews and previous umbrella reviews with other research aims (8), we did not pre-specify specific outcomes of interest. This is because the aim of umbrella reviews in general and our specific aim here was broad-reaching, i.e., to identify all systematic reviews of the association of CHD with any long-term health (physical or mental), social (e.g., education, occupation) or well-being (e.g.,

QoL) outcome in adulthood, so that we could summarize current evidence on associations and identify research gaps.

Search Strategy

A comprehensive search of electronic databases MEDLINE (*via* PubMed), EMBASE, SCOPUS, PsycINFO and Cochrane library was conducted to identify relevant systematic reviews published between the beginning of each database and April 2020 without language restrictions. We also manually screened reference lists of the retrieved systematic reviews to identify any additional relevant systematic reviews. Searches were re-run prior to the final submission of the paper (October 2021). **Supplementary Appendix 1** provides a detailed search strategy for the Medline, EMBASE, PSYCINFO, SCOPUS and the Cochrane Database of Systematic Reviews. The search strategy was developed around the key terms: [(Systematic Review [All]) or (meta-analysis[All])] and [(tetralogy of Fallot [TIAB]) or (pulmonary stenosis [TIAB]) OR (pulmonary valvar stenosis[TIAB]) or (congenital heart disease[TIAB]) or (congenital heart [TIAB])or (congenital cardiac disease [TIAB]) or (congenital heart defect [TIAB]) or (congenital heart malformation [TIAB]) or (ACHD [TIAB]) OR (GUCH [TIAB)] or (fontan circulation [TIAB]) or (cavo-pulmonary connection [TIAB]) or (univentricular heart [TIAB]) or (hypoplastic left heart syndrome [TIAB]) or (single ventricle [TIAB]) or (Norwood Procedure [TIAB]) or (double inlet left ventricle [TIAB]) or (double outlet right ventricle [TIAB]) or (Truncus arteriosus [TIAB]) or (ebstein [TIAB]) or (tricuspid atresia [TIAB]) or (ventricular septal defect [TIAB]) or (atrial septal defect [TIAB]) or (transposition of great arteries [TIAB]) or (transposition of great vessels[TIAB]) or (arterial switch [TIAB]) or (Senning [TIAB]) or (Mustard [TIAB]) or (aortic coarctation [TIAB])or (Interrupted aortic arch [TIAB])or (atrioventricular septal defect[TIAB]) or (total anomalous pulmonary venous connection [TIAB]) or (partial anomalous pulmonary venous connection [TIAB]) or (TAPVC [TIAB]) or (Cor triatriatum [TIAB]) or (Ross [TIAB]) or (Anomalous coronary artery [TIAB]) or (patent ductus arteriosus [TIAB])].

Furthermore, a librarian performed a separate search for individual clinical studies (with at least 500 cases) on each specific topic published after the reviews we identified (**Supplementary Appendix 2**). However, due to the large number of publications, these were not analyzed, and the search outcome is reported as a supplement.

Study Selection and Data Extraction

Two authors (LC and KT) independently screened the titles and abstracts to exclude publications that did not meet our inclusion criteria. After selecting systematic reviews for inclusion, they then independently extracted relevant data according to a prior agreed form (**Supplementary Appendix 3**). Data extracted included: author, year of publication, number of studies included, number of participants and cases included for each study and each analysis, outcomes assessed, findings, subgroup analyses, confounders controlled for and assessment of heterogeneity. The study used two data extraction tools (one for selecting studies to be excluded and one for extracting data) developed *a priori*. LC and KT were blinded to each other's decisions. Disagreements between them were resolved by asking one or more of the other authors to extract data (using the same form) for specific papers and then discussing results from all the extractions. If systematic reviews or meta-analyses examined more than one health outcome of interest, data for each outcome was recorded separately in the extraction process. Review authors were contacted for additional data where necessary.

Risk of Bias Assessment

One author (LC) performed the risk of bias assessment with all the results checked by another author (KT). We assessed the risk of bias of the included systematic reviews using the ROBIS tool. ROBIS is a tool developed for assessing the risk of bias in systematic reviews regarding interventions, diagnosis, prognosis and etiology (9). The tool includes three phases. Phase 1 assesses the relevance of the study. Phase 2 identifies concerns with the review process across four domains (study eligibility criteria, identification and selection of studies, data collection and study appraisal, synthesis and findings). Phase 3 judges the overall risk of bias and summarizes the concerns identified during the Phase 2 assessment.

Data Synthesis

We presented data from the original papers. Where a meta-analysis was carried out, we reported the pooled effect estimate with 95% confidence interval. Results were summarized with a narrative synthesis, forest plot and summary tables describing review characteristics and findings. Results from subgroup analyses or meta-regression analyses - when presented - were commented on.

RESULTS

Literature Search

Figure 1 summarizes the study selection process. In total, 1,330 unique citations were identified after an initial search. Of these, 1,247 were excluded after screening titles and abstracts. The full text of the remaining 83 articles were reviewed, and a further 78 excluded (key reasons for exclusions are provided in **Supplementary Table 1**) and the remaining five were included in the umbrella review.

Table 1 summarizes the characteristics of the five systematic reviews meeting our inclusion criteria. Three included studies of patients with any CHD compared to those with no CHD and explored associations with cardiovascular (one review) and mental health (two reviews) outcomes. One compared mortality after a cardiac transplant between CHD patients and those receiving a transplant for other diseases. One compared quality of life between CHD patients with a Fontan's circulation (i.e., patients treated for single ventricle disease with a series of operations across childhood that allow oxygenated and deoxygenated blood to be separated in the heart) to non-CHD adults. We summarize the results for each outcome separately below.

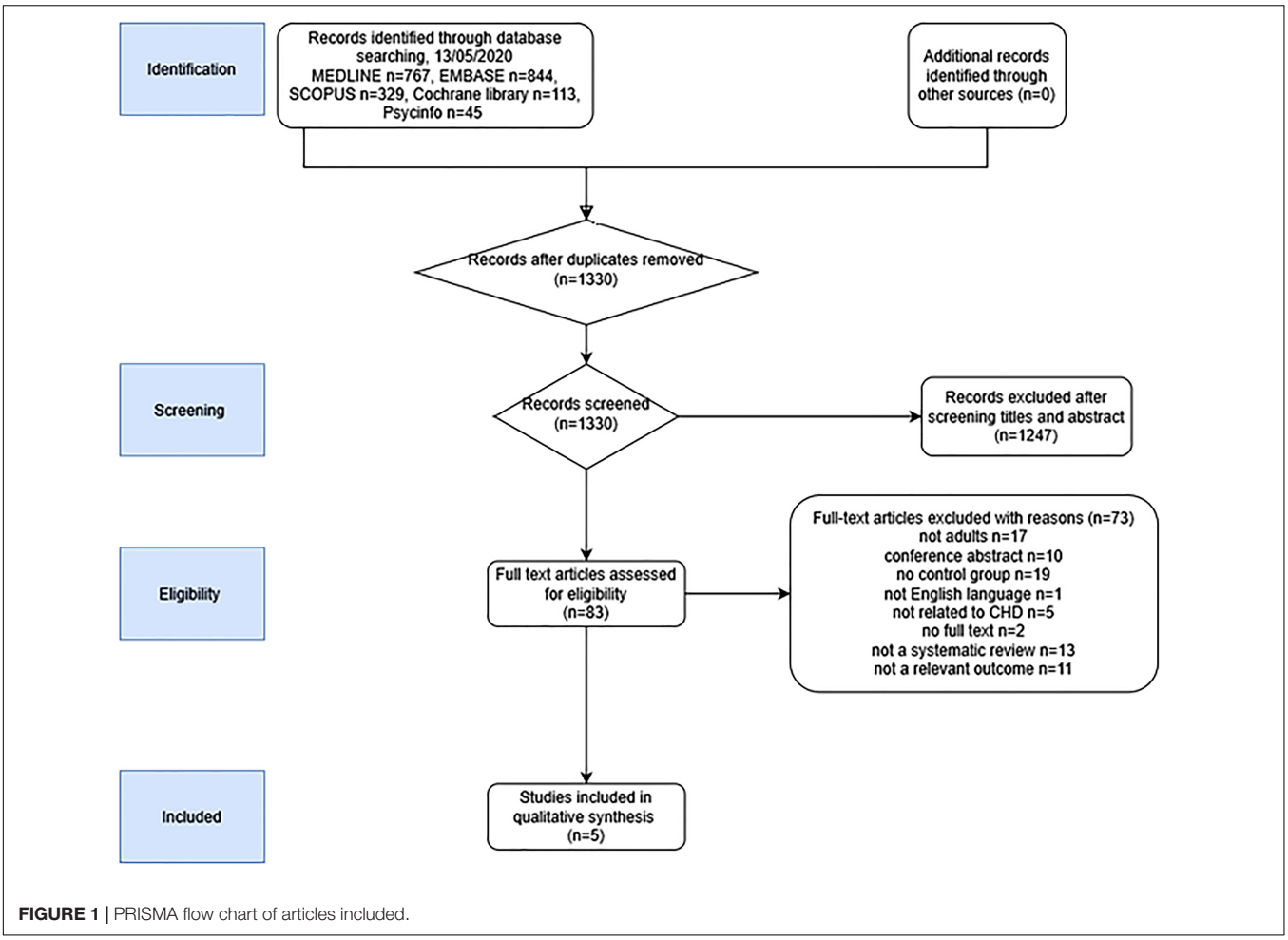

FIGURE 1 | PRISMA flow chart of articles included.

Cardiovascular Disease

We found one systematic review and meta-analysis exploring the association of being a CHD patient with risk of CVD, which pooled 9 cohort studies including a total of 684,200 participants (N = 81,137 CHD cases, N = 603,063 non-CHD) (10). CVD was defined as a composite of any study assessing stroke, coronary artery heart disease, heart failure, and cardiac arrest. Stroke was defined as any acute cerebrovascular event, composite stroke, stroke unspecified, and stroke/transient ischemic attack. Coronary artery heart disease was defined as ischemic heart disease, acute myocardial infarction, and coronary artery disease. In all studies, the association between CHD and risk of CVD was adjusted for age and sex; three studies adjusted for additional risk factors such as ethnicity, smoking and education. The relative risk (RR) in individual studies ranged from 1.48 to 10.76 across the range of different CVD outcomes. The pooled RR for any CVD outcome comparing CHD to non-CHD patients was 3.12 (95% CI: 3.01 to 3.24), with substantial between study heterogeneity (I^2 = 99%). When outcomes were analyzed separately, the strongest association was found for heart failure (RR = 5.89 [5.58 to 6.21]; I^2 = 93%; **Figure 2**). Geographic region (higher risk in European countries compared with other regions) and age (higher risk in studies including both adults and children compared to studies including adults or children only) were key sources of between study heterogeneity (**Figure 2**). The majority of the ROBIS tool criteria were at low risk of bias, with the exception that only studies written in English or Chinese were included.

Mental Health

Two systematic reviews of mental health outcomes were identified. One explored the incidence of symptoms of depression or anxiety specifically in CHD adults, based on 22 studies with a total of 3,723 CHD patients; (11) the second was a systematic review focusing on depression and anxiety in adults with history of different childhood diseases, including CHD, compared to healthy controls (12). Specific to our interest, the latter pooled data from two studies of CHD patients (n = 999 patients vs. 229 healthy controls). In the first review, differences in the depression/anxiety symptom score were presented using Hedge's g, which is the difference in the mean scores (comparing CHD to non-CHD adults) divided by the pooled standard deviation (SD) from the two groups. Thus, if the SDs in CHD and non-CHD participants were similar within each study included in the meta-analysis the result would be equivalent to a standardized differences in means (SMD). The overall difference

TABLE 1 | Overview of studies.

References	Exposure		Outcome	Inclusion criteria	Age at outcome assessment	Risk of bias/quality assessment (author's conclusion)
	CHD definition	Comparison group¥				
Wang et al. (10)	Any CHD *N* = 81,137	Adults without CHD selected from clinical records or health insurance databases *N* = 603,063	CVD defined as any of the following events: stroke, coronary artery, heart disease, heart failure, and cardiac arrest. Stroke was defined as any acute cerebrovascular event, composite stroke, stroke unspecified, and stroke/transient ischemic attack. Coronary artery heart disease was defined as ischemic heart disease, acute myocardial infarction, and coronary artery disease	Cohort study. Chinese or English language. Reported on CVD among patients with CHD.	Adults, adults and children, children	Study quality was generally good assessed using the Newcastle-Ottawa Scale. In particular overall sample representativeness, methods of ascertaining CHD and CV outcomes, and the description of the follow-up time.
Marshall et al. (14)	Fontan's procedure* *N* = 197–346 numbers vary depending on specific outcomes	Healthy control sample or normative sample *N* = 327–2137 numbers vary depending on specific outcomes	Health related quality of life measured with the 36-item short-form health survey (SF-36)	All study designs and comparison group types Used a validated, quantitative self- or proxy-reported HRQOL measure English- language, peer-reviewed format	Mean patient age ranged from 20.7 to 27 years	Risk of bias assessments were performed using the 14-item criteria proposed by Kmet et al. (22), Risk of bias was low, and no studies were excluded because of bias.
Jackson et al. (11)	Any CHD *N* = 3,723	Healthy controls or normative sample N = not provided anywhere in the paper	Emotional functioning was defined as psychological symptoms, including symptoms of depression (i.e., feeling down, loss of energy, irritability, etc.) and anxiety (i.e., nervousness, worry, tension, etc.)	Studies that used a measure of emotional functioning, such as symptom-based assessment tools (e.g., Beck Depression Inventory) or quality of life surveys that had subscales measuring emotional functioning (e.g., The Medical Outcomes Study 36-Item Short-Form Health Survey – Mental Health Subscale) Participants > 14 years old Had a sample with < 10% with a genetic disorder	Patients age ranged from 13 to 87 years	The quality of each study was rated by using a modified instrument by Downs and Black (23), the author reported study quality did not moderate the effect sizes reported by the observed studies.
Secinti et al. (12)	Any CHD *N* = 999	Healthy control *N* = 229	adult emotional problems (i.e., depression, anxiety and unspecified emotional symptoms).	Longitudinal prospective, cross-sectional, or case-control designs Published in an English-language Participants > 16 years old	Mean age 27.7 years	The quality of each study was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, STROBE range from 63.6 to 66.7%
Doumouras et al. (24)	Any adult CHD recipient of a cardiac transplant *N* = 64–856, varies for different meta-analyses	Non-CHD adult recipients of a cardiac transplant *N* = 3,420–42,826, varies for different meta-analyses	Post cardiac transplant outcomes: mortality at 30 days, 1 year, 5 years and 10 years and cause-specific mortality	Observational Post-transplant outcome Participants ≥ 18 years old	Mean patient age ranged from 18 to 39 years	Risk of bias assessment, defined by the grade of recommendation, assessment, development and evaluation, highlighted risk of bias due to report in an unadjusted manner and unclear about length of follow up.

**Fontan's procedure would be done in single ventricle disease.*

¥ As defined by authors.

CHD, congenital heart disease; HRQOL, health-related quality of life.

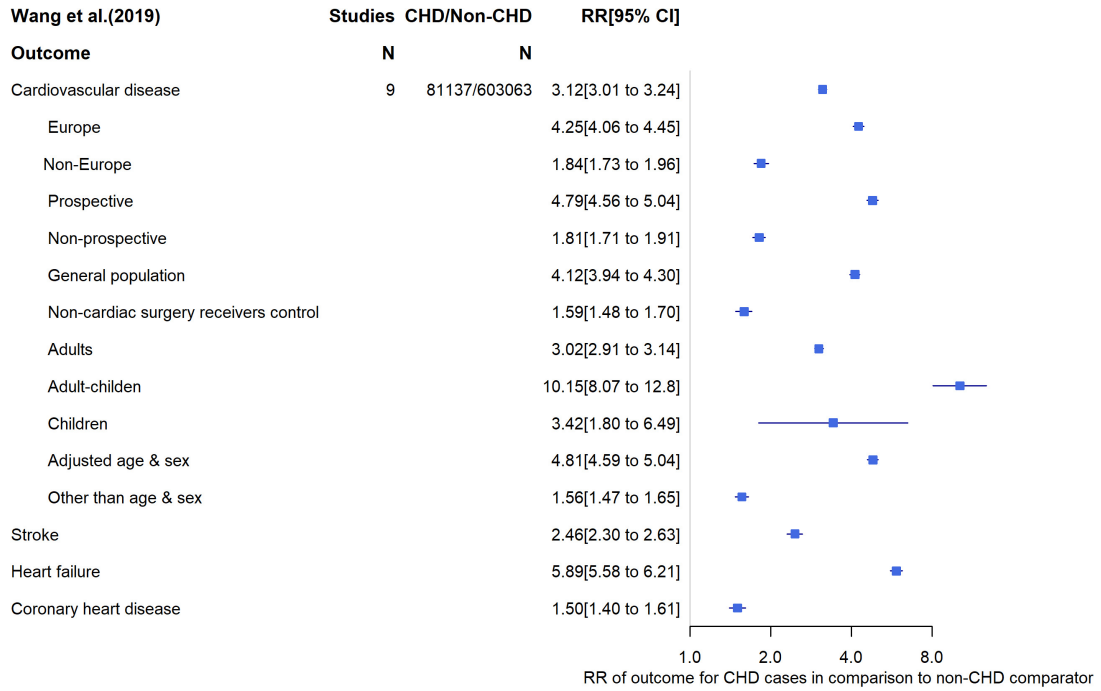

FIGURE 2 | Relative risk for cardiovascular outcome and subgroup analysis.

in mean symptom scores suggested those with CHD had more symptoms on average [SMD = −0.11 (95%CI −0.28 to 0.06)], though this estimate is imprecise with wide confidence intervals (**Figure 3**). There was evidence of between study heterogeneity for the overall pooled result (I^2 = 94%), which appeared to be influenced by disease complexity. Lesion complexity was divided into simple, moderate and great, using classifications outlined by the American College of Cardiology/American Heart Association 2008 guidelines (13). In subgroup analyses based on lesion complexity, when compared to the non-CHD peers, patients with simple or moderate lesions showed lower level of depression and anxiety symptoms, whereas patients with great complexity lesions were more likely to have higher symptom scores. The ROBIS tool indicated that there was risk of bias related to the lack of clear outcome definition, particularly on how a continuous measure across different scores was generated (11). In the second review, which pooled two studies to assess associations with binary mental health outcomes, patients with CHD had a higher odds of depression [OR = 1.63 (0.39, 6.77) and anxiety (OR = 2.58 (1.45, 4.59)] and, to a weaker extent, unspecified emotional problem (**Figure 4**). However, the small sample size meant results were imprecise, with wide confidence intervals and, with just two studies, it was not possible to explore between study heterogeneity. According to the ROBIS tool, there was low risk of bias.

Cardiac Transplant

A systematic review and meta-analysis of nine studies (N = 861 CHD patients) compared mortality and morbidity between adult CHD patent recipients of a cardiac transplantation and patients with other (non-CHD) diseases who had received a cardiac transplant. It found that CHD patients had a higher short term risk of mortality (RR for 30-day mortality = 2.18; 95% CI, 1.62 to 2.93) which decreased over time such that there was an apparent lower 10-year risk of death (RR = 0.75; 95% CI, 0.60 to 0.95) compared with non-CHD patients after cardiac transplantation; it was hypothesized that the latter was likely due to survivor bias (i.e., overall mortality potentially higher in CHD patients but as larger numbers die soon after the operation there are fewer living to 10 years). In subgroup analyses CHD patients who had undergone Fontan or Glenn operation were at higher risk of short-term mortality than those with other CHDs, and the short-term risk of death was higher in subgroups where death was related to primary graft failure, stroke and hemorrhage (**Figure 5**). According to the ROBIS tool, we found low risk of bias (**Supplementary Table 2**).

Quality of Life

The review of differences in QoL between CHD patients with a Fontan circulation and healthy controls included between four and eleven studies depending on which outcome was investigated (14). While the original review included studies on both children and adults, we only reported studies on adults (N = 346). SF-36 was used to assess QoL in all of those studies. SF-36 measures a set of generic, coherent, and easily administered QoL domains (summarized in **Supplementary Figure 1**) (15). Compared to healthy controls, the review found that CHD Fontan patients had reduced scores in all domains with standardized differences in means (SMD) of −0.77 (95% CI, −1.01 to −0.53), −0.21 (−0.42 to −0.01), −0.23 (−0.57 to 0.12), and −0.18 (−0.60 to 0.24) for

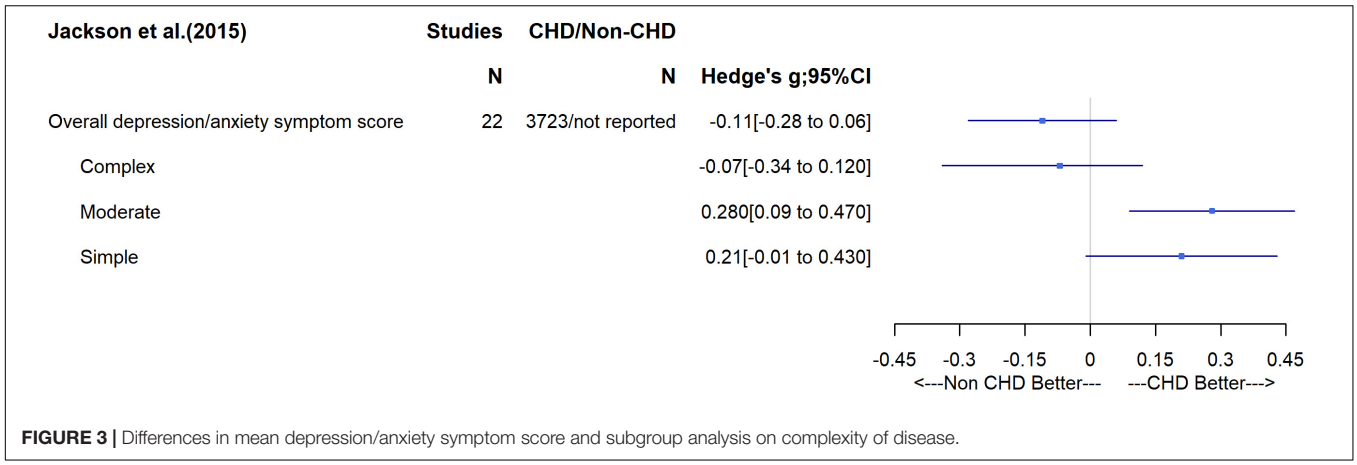

FIGURE 3 | Differences in mean depression/anxiety symptom score and subgroup analysis on complexity of disease.

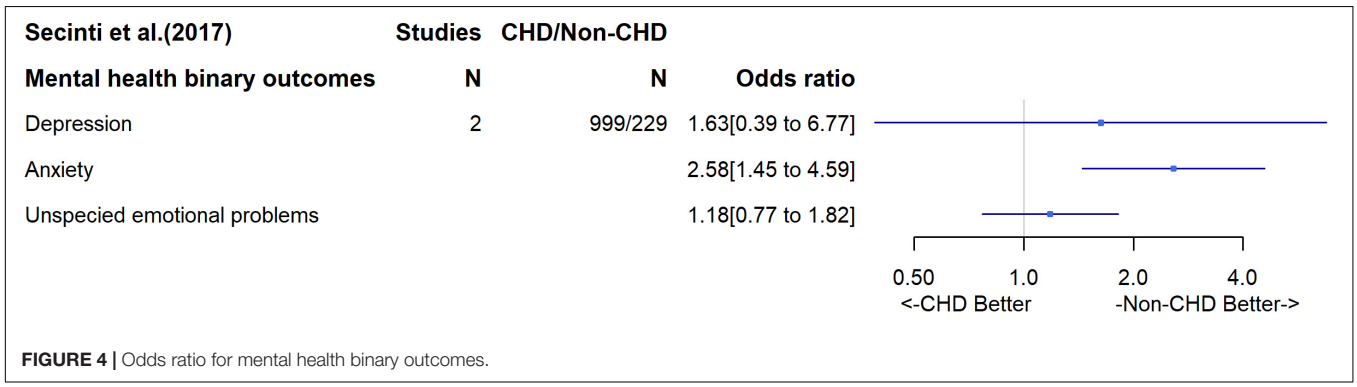

FIGURE 4 | Odds ratio for mental health binary outcomes.

the physical, social, mental health (i.e., anxiety and depression) domains and mental health score (a combination of vitality, social functioning, emotional role and mental health), respectively (**Figure 6**). Between study heterogeneity was high (I^2 = 67%, 45%, 82%, 80% for physical, social, mental health domains and mental health component, respectively). Meta-regression suggested a tendency toward the poorer physical function in CHD patients being stronger in male patients (difference in SMD = −0.041 per% of males participating in the study; 95% CI, −0.075 to −0.007) and patients who underwent Fontan operation at later stage having lower mental health (difference in SMD = −0.25 per 1 year increase, 95% CI, −0.31 to −0.136).

The majority of the ROBIS tool criteria were met with the exception of including only English articles; however, this was acknowledged by authors (**Supplementary Table 2**).

DISCUSSION

The present umbrella review aimed to compare health and well-being in adults with CHD compared to adults without CHD. We identified only five systematic reviews that compared CHD to non-CHD, with these showing increased risk of cardiovascular diseases, depression/anxiety symptoms, 30-day and 1-year mortality after cardiac transplantation, and poorer quality of life, across physical, social and mental health domains compared to adults without CHD. Notably, we did not identify systematic reviews of several key outcomes that have been identified by patients, their families and health professionals as important, such as comorbidities (e.g., lung disease, liver disease, cancer), behaviors (e.g., physical activity, sex, contact sport), and social outcomes (e.g., education, careers). Perhaps unsurprisingly, patients with CHD were reported to have higher incidence of CVD in their adult life (10). In particular, they experienced a higher rate of heart failure. This conclusion is supported by a recent United Kingdom Biobank study that compared 2,006 adults with CHD to 497,983 without CHD and found a higher risk of major adverse cardiovascular events in the CHD patients, even after adjustment for a wide range of common cardiovascular risk factors (16). The mechanisms underlying these associations are unclear, as is the extent to which risk emerges in early life. Whilst findings from the United Kingdom Biobank study are broadly consistent with the systematic review included in this umbrella review, the findings may be biased by selection, given that only 5.5% of those who were invited to United Kingdom Biobank participated and they are known to be a healthy sub-sample of the population from which they were drawn (17).

Research on CHD patients has traditionally focused on children while little attention has been paid in the past to adult survivors. With improvements in peri-operative management, the number of children with CHD who reach adult life has increased dramatically and this has prompted interest and research on aspects of adult life in this challenging group of

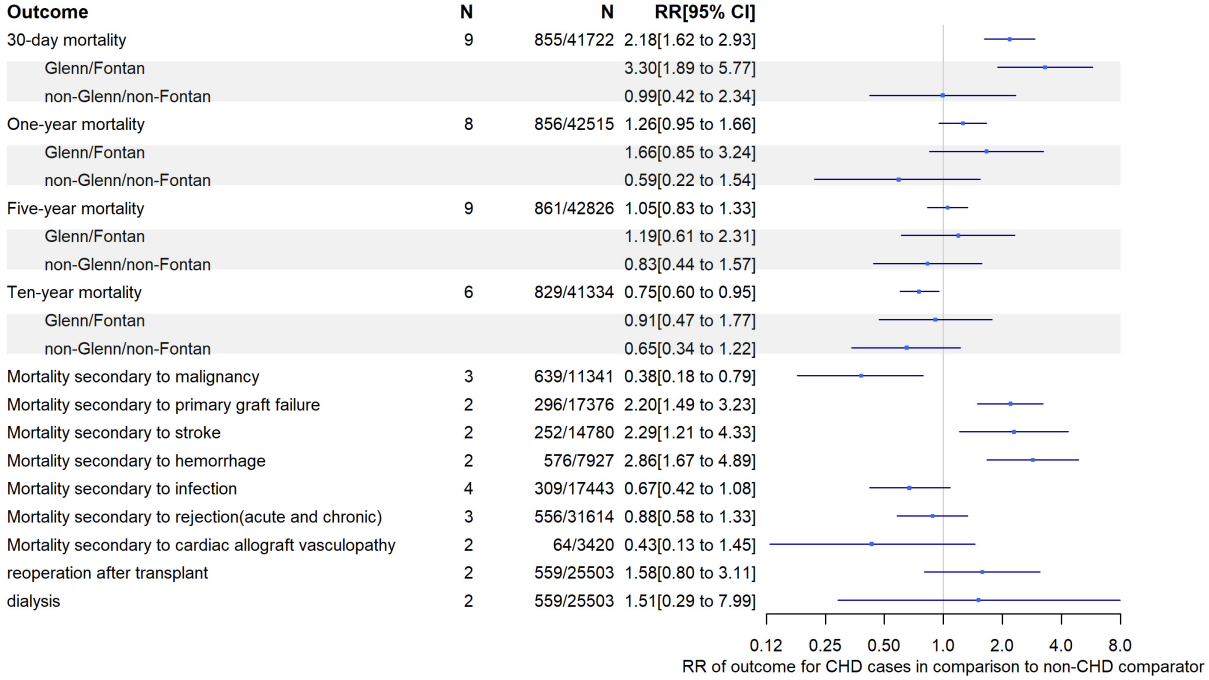

FIGURE 5 | Relative risk of mortality, repeat operation and need for renal dialysis following cardiac transplantation in CHD patients compare with patients receiving transplant for other diseases.

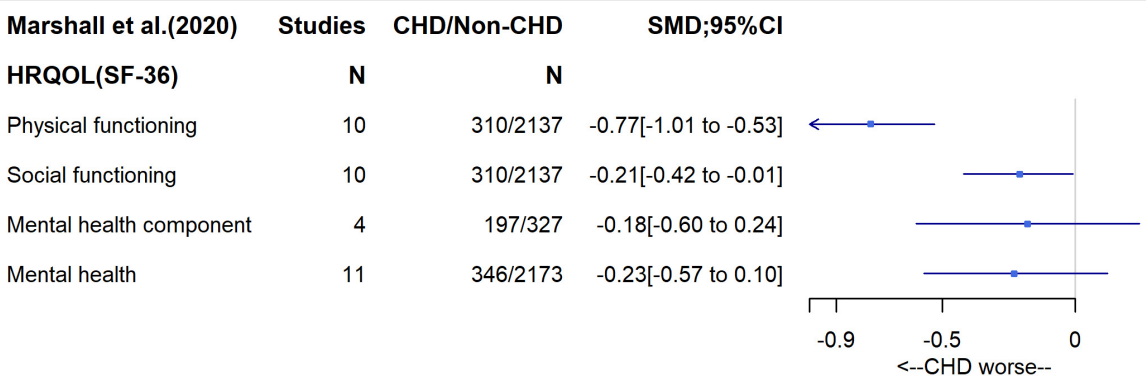

FIGURE 6 | Standardize mean difference for health-related quality of life domains (SF-36).

patients. It remains unclear whether adult life of CHD-corrected patients is comparable to their non-CHD peers and, if not, which areas should be addressed by clinicians and research.

The present umbrella review has shown that there is still little evidence on this subject, and the existing evidence is mainly focused on traditional outcomes (e.g., CVD outcomes, QoL) and there is still a lack of insights on many aspects of life among adults with CHD such as reproductive capacity, educational attainment and career prospects. The James Lind Alliance, a national non-profit making initiative, has launched an initiative to identify research priorities in CHD by bringing together patients, carers and clinicians and results will be soon available (5). Previous initiatives, such as the Working Group on adult CHD research supported by the National Heart, Lung and Blood Institute (4) has identified reproductive outcomes (e.g., the safety of pregnancy in women with CHD and potential impact on their offspring's health and survival) (18). The present review, by highlighting the topics where there is lack of evidence, can be used as guidance for similar initiatives by highlighting what is already known and what remains unknown.

Limitations

The nature of an umbrella review is to review and summarize evidence from published systematic reviews. However, this means that we cannot distinguish between there being very little

or no research for outcomes, such as reproductive health for which we found no systematic reviews, and there being some research that has not yet been systematically reviewed. Thus, in relation to such outcomes our recommendation would be for researchers to develop systematic review protocols and undertake the systematic searches (and full reviews where relevant studies are identified) so that primary research can be directed to areas of relevance to patients and other stakeholders for which there is currently little research. One of the main problems in studying long-term outcomes of patients with CHD is the tracking of these patients. Many patients are lost in the transition between childhood and adulthood, and this may have influenced individual studies' findings.

A key limitation of any research in this area is survivor bias. Although survival in CHD patients has progressively increased, patients with complex lesions still present lower survival rates compared to the general population (19). The proportion of deaths related to CHD among children under 1 year of age has fallen from 60–70% in the 1960s to 20–30% in 2000 (20), and this can affect comparisons with their adult non-CHD peers by masking underlying differences. The rarity of CHDs in the general population (∼1%) represents a possible obstacle in reaching meaningful conclusions from individual cohorts. To overcome these limitations, national and international collaborative health record-linkage studies, large cohorts with relevant data, such as the United Kingdom Biobank, and birth cohort collaborations such as the LifeCycle project (21) have the potential to address questions about future health and well-being in CHD patients and we would urge funders and researchers to explore and exploit these opportunities.

CONCLUSION

Even though most children with CHD now reach adulthood, (20) our umbrella review identifies major gaps in the evidence around the health and other problems that patients with CHD and their families have highlighted as research priorities. Further insights into relevant aspects of adult life among CHD patients could be gained by analyzing available large prospective collaborative record-linkage and birth cohort studies (25, 26).

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/ **Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

LC: planning, conduct, and reporting of the work described in the article, and being responsible for the overall content as guarantor, and attests that all listed authors meet authorship criteria. KT: conduct and reporting of the work described in the article. MC: reporting of the work described in the article. RC: planning, conduct, and reporting of the work described in the article. DL: planning, conduct, and reporting of the work described in the article, and being responsible for the overall content as guarantor. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.870474/full#supplementary-material

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Using Telemedicine Strategy to Implementing Nutrition Management for Neonates After Congenital Heart Disease Surgery: A New Nutrition Management Strategy

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Objective: The purpose of this study was to investigate the effect of remote nutrition management on promoting the growth and development of neonates after congenital heart disease (CHD) surgery.

Materials and Methods: This study retrospectively analyzed the clinical data of 32 neonates after CHD surgery who received remote nutrition management from January 2021 to July 2021 in our hospital. The clinical data of 30 neonates after CHD surgery, who did not receive remote nutrition management from June 2020 to December 2020, was used as control. The growth and development of the two groups were compared.

Results: Three months after discharge, the weight, height, and weight-for-age z score (WAZ) of the intervention group was significantly higher than those of the control group. The amount of milk in the intervention group was also significantly more than that of the control group, and more neonates in the intervention group added high-energy milk or breast milk fortifier than the intervention group. The parental care ability of the intervention group was significantly higher than that of the control group. The incidence of respiratory tract infection and readmission in the intervention group was significantly lower than that in the control group.

Conclusion: As a new nutrition management strategy for neonates after CHD surgery, remote nutrition management can effectively improve the nutritional status of neonates and promote their growth and development.

Keywords: remote nutrition management, congenital heart disease, neonates, growth and development, nutrition

Abbreviations: CHD, congenital heart disease; FCTI, family caregiver task inventory; WAZ, weight-for-age z score.

INTRODUCTION

Congenital heart disease (CHD) is one of the most common congenital structural malformations, and surgery is the main treatment (1–3). With improvements in surgical techniques and intensive care, an increasing number of neonates survive after CHD surgery (4). Poor weight gain after CHD surgery is associated with an increased risk of post-operative infection and readmission and is also a risk factor for death in late infancy (5). Due to the immature organs of neonates and the injury of cardiac surgery, neonates, after CHD surgery, are more vulnerable, and severe feeding and nutrition problems are common after discharge (6, 7). Studies show that feeding difficulties, malnutrition, and growth disorders are the biggest stressors for families after discharge (8, 9).

At present, there are few studies on the feeding programs of these patients, and they mainly focus on the preoperative and perioperative periods. Few studies have focused on home nutrition management strategies for neonates with CHD surgery after discharge (10). Therefore, formulating a strategy for neonatal nutrition management with CHD surgery after discharge is essential. In recent years, telemedicine has been widely used as an educational health promotion strategy for disease management, such as diabetes, hypertension, depression, and so on (11–13). We used telemedicine to implement a new nutrition management strategy for neonates with CHD after discharge. It remotely monitors and manages the nutritional status of neonates and adjusts the nutrition program in real-time to promote their growth and development and realize nutritional catch-up.

MATERIALS AND METHODS

This study was approved by the ethics committee of our hospital and strictly adhered to the tenets of the Declaration of Helsinki. In addition, all parents of patients signed an informed consent form before the study.

This was a retrospective study. We retrospectively analyzed the clinical data of 32 neonates after CHD surgery who received remote nutrition management from January 2021 to July 2021 in our hospital. These patients were included in the intervention group. The clinical data of 30 neonates after CHD surgery who did not receive remote nutrition management from June 2020 to December 2020 were used as controls. We evaluated the effect of remote nutrition management on promoting the growth and development of neonates after CHD surgery.

Inclusion criteria: neonates undergoing CHD surgery in the neonatal period. Exclusion criteria: (1) neonates with liver failure and kidney failure; (2) combined with other severe structural malformations; (3) died after surgery or after discharge; and 4 parents of patients refused to participate in this study.

Nutritional Management Method

We calculated energy requirements according to Leonberg et al.'s guidelines with a target caloric intake of 120–150 kcal/kg/day to ensure adequate energy intake without refeeding syndrome risk (14). Parents were asked to record the amount of milk and body weight daily. Parents were also asked to calculate patients' daily caloric intake. The amount of milk was added according to the weight. If the patients cannot absorb enough milk and the target calorie cannot be achieved, breast milk can be fortified with a breast milk fortifier or a high-density formula milk can be used. If the patients have feeding difficulties and cannot be fed by mouth, nasal feeding should be used.

Remote Nutrition Management After Discharge

We used WeChat (Tencent Ltd., Shenzhen, China) as the remote nutrition management tool. WeChat is the most popular mobile social media application in China, with 1.12 billion users (15). WeChat is a convenient and intuitive information exchange platform with functions such as graphics, text, audio, and video to maximize information coverage.

We set up chat groups through WeChat. At the time of discharge, parents in the intervention group were guided to join the WeChat group and taught to use WeChat functions correctly and skilfully by the doctor. Parents needed to know how to check WeChat information and send messages. It was simple and can

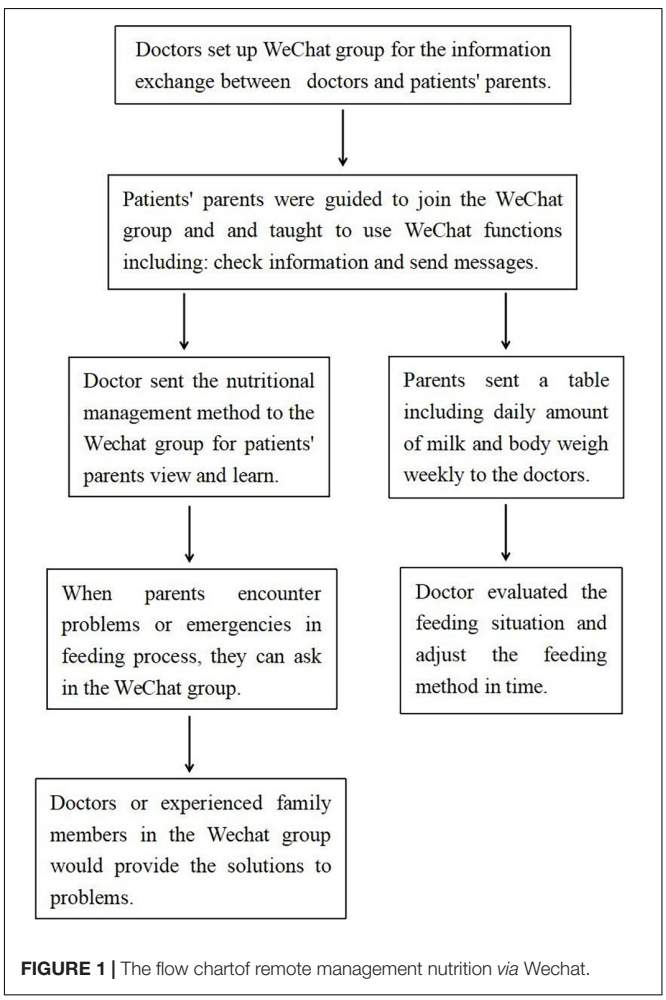

FIGURE 1 | The flow chartof remote management nutrition *via* Wechat.

TABLE 1 | Demographic data of patients and their parents in two groups at discharge.

	Intervention group	Control group	*P*
Number	32	30	
Age (Day)	19.4 ± 6.3	20.2 ± 6.6	0.346
Weight (kg)	3.4 ± 0.4	3.3 ± 0.5	0.456
Height (cm)	47.1 ± 1.5	46.9 ± 1.7	0.405
WAZ	−2.1 ± 0.4	−2.0 ± 0.5	0.539
Disease			
Ventricular septal defect	7	6	0.995
Patent ductus arteriosus	8	9	
Pulmonary stenosis	2	2	
Aorta arch constriction	3	2	
Ventricular septal defect with patent ductus arteriosus	6	7	
Total anomalous pulmonary venous connection	2	2	
Complete transposition of great arteries	2	1	
Aortic arch interrupt	2	1	
Feeding patterns			
Nasogastric	7	6	0.925
Bottle-feeding	21	21	
Direct breastfeeding	4	3	
Age of parents (year)	39.6 ± 3.8	30.5 ± 5.2	0.306
Family income			
Low income	9	10	0.897
Middle-income	18	16	
High income	5	4	
Parents' education level			
Under high school	6	5	0.905
High school	8	7	
Junior college	12	10	
Bachelor degree or higher	6	8	
Living condition			
Rural area	20	19	0.946
City	12	11	

The age of premature infants was calculated after corrected gestational age.

TABLE 2 | Comparison of feeding, growth and development between the two groups 3 months after discharge.

	Intervention group	Control group	*P*
Weight (kg)	5.8 ± 0.5	5.3 ± 0.8	0.016
Height (cm)	57.7 ± 3.7	55.4 ± 2.9	0.010
WAZ	−0.7 ± 0.5	−1.3 ± 0.8	0.006
Adding high-energy milk or breast milk fortifier	15	6	0.025
Amount of milk	142.2 ± 14.7	115.0 ± 13.2	0.000
FCTI score of parents	20.9 ± 5.9	24.5 ± 4.6	0.011

be easily mastered. We sent the nutritional management method to the WeChat group for all parents of patients to view and learn. A doctor on our team was available to answer parents' questions on WeChat from 18:00 to 21:00 every day. If the parents encountered problems or emergencies in the feeding process, they could also seek help from doctors or experienced family members in the WeChat group, and problems could be solved in time. Parents could also communicate with each other in the WeChat group to share their care and feeding experiences. Parents were asked to send a weekly table to the doctor *via* WeChat. The table included the amount of milk and body weight daily, so that the doctor could evaluate the feeding situation and adjust the feeding method accordingly (**Figure 1**).

Traditional Nutrition Management After Discharge

The nutritional management method was printed in the manual and sent to the parents of the control group at discharge. If the situation was abnormal, they were instructed to return to the

hospital for timely review. If there was an emergency, they were instructed to go to a nearby hospital in time.

All patients in our department were reviewed in the outpatient department 3 months after discharge. The data collected at the 3-month follow-up included growth and development data, as well as complication data, such as pneumonia, feeding difficulties, feeding intolerance, liver insufficiency, times of readmission, and the Family Caregiver Task Inventory (FCTI) scale.

Family Caregiver Task Inventory Scale

The FCTI scale was used to evaluate the care ability of the parents. The scale consists of 25 items, including 5 dimensions: adapting to care roles, responding, and providing assistance, addressing personal emotional needs, assessing family and community resources, and adjusting personal life and care needs. Each entry adopts the Likert 3-grade scoring method: 0 points mean not difficult, 1 point means difficult, and 2 points mean extremely difficult. The total score on the scale is 50 points. The higher the score, the more difficulty the caregiver faces, and the lower the care ability (16).

Statistical Analysis

The SPSS 25.0 software was used for statistical analysis. Continuous data are presented as the mean ± standard deviation (SD). The continuous data conformed to a normal distribution by the normal distribution test. Continuous data between the two groups were compared by *t*-test, and a *p*-value of <0.05 was defined as a statistically significant difference. Qualitative data between the two groups were compared by Fisher's test, and a *p*-value of <0.05 was defined as a statistically significant difference.

RESULTS

The general information of patients and their parents at discharge in the two groups, including age, height, weight, weight-for-age z score (WAZ), disease, type of feeding, parents' age, parent's education level, family income, and family living environment, showed no statistical significance (**Table 1**).

Three months after discharge, the comparison of feeding situation, growth, and development between the two groups showed that the weight, height, and WAZ of the intervention group were significantly higher than those of the control group. The amount of milk and patients eating high-energy milk or breast milk fortifiers in the intervention group were also significantly higher than those in the control group. The care ability of the parents in the intervention group was significantly higher than that in the control group (**Table 2**).

During the follow-up period 3 months after discharge, the incidence rates of respiratory tract infection and readmission in the intervention group were significantly lower than those in the control group. There was no significant difference in the incidence of feeding intolerance, cardiac insufficiency, or arrhythmia between the two groups. No necrotizing enterocolitis, liver insufficiency, renal insufficiency, or gastrointestinal bleeding occurred in the two groups (**Table 3**).

TABLE 3 | Comparison of complications between the two groups during 3 months follow-up time.

	Intervention group	Control group	*P*
Respiratory tract infection	3	9	0.040
Feeding intolerance	7	4	0.379
Necrotizing enterocolitis	0	0	–
Readmission	1	6	0.036
Liver insufficiency	2	1	0.593
Renal insufficiency	0	0	–
Gastrointestinal hemorrhage	0	0	–
Cardiac insufficiency	0	1	–
Arrhythmology	3	2	0.696

DISCUSSION

Malnutrition and disturbance of growth have always been common and serious problems in infants with CHD, and the more complex and severe CHD is, the more serious these problems are (17). For patients who need surgical treatment in the neonatal period, their condition is critical before surgery, and after surgical trauma, extracorporeal circulation trauma, and post-operative fluid restriction treatment, patients face serious malnutrition at discharge (18, 19). Homecare for neonates after CHD surgery is a daunting task (20). Nutrition and feeding problems are the biggest source of stress for parents (8, 9). Malnutrition and growth disorders are highly prevalent and associated with poor clinical outcomes (21). However, at present, there is no optimal nutritional management strategy for infants with CHD after discharge, especially for neonates with severe CHD.

In recent years, with the rapid development of medical information technology, telemedicine has been widely used in the home management of chronic diseases, which is conducive to improving home care ability, improving the prognosis of patients, and reducing the incidence of complications (22, 23). To solve the feeding and nutrition problem of neonates with CHD surgery, promote weight, growth and development catch-up, and reduce the incidence of complications, we performed nutrition management *via* remote medicine, which can extend high-quality medical services from hospitals to families, children with remote management of feeding, and implementation of nutritional support. We remotely managed the patients' feeding and implemented nutritional support. WeChat is the most widely used medical media in China, so WeChat was chosen as the media for remote nutrition management. Through remote nutrition management, we can regularly remind families to learn about feeding programs and monitor their feeding and weight gain. When parents have problems learning about feeding programs or feeding, we also guided them remotely to learn and improve. In these ways, parental care ability in the intervention group was significantly better than that in the control group.

Weight gain, or even weight catch-up, mainly depends on the amount of milk consumed and the energy density of milk, therefore, improving the amount of milk and energy density of milk promotes maximum weight gain (24). Neonatal

gastrointestinal function after CHD surgery is often inadequate, and they are prone to feeding-related complications, such as vomiting, diarrhea, and abdominal distension (25, 26). Many parents of these neonates lack care ability, skill, and experience. To prevent feeding-related complications, they cannot add milk, do not dare to add high-energy milk or breast milk fortifier, and feed in small amounts and many times. This often makes neonates perpetually hungry, leading to poor sleep, which is not conducive to weight gain, growth, or development. Remote nutrition management can regularly monitor the feeding situation, correct bad feeding habits, and help neonates reach the target milk volume and target calories as often as possible. For those who did not meet the standard, we guided the addition of high-energy milk or breast milk fortifier to improve energy density. Although adding high-energy milk or breast milk fortifier potentially increases complications of feeding intolerance, (27) we instructed parents to closely observe the related complications. In cases of abdominal distention, diarrhea, constipation, etc., probiotics, glycerine enema, or Montmorillonite powder was used in the early stage for symptomatic treatment. There was no increase in the incidence rate of feeding intolerance complications in the intervention group compared with the control group in this study. Our study showed that after remote nutrition management, the feeding volume in patients who received high-energy milk or breast milk fortifier in the intervention group was significantly better than those in the control group. As a result, the weight and WAZ of the intervention group were significantly higher than those of the control group.

Gastrointestinal and feeding complications, such as dysphagia, feeding intolerance, and necrotizing enterocolitis, are common problems of neonates after CHD surgery and persist for a long time after discharge (25, 26). Gastrointestinal and feeding problems have a significant impact on weight gain, growth, and development, and they are also associated with post-operative complications and readmission. Thirteen patients in this study had dysphagia at discharge and required nasogastric feeding. If such patients cannot be meticulously cared for during the feeding process, they are prone to vomiting and choking milk, which can easily lead to respiratory tract infections. Malnourished infants are also prone to respiratory tract infections and other complications, leading to readmission (28). Remote nutrition management can effectively improve the nutritional status and growth and development of infants, improve the parenting ability of children, and reduce the incidence of respiratory complications and readmission rates.

This study has some limitations. First, this study was a single-center retrospective study with small sample size. Second, due to unstable internet support, poor patients could not participate in the study.

CONCLUSION

Remote nutritional management as a new nutritional management strategy for neonates with CHD surgery after discharge can effectively improve nutritional status and promote growth and development.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

This study was approved by the ethics committee of our hospital and strictly adhered to the tenets of the Declaration of Helsinki. There were no human subjects involved in this work. In addition, all patients' guardians signed an informed consent form before the study.

AUTHOR CONTRIBUTIONS

Q-LZ designed the study, acquired and interpreted the data, and drafted the manuscript. S-HL analyzed and interpreted the data. W-HL acquired and analyzed the data. HC had made substantial contributions to conception and design. QC was involved in the analyzes and interpretation of data, revising the manuscript, and given final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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Anxiety and Depression in Adults With Congenital Heart Disease

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Introduction: Anxiety and depression can worsen outcome in patients with heart disease. We elucidate the prevalence of anxiety and depression in a cohort of adults with congenital heart disease (ACHD).

Materials and Methods: Prospective screening for anxiety or depression was performed in 204 consecutive patients of the outpatient clinic of our tertiary care center using the Hospital Anxiety and Depression Scale (HADS) questionnaire and the distress thermometer (DT) as a potential ultra-short screening test. Functional data were assessed at liberty of the responsible physician. HADS scores $\geq$ 8 were considered doubtful and scores $\geq$ 11 as confirmed cases of anxiety or depression, respectively. HADS results were compared with a historical group of 100 patients with non-Hodgkin Lymphoma (NHL) as well as German reference values from the literature.

Results: Patients from the ACHD cohort were 28 $\pm$ 10 years old (mean $\pm$ *SD*, 54% male), 34% had a simple, 51% a moderate, including 52 patients with transposition of the great arteries after arterial switch operation, and 15% a heart defect of severe complexity. Prevalence of depression in ACHD was comparable to the German normal population (5.9% ACHD vs. 5.4% control). In contrast, prevalence of anxiety was higher than expected from reference values (12.7% ACHD vs. 5.6% control). There was a positive association between psychological distress and NYHA class [anxiety: OR 2.67 (95% CI, 1.50–4.76) p = 0.001; depression: OR 2.93 (95% CI, 1.60–5.35) p = 0.0005], but not with age, gender, or heart defect severity. Percentages of patients with ACHD with anxiety were significantly higher than in a cohort of patients with indolent non-Hodgkin lymphoma (NHL) but comparable to those with aggressive NHL (HADS-A $\geq$ 11: ACHD 12.7%, indolent NHL 2.2%, aggressive NHL 13.2%; p = 0.037 ACHD vs. indolent NHL; p = 0.929 ACHD vs. aggressive NHL). The distress thermometer screening

test had only a fair discriminatory ability (AUC 0.708; p = 0.002) and is therefore of limited usability.

Conclusion: Adults with congenital heart disease exhibit an increased risk for anxiety disorders independently of the severity of the underlying heart defect. Anxiety prevalence was comparable to a historical cohort of patients with aggressive NHL underlining the importance of a routine screening for psychosocial distress in adults with congenital heart disease.

Keywords: anxiety, depression, ACHD adult congenital heart disease, locus of control, Hospital Anxiety and Depression Scale (HADS)

INTRODUCTION

Most of the children born with congenital heart defects survive well into adulthood. However, depending on the complexity of the heart defect, the children might need to undergo several staged operations during their first years of life. In patients with very complex heart disease, even then, only a palliative situation can be accomplished. However, life-long cardiac supervision is mandatory not only for patients with severe congenital heart defects, but also with mild or moderate congenital heart defects to detect potential problems, arising from not yet cared for lesions or late sequelae of previous operations, early enough to circumvent long-lasting limitations of the cardiac function.

Previous studies evaluated anxiety and depression levels as well as the quality of life in children and adults with congenital heart disease. Quality of life was mainly affected by subjective measures such as functional NYHA class and socio-demographic factors (1, 2) whereas objective measures such as the severity of the underlying heart defect or maximum exercise capacity did not. Indeed, due to lifestyle adaptations and resilience adults with congenital heart disease tend to overestimate their functional capacity (3). Besides the quality of life, the prevalence of depression and anxiety is significantly increased in patients with congenital heart disease afflicting up to 30% of the study population (4, 5). The long-term cardiovascular effects of this phenomenon are not yet determined.

The link between psychological distress and worse cardiovascular outcome has been well established in patients with acquired heart disease as depression is a known independent predictor of all-cause mortality in patients with acquired heart failure (6). As such, the risk for major cardiovascular events in the coronary heart disease is increased 3.7 times in patients with anxiety disorder and 3.1 times in patients with depression (7). In addition, patients with coronary artery disease and concomitant depression or anxiety have increased all-cause mortality (8). Vice versa, psychosocial stress is a risk factor for the development of myocardial infarction (9).

Therefore, besides the physical wellbeing of their patients, cardiologists should also spotlight concealed psychosocial distress as it has been emphasized by a recent position statement of the European Association of Preventive Cardiology (10). Questionnaires such as the "Hospital Anxiety and Depression Scale (HADS)" or structured interviews are time consuming, and hence difficult to incorporate into clinical routine. Thus, easily implementable screening tests are needed for a wide acceptance of patients and doctors.

The aim of this study was to evaluate prevalence of anxiety and depression in adults with congenital heart defects presenting in the out-patient clinic of our specialized tertiary care center. In addition, we wanted to assess the sensitivity of the ultra-short-scale pencil and paper "distress thermometer (DT)" as a potential screening tool being frequently applied in psycho-oncology settings (11).

MATERIALS AND METHODS

This is a single center prospective cohort study which was conducted between 01 October 2015 and 31 December 2016. During a routine visit in the outpatient clinic of the specialized tertiary care for adults with patients with congenital heart defect were asked to complete four questionnaires to detect psychosocial distress and collect demographic data. Participation was optional, meaning that the routine follow-up was performed independently of the study. Inclusion criteria were age $\geq$ 18 years, presence of congenital heart disease and ability to consent. Clinical examination and cardiac diagnostic tests were performed at liberty of the responsible physician independent of the study. Complexity of the heart defect was classified as simple (class I), moderate (class II), or severe (class III) according to the Warnes classification. The study was approved by the ethics committee CTC-A Nr. 14-159. The following questionnaires were used:

(1) Distress thermometer (DT): an ultra-short screening tool consisting of a visual analog scale drawn as a thermometer (12). The scale ranges from 0 (no distress) to 10 (severe distress). The patient has to mark his subjective stress level during the past week. There is a complementary list with various problem areas that can be checked as well.

(2) Hospital Anxiety and Depression Scale (HADS): a self-rating questionnaire developed for patients with somatic diseases, consisting out of 14 questions/items. The score for each item can range between 0 and 3. The questionnaire covers 7 items for depression and 7 items for anxiety. Scores for each question are added up. A score $\geq$ 8 is considered as suspect and a score $\geq$ 11 as probable for the respective condition (13). Results were compared with published reference values (14) and a historical control of 100 patients with indolent or aggressive NHL published previously. (15).

(3) Questionnaire for the locus of control (LoC): analyses to what extent the individual believes in the fact that health and disease can be impacted internally by the person itself or externally by caregivers or just by fate (16). The test encompasses 21 questions using a Likert-type style.

Statistics

Statistical analysis has been performed using SPSS IBM statistics software version 28.

Baseline characteristics and test scores were compared between the groups using two-sample *t*-tests for continuous variables and Pearson chi-square tests for categorical data.

Multivariable ordinal logistic regression analyses were performed with HADS anxiety or depression levels as a dependent variable. The variables Warnes classification and NYHA classification are ordinal parameters. Gender, history of arrhythmia, use of cardiovascular drugs, and reduced ejection fraction of the main chamber are binary parameters. Age was the only metric parameter.

Binary logistic regression analysis evaluating the association of HADS questionnaire with Locus of Control or Distress Thermometer performed with HADS anxiety or depression levels as dependent variable. HADS–A (anxiety) or HADS–D (depression) levels $\geq$ 8 were coded as 1. The three Locus of Control subscales are included as ordinal denominator.

Receiver operating characteristic curve (ROC) analyses were performed according to the SPSS ROC curve tool with HADS–A or HADS–D levels $\geq$ 8 or $\geq$ 11 as binary parameter.

A *p*-value less than 5% was considered as statistically significant in each analysis.

RESULTS

Study Population Characteristics

In total, 204 patients completed the questionnaires along with their routine cardiology tests, reflecting approximately 25% of all patients with ACHD consulting the outpatient clinic during the study period. Most of the participants had a congenital heart defect of moderate complexity (51%, *n* = 103) including a large group of patients with transposition of the great arteries after arterial switch operation (*n* = 52). One third of patients had a congenital heart defect of simple complexity (34%, *n* = 70), 15% of severe complexity (*n* = 31) (**Table 1**).

Baseline characteristics of the evaluated patient cohort are depicted in **Table 2**. In total, 54% of the participants were male (*n* = 111), 46% female (*n* = 93) with a mean age of 28 $\pm$ 10 years. More than half of the patients underwent at least one operation in the past (57% one operation, 14% two, 13% more than two operations). In the majority of cases, echocardiographic systolic function of the systemic ventricle was normal (80%, *n* = 163) and only about one-third of the patients had a cardiovascular medication (35%, *n* = 71). In total, 27% of the participants had a history of arrhythmia and 7% a cardiac device implanted. Following the clinical criteria, 63% of the patients were in NYHA class I (no symptoms or limitation during exercise, *n* = 128), 33% in NYHA class II (strenuous exercise causes symptoms, *n* = 67), and only 4% in NYHA class III (marked limitation of exercise capacity, less than ordinary activity causes symptoms, *n* = 8). This went along with a self-reported exercise frequency exceeding once a week in 45% of the patients (*n* = 92), once a week in 24% of the patients (*n* = 49), once a month in 9% (*n* = 19), and less than once a month or never in 6% (*n* = 12) and 14% of the patients (*n* = 29), respectively.

TABLE 1 | Overview of the distribution of the underlying heart defects.

	Heart defect	*n*	%
I- mild	Aortic valve disease	34	16.7
	Mitral valve disease	6	2.9
	Congenital AV-block III	1	0.5
	Cor triatrium sinistrum	1	0.5
	ASD II	9	4.4
	ASD I or sinus venosus defect	5	2.5
	VSD	14	6.9
II- moderate	Coarctation aorta	14	6.9
	AVSD (partial, complete)	7	3.4
	Pulmonary valve disease	5	2,5
	Fallot tetralogy	23	11.2
	Tricuspid valve disease	2	1.0
	dTGA-arterial switch	52	25.5
III- severe	dTGA-Senning/Mustard	9	4.4
	ccTGA	2	1
	Truncus arteriosus	3	1.5
	Pulmonary atresia	7	3.5
	Univentricular heart	10	4.9

Cardiovascular risk factors were dominated by smoking (13%, *n* = 26), arterial hypertension (10%, *n* = 20), and dyslipidemia (7%, *n* = 14) whereas diabetes was only reported rarely (1.5%, *n* = 3). In total, 12% of the participants had a history of a psychiatric disease and 6% took a psychiatric medication.

Prevalence of Anxiety Disorder

Anxiety and depression levels were evaluated using the HADS questionnaire. The items of the questionnaire can be sorted into the HADS-A (anxiety) and HADS-D (depression) subscale to distinguish both conditions. Scores equal or above 8 in each subscale suggest the presence of anxiety or depression, whereas scores equal or above 11 affirm the diagnosis with a high certainty.

There were signs for an anxiety disorder with a HADS-A score $\geq$ 8 points in 22.5% and evidence for anxiety with a HADS–A score $\geq$ 11 in 12.7% of the participants of the whole congenital heart disease patient cohort of our study. According to Hinz and Brahler (14), percentages of subjects with HADS–A cut-off values $\geq$ 8 and $\geq$ 11 in the German population were 21% and 6.8% (*n* = 4,410, 55% women, age 50.3 $\pm$ 17.2 years), respectively. In those subjects with an age less than 40, more closely resembling our ACHD study group, the percentages of participants scoring $\geq$ 8 and $\geq$ 11 in the HADS–A anxiety subscale were 17.4% and 5.6%, respectively (*n* = 609 men and *n* = 833 women). Just looking at confirmatory cases with an HADS–A score $\geq$ 11, the prevalence of anxiety in the ACHD group is higher than

TABLE 2 | Cardiovascular baseline characteristics of the study population.

	Baseline characteristics		Severity congenital heart defect		
		All *n* (%)	Mild *n* (%)	Moderate *n* (%)	Severe *n* (%)
		204	70	104	30
Age	Mean ± *SD* (min-max)	28 ± 10 (18–59)	29 ± 11 (18–59)	26 ± 9 (18–57)	30 ± 9 (18–54)
Gender	Male	111 (54)	36 (51.4)	58 (55.8)	17 (56.7)
	Female	93 (46)	34 (48.6)	46 (44.2)	13 (43.3)
Number of cardiac operation	0	30 (15)	26 (37.1)	3 (2.9)	1 (3.3)
	1	117 (57)	33 (47.1)	76 (73.1)	8 (26.7)
	2	28 (14)	6 (8.6)	18 (17.3)	4 (13.3)
	≥ 3	26 (13)	4 (5.7)	7 (6.8)	15 (50)
NYHA class	I	128 (63)	47 (67.1)	73 (70.2)	8 (26.7)
	II	67 (33)	20 (28.6)	30 (28.8)	17 (56.7)
	III	8 (4)	2 (2.9)	1 (1)	5 (16.7)
Exercise	Never	29 (14)	7 (10)	12 (11.5)	10 (33.3)
	<1 a month	12 (6)	6 (8.6)	3 (2.9)	3 (10)
	Once a month	19 (9)	6 (8.6)	10 (9.6)	3 (10)
	Once a week	49 (24)	17 (24.3)	25 (24)	7 (23.3)
	Several times a week	92 (45)	32 (45.7)	53 (51)	7 (23.3)
Pacemaker/ICD		14 (7)	4 (5.7)	2 (1.9)	8 (26.7)
History of arrhythmia		55 (27)	15 (21.4)	20 (19.2)	20 (66.7)
Cardiac medication	Yes	70 (34)	27 (38.6)	20 (19.2)	23 (76.7)
	Beta-blocker	39 (19)	16 (22.9)	10 (9.6)	13 (43.3)
	ACE-inhibitor, ARB	21 (10)	11 (15.7)	5 (4.8)	5 (16.5)
	Diuretics	8 (4)	2 (2.9)	2 (1.9)	4 (13.3)
	MRA	4 (2)	1 (1.4)	0	2 (6.5)
	Antiarrhythmic drugs	5 (2.5)	1 (1.0)	0	4 (13.3)
	OAK	34 (17)	16 (22.9)	4 (3.8)	14 (46.7)
	ASS	9 (4.4)	2 (2.9)	1 (1)	6 (20)
Systemic ventricle systolic function	Normal	163 (80)	59 (84.3)	94 (90.4)	10 (33.3)
	Mildly reduced	14 (6,8)	3 (4.3)	5 (4.8)	6 (20)
	Moderately reduced	3 (1,5)	0	1 (1)	2 (6.7)
	Severely reduced	2 (1)	0	1 (1)	1 (3.3)
Cardiovascular risk factors	Arterial hypertension	20 (10)	8 (11.4)	10 (9.6)	2 (6.7)
	Diabetes mellitus	3 (1.5)	2 (2.9)	0	1 (3.3)
	Smoking	26 (13)	8 (11.4)	12 (11.5)	6 (20)
	Hypercholesterolemia	14 (7)	6 (8.6)	4 (3.4)	4 (13.3)
Non-cardiac comorbidities (all)		83 (40.7)	33 (47.1)	36 (34.6)	14 (46.7)
Neurologic disorder		22 (10.8)	9 (12.9)	12 (11.5)	1 (3.3)
Psychiatric disorder		25 (12.3)	8 (11.4)	12 (11.5)	5 (16.7)

expected if compared to the published reference value (12.7% ACHD vs. 5.6% control). Since a statistical comparison with the results of the literature was not possible, we included a historical cohort of patients with indolent or aggressive non-Hodgkin lymphoma (NHL) investigated previously in the Department of Psychiatry, Psychotherapy, and Psychosomatics of our hospital. This study group comprises of 100 patients with NHL (44 women, 61.3 ± 13.6 years). For detailed baseline characteristics, we refer to the original analysis (15). There was no difference in percentages of subjects meeting the criteria HADS–A ≥ 8 between patients with congenital heart disease and indolent or aggressive lymphoma (HADS–A ≥ 8: ACHD 22.5%, NHL indolent 21.7%, NHL aggressive 34%; ACHD vs. NHL indolent: $p = 0.90$; ACHD vs. NHL aggressive $p = 0.25$) **Table 3**. The number of cases with strong signs for anxiety reflected by an HADS–A ≥ 11 was significantly higher in the ACHD group compared with those patients with indolent NHL but comparable to those patients with aggressive NHL (HADS–A ≥ 11: ACHD 12.7%, NHL indolent 2.2%, NHL aggressive 13.2%; ACHD vs. NHL indolent $p = 0.037$; ACHD vs. NHL aggressive $p = 0.929$) (**Figure 1**).

Prevalence of Depression

Hospital Anxiety and Depression Scale sub-scale Depression score ≥ 8 was found in 10.8%, HADS–D score ≥ 11 in 5.9% of the patients with congenital heart disease. The number of patients with depression was therefore comparable to published

TABLE 3 | Percentage of subjects reaching the HADS cut-off values ≥ 8 or ≥ 11 in the respective groups and HADS as well as DT mean + *SD* values if available.

	HADS-A mean (*SD*)	HADS-A ≥ 8 *n* (%)	HADS-A ≥ 11 *n* (%)	HADS-D mean (*SD*)	HADS-D ≥ 8 *n* (%)	HADS-D ≥ 11 *n* (%)	DT mean (*SD*)
Study group- ACHD							
All	5.20 (4.19)	46 (22.5)	26 (12.7)	3.07 (3.49)	22 (10.8)	12 (5.9)	4.7 (2.5)
Simple complexity	6.03 (4.69)	22 (31.4)	14 (20.0)	3.80 (4.15)	11 (15.7)	7 (10.0)	4.7 (2.3)
Moderate complexity	4.52 (3.53)	16 (15.4)	8 (7.7)	2.52 (2.89)	7 (6.7)	3 (2.9)	4.7 (2.5)
Severe complexity	5.60 (4.83)	8 (26.7)	4 (13.3)	3.27 (3.48)	4 (13.3)	2 (6.70)	5.0 (2.6)
TGA (ASO)	4.06 (3.62)	7 (13.5)	4 (7.7)	2.44 (2.76)	3 (5.8)	0 (0)	5.0 (2.6)
Historical control–NHL							
All	5.23 (3.86)	28 (28.3)	8 (8.1)	5.14 (4.38)	26 (26.3)	14 (14.1)	
Indolent	4.46 (3.51)	10 (21.7)	1 (2.2)	4.57 (4.37)	9 (19.6)	5 (10.9)	
Aggressive	5.91 (4.16)	18 (34.0)	7 (13.2)	5.64 (4.36)	17 (32.1)	9 (17.0)	
Normative reference according to Hinz and Brahler (14)		(21.0)	(6.8)		(23.7)	(9.4)	

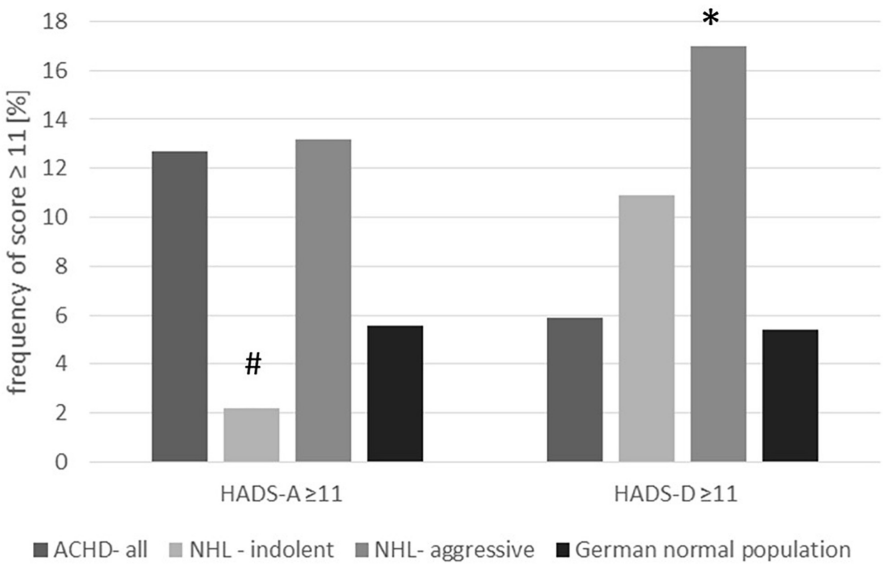

FIGURE 1 | Percentage of subjects with confirmed cases of anxiety or depression (HADS cut-off value ≥ 11). The figure compares the congenital heart disease cohort with the lymphoma cohort and the reference value from the literature. *p = 0.009 ACHD vs. aggressive lymphoma; #p = 0.037 ACHD vs. indolent lymphoma.

HADS data of the German reference population (14) (HADS–D ≥ 11: 5.9% ACHD vs. 5.4% control group age less than 40) as well as the reported prevalence of major depressive disorder in the German population according to Jacobi using structured interviews [(17) overall 12 month prevalence of major depressive disorder 6%, age group 18–34 years 9%, age group 35–49 6.5%; see **Table 3**]. Percentage of subjects with an HADS–D score ≥ 11 or HADS–D score ≥ 8 were significantly lower in patients with congenital heart disease compared with patients with aggressive lymphoma (HADS–D ≥ 8: ACHD 10.8%, aggressive NHL 32.1%, ACHD vs. aggressive NHL: p = 0.001; HADS–D ≥ 11: ACHD 5.9%, aggressive NHL 17%; ACHD vs. aggressive NHL, p = 0.009), but comparable to patients with indolent lymphoma (HADS–D ≥ 8; indolent NHL 19.6%, ACHD vs. indolent NHL, p = 0.103; HADS–D ≥ 11: indolent lymphoma 10.9%; p = 0.225 ACHD vs. indolent NHL) (see **Figure 1**). Previously, Westhoff-Bleck suggested a lower HADS–D cut-off value > 5 for the detection of depression in adults with congenital heart disease (18). In the current cohort, 18.6% of the participants had an HADS–D score > 5, that was significantly lower compared with the NHL patients (p < 0.001 vs. aggressive lymphoma, p = 0.027 vs. indolent lymphoma) and also less than the 25.7% reported in the study by Westhoff-Bleck (**Supplementary Table 1**).

Factors Associated With Anxiety or Depression

Hospital Anxiety and Depression Scale mean values and percentage of subjects reaching the cut-off values are depicted in **Table 3**. There was a trend toward a lower HADS anxiety score in the congenital heart disease of moderate complexity compared

with simple or severe complexity which, however, did not reach statistical significance (HADS–A mean ± *SD*: simple Warnes I 6.03 ± 4.69, moderate Warnes II 4.52 ± 3.53, severe complexity ACHD Warnes III 5.60 ± 4.83, $p = 0.056$).

Participation in the study was optional and all patients presenting in the out-patient clinic during the respective time frame were asked to participate. In the subgroup of patients with congenital heart disease of moderate complexity, we identified 52 patients with transposition of the great arteries after arterial switch operation (ASO). HADS anxiety score ≥ 8 was found in 13.5% and ≥ 11 in 7.7% of the patients with ASO which was not significantly different compared with the total group of patients with ACHD with moderate complexity or the whole ACHD cohort. However, mean HADS–A score was significantly lower in patients with ASO compared with all patients with ACHD (mean ± SD 4.06 ± 3.6 $p = 0.183$ vs. Warnes II, $p = 0.023$ vs. all ACHD; HADS ≥ 8: $p = 0.587$ vs. Warnes II, $p = 0.069$ vs. all ACHD, HADS ≥ 11: $p = 1.00$ vs. Warnes II, $p = 0.208$ vs. all ACHD) **Table 3**.

In the total ACHD group, there was no difference in HADS depression scores with respect to the underlying complexity of the congenital heart disease (HADS–D mean ± *SD*: simple complexity 3.8 ± 4.15, moderate complexity II 2.52 ± 2.89, severe complexity ACHD 3.27 ± 3.48, $p = 0.056$).

In the subgroup of patients with ASO, HADS depression score ≥ 8 was found in 5.8% and ≥ 11 in none. Therefore, the percentage of patients with ASO reaching the cut-off ≥ 11 was significantly lower in comparison to the whole ACHD group. However, if mean HADS–D scores were evaluated they were comparable between ASO and all patients with ACHD (ASO mean ± *SD* 2.44 ± 2.76 $p = 0.788$ vs. Warnes II and $p = 0.134$ vs. all ACHD; HADS ≥ 8: $p = 0.696$ vs. Warnes II and $p = 0.177$ vs. all ACHD, HADS ≥ 11: $p = 0.079$ vs. Warnes II and $p = 0.037$ vs. all ACHD) (**Table 3**).

Multivariate logistic regression analyses were performed revealing a strong association of NYHA class with levels of anxiety and depression [anxiety OR 2.67 (95% CI, 1.50–4.76) $p = 0.001$; depression OR 2.93 (95% CI, 1.60–5.35) $p = 0.0005$]. There was no correlation with age, gender, number of conducted operations, arrhythmia, CV drugs, or systolic heart function (**Figure 2**).

Patients with high anxiety and depression scores reported a higher frequency of doctor visits compared to those patients with normal HADS levels (anxiety $p = 0.047$; depression $p < 0.001$). In 50% of the patients with elevated anxiety scores, a psychiatric diagnosis had been made already before participation in this study, whereas in 50%, there was no previously known anxiety disorder.

In 19 patients, HADS subscales anxiety and depression were both elevated. Patients in this sub-cohort were 36 ± 12 years old (19–57 years). Warnes and NYHA class distribution (I/II/III) were $n = 10/5/4$ and $n = 5/12/2$, respectively. We did not find markers to predict both anxiety and depression.

There was no association between cardiovascular risk factors such as arterial hypertension or non-cardiac, i.e., neurological comorbidities with anxiety or depression. However, a significant positive association between pre-diagnosed psychological disorders and fulfilled HADS criteria for anxiety and depression could be confirmed (**Supplementary Table 2**).

Association of Anxiety and Depression With Locus of Control and Distress Thermometer

The locus of control (LoC) questionnaire evaluates the patient's conception of its influence on disease progression with the three sub-categories chance, internal or external control. In our study, the LoC identified different personality traits of patients with high anxiety scores in contrast to those with high depression subscale levels. Patients with signs for anxiety, according to the HADS analysis, showed a significant inverse correlation with the LoC chance subscale as well as a positive association with the internal control subscale reflecting a perception of having internal control over the outcome of their life. In contrast, patients with depression showed a highly significant positive association with the LoC subscale chance and an inverse correlation with internal control indicating a personality that accredits its wellbeing mainly to chance but not to its own action (**Figures 3A,C**). In 19 patients presented with a combination of anxiety and depression, the feelings were dominated by a positive correlation with internal control and a negative association with chance LoC (internal control OR 1.41; CI, 95% 1.03–1.26, $p = 0.009$; chance OR 0.9; CI, 95% 0.84–0.97, $p = 0.004$).

Neither patients with anxiety nor with depression showed a correlation with the subscale external control implying that external factors such as the peer group or the responsible physician do not have an important influence on the mental state of health in this cohort.

The Distress Thermometer (DT) score revealed a significant but only fair discriminative ability to detect clinically highly relevant anxiety defined as HADS–A level ≥ 11 (AUC (area under the curve) 0.708; $p = 0.002$). A DT level > 3.25 went along with a good sensitivity of 90% but a low specificity of 36%, whereas a DT level > 4.75 detected anxiety with a sensitivity of 77% and a specificity of 47% (**Figure 3B**).

Comparably, clinically significant depression with HADS–D levels ≥ 11 was determined only moderately well with the DT questionnaire (AUC 0.708; $p = 0.002$). A DT level > 3.25 went along with a good sensitivity of 91% but a low specificity of 35%, whereas a DT level > 4.75 detected depression with a sensitivity of 77% and a specificity of 49% (**Figure 3D**). The DT was not able to reliably detect HADS–A or HADS–D levels ≥ 8 in ROC analyses (HADS–A: AUC 0.656; $p = 0.002$; HADS–D: AUC 0.688, $p = 0.007$).

DISCUSSION

This study shows an increased prevalence of anxiety in adult patients with congenital heart disease compared with the published reference values of the German population. Best predictor for the presence of an anxiety disorder was the functional capacity reported as NYHA class. Neither the severity

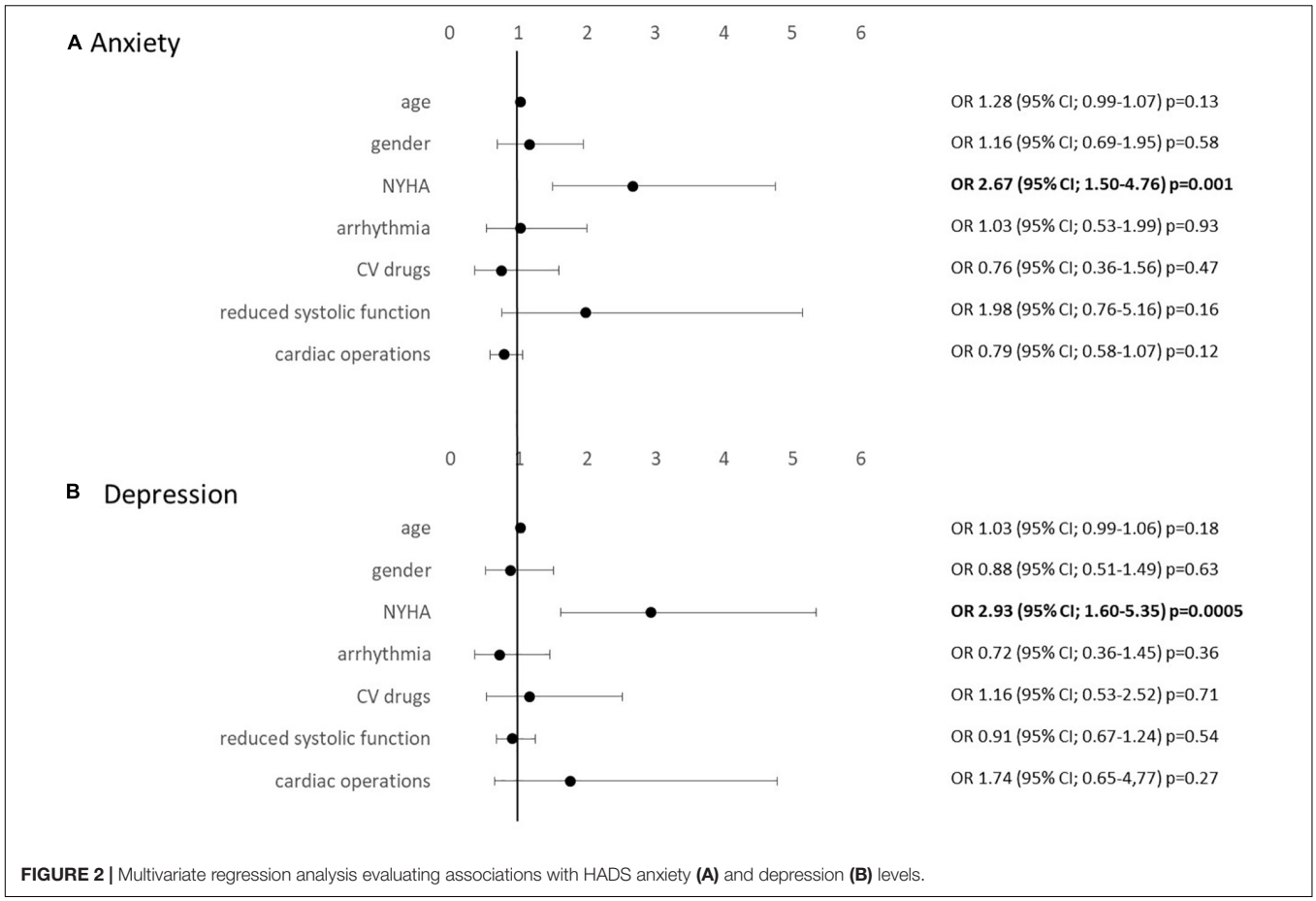

FIGURE 2 | Multivariate regression analysis evaluating associations with HADS anxiety **(A)** and depression **(B)** levels.

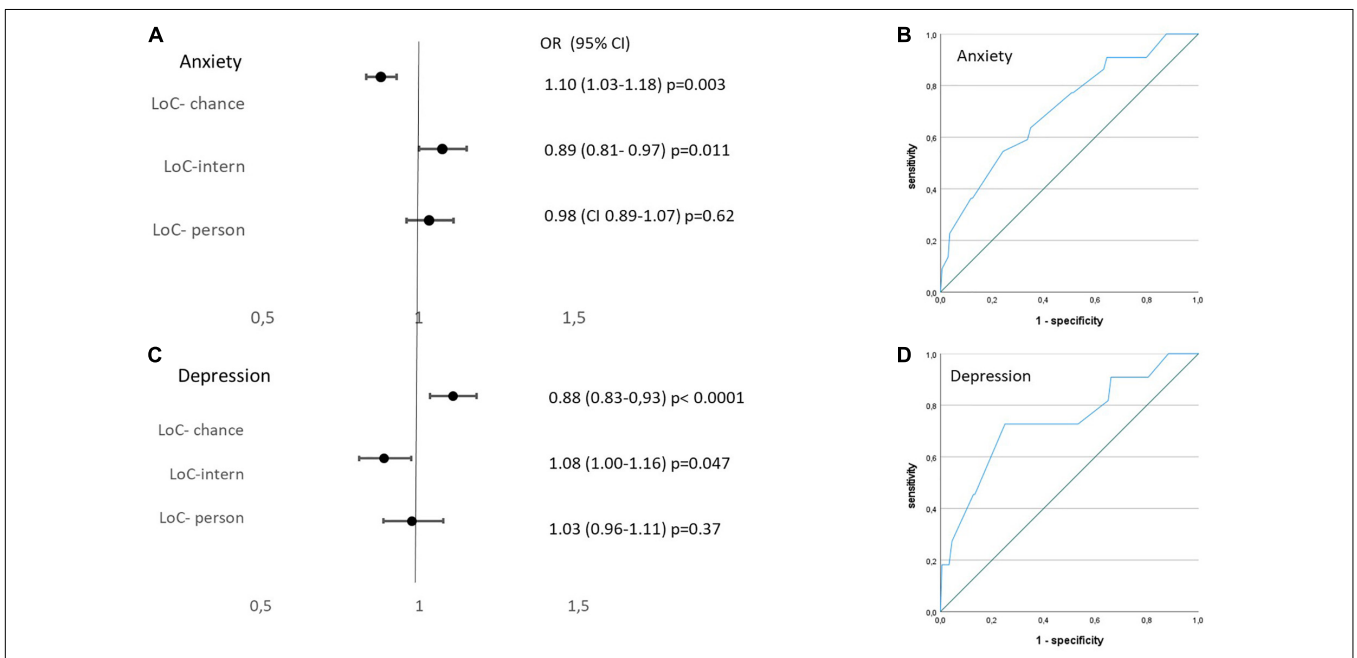

FIGURE 3 | Left: Multivariate regression analysis evaluating associations of locus of control (LoC) with **(A)** HADS A-anxiety and **(C)** HADS-D-depression levels. Right: Receiver operating curve analysis evaluating discriminatory ability of Distress Thermometer for **(B)** HADS A-anxiety and **(D)** HADS-D-depression levels.

of the underlying congenital heart defect nor the global systolic heart function affected the level of anxiety.

We were able to show that anxiety levels in adults with congenital heart disease are equal to patients with a malignant disorder sending a strong signal for the necessity to implement screening tools to detect psychological distress during routine cardiology follow-up examination.

The influence of personality traits and coping strategies on psychological distress has been evaluated using the LoC questionnaire. Patients who met the HADS criteria for anxiety showed high internal LoC but a low LoC subscale "chance." This would suggest that patients with anxiety disorder rather implement coping strategies that are based on their own actions and not on external random circumstances or persons. The strong internal belief of control however might paradoxically cause distress itself (anything is the patient's fault) and may rather yield in a worse behavioral health outcome and increased anxiety level among others reflected by an increase number of clinical appointments.

In contrast, depression levels were not increased in ACHD as we would have expected from the literature. Those patients identified with depression showed personality traits consistent with a low belief in internal control but a high conviction of the factor "chance" in their clinical wellbeing.

Kovacs was able to identify a high prevalence of lifetime mood or anxiety disorder in 50% of 280 patients with congenital heart disease, that was mainly predicted by non-disease specific factors such as loneliness and fear of negative evaluation (19). The group of Westhoff-Bleck performed a study including 150 adults with congenital heart disease, 28% of the participants showed signs of anxiety and 31% of mood/depressive disorders (20). In this study, psychiatric diagnosis was based on structural interviews as well as the HADS and the Beck Depression Inventory-2. Comparable to our results, the presence of mental disorders was negatively correlated with the functional NYHA class. Another study from the same group including 206 patients with adult congenital heart disease reported a prevalence of 25.7% for major depressive disorders. In contrast to our study, the cut-off value for the HADS–D scale was chosen much lower with a cut-off of > 5, due to an internal validation of the lower cut-off using standardized interviews. Even if the lower HADS cut-off points would be applied to our results or the mean values considered, prevalence of depression is lower than expected. The observed differences might be due to differences in the baseline characteristics or confounding co-morbidities of the respective study population. Participants of the study by Westhoff-Bleck were older and had a higher grade of congenital heart defect of severe complexity (18).

In line with the results of our study, prevalence of depression in a cohort including 767 patients with ACHD was lower than what would have been expected for the normal population (8.6%) with no relevant difference between the diagnostic heart disease groups. However, presence of depression was associated with a significant reduction of all dimensions of quality of life. In addition, depression was a stronger predictor for a decreased quality of life than a reduction in exercise capacity (21).

Psychological distress such as anxiety and depression has also been associated with non-adherence to medication and treatment in 451 outpatients with congenital heart disease. Assuming that non-adherence is associated with an increase in cardiovascular events, there is imminent need to reflect the psychological problems in cardiology follow-up visits (22). Indeed, there was an increase in cardiology clinic visits and hospitalization as well as an increased mortality observed in patients with ACHD with anxiety and depression [HR 1.40 (95% CI, 1.17–1.67 for study period depression/anxiety diagnosis, $n = 8{,}334$ (23)]. Vice versa, interventions focused on training the patient's comprehension of the disease and the prognosis proved efficient in patients with acquired heart disease after myocardial infarction. Prevalence of anxiety and depression decreased 3 months post myocardial infarction in the trained group compared with the control group (24).

Kasmi et al. evaluated the prevalence of mood disorder specifically in the young adult patients with transposition of the great arteries and status post arterial switch operation (ASO) (25). The lifetime prevalence for anxiety and depressive disorders was 54 and 43%, respectively, reflecting a highly significant increase compared with the control group. In contrast, the same group reported no increase of depression or anxiety in adult patients with TGA after ASO if the current and not the life-time prevalence was evaluated for example using the HADS questionnaire (25, 26). These findings underline the need for repetitive testing for psychiatric distress in adults with congenital heart disease.

Reliable screening tools are required to implement the evaluation of the psychosocial disorders into routine cardiology follow-up visits. The ultra-short Distress Thermometer (DT) test has been validated in patients with oncological diseases and is now widely used in the clinical setting. DT levels ≥ 3 corresponded well with the HADS test result ≥ 8 with a sensitivity of 77–88% and specificity of 72–79% in 1,323 adult cancer survivors at 6 months post diagnosis in Australia (27). A Swedish group also reported a positive association of the DT with the HADS score with an area under the curve of 0.86 (95% CI, 0.82–0.9). DT score ≥ 4 was associated with a sensitivity of 87%, specificity of 73%, and negative predictive value of 95% (28).

Notably, in our cohort of patients with congenital heart disease, the correlation of the Distress Thermometer with the HADS questionnaire did not reach the acceptable sensitivity and specificity of ≥ 85 and $\geq 75\%$, respectively. Studies with the detailed psychometric analysis (15) and a recent meta-analysis (29) also indicated limitations to the validity of the DT.

Therefore, the evaluation of psychosocial distress in ACHD should make use of standardized questionnaires such as HADS, especially, if staff or time resources are limited and structured clinical diagnostic interviews are difficult to schedule.

STUDY LIMITATION

Limitation of the study is the lack of structured psychiatric interviews in addition to the HADS questionnaire and also an age-matched internal control. However, validity of the HADS test has been confirmed previously in various patient groups with somatic diseases and also in the general population

and may surpass some unstructured assessments (30). The updated S3 guideline in psycho-oncology even requires validated screening tools such as HADS to be conducted and not being replaced by clinical interviews. Our focus was therefore to establish a screening system also if the resources for structured clinical interviews are not available. This, of course, should not stop the physician treating to perform a clinical evaluation independently. In addition, a selection bias cannot be ruled out since participation was voluntary and only a fraction of the patients seen in the outpatient clinic did participate.

CONCLUSION

This prospective evaluation of psychological disorders in a cohort of adults with congenital heart defects shows an increased prevalence of anxiety disorder in this patient group comparable to patients with an active malignant disease. Since a negative impact of anxiety on the long-term outcome of the cardiovascular disease has been suggested in various studies for acquired heart disease, cardiologists should reflect on tools to identify mood disorders and counsel the patients accordingly. Coping strategies that take the disease burden from the patient by providing external psycho-social care should be preferred.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors. Original data will be made available upon request within the terms of a data use agreement and within the general rules of the general data protection and ethics guidelines.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the RWTH Aachen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CL, HH-G, KB, and KM designed the study. PW, HH-G, JP, and CL acquired the data. CL, MF, and KM performed the data analysis. CL, HH-G, KM, MF, JP, GK, and NM did the composition of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.906385/full#supplementary-material

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Functional hepatic deterioration determined by ^{13}C-methacetin breath test is associated with impaired hemodynamics and late Fontan failure in adults

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Background: Despite improved survival a substantial number of Fontan patients eventually develop late failure. Fontan-associated liver disease (FALD) is the most frequent end-organ dysfunction. Although impaired hemodynamics and Fontan failure correlate with FALD severity, no association between hepatic functional metabolic impairment and Fontan hemodynamics has been established.

Hypothesis: Metabolic liver function measured by liver maximum function capacity test (LiMAx®) correlates with Fontan hemodynamics and Fontan failure.

Methods: From 2020 to 2022, 58 adult Fontan patients [median age: 29.3 years, IQR (12.7), median follow-up time after Fontan operation: 23.2 years, IQR (8.7)] were analyzed in a cross-sectional study. Hemodynamic assessment included echocardiography, cardiopulmonary exercise testing and invasive hemodynamic evaluation. Fontan failure was defined based on commonly applied clinical criteria and our recently composed multimodal Fontan failure score.

Results: LiMAx® test revealed normal maximum liver function capacity in 40 patients (>315 μg/h*kg). In 18 patients a mild to moderate impairment was detected (140–314 μg/h*kg), no patient suffered from severe hepatic deterioration (≤139 μg/kg*h). Fontan failure was present in 15 patients. Metabolic liver function was significantly reduced in patients with increased pulmonary artery pressure ($p = 0.041$. $r = -0.269$) and ventricular end-diastolic pressure ($p = 0.033$, $r = -0.325$), respectively. In addition, maximum liver function capacity was significantly impaired in patients with late Fontan failure (289.0 ± 99.6 μg/kg*h vs. 384.5 ± 128.6 μg/kg*h, $p = 0.007$).

Conclusion: Maximum liver function capacity as determined by LiMAx® was significantly reduced in patients with late Fontan failure. In addition, elevated pulmonary artery pressure and end-diastolic ventricular pressure were associated with hepatic functional metabolic impairment.

KEYWORDS

late Fontan failure, Fontan-associated liver disease, end-organ dysfunction, Fontan hemodynamics, metabolic liver function

Introduction

Despite its tremendous success in treating patients with univentricular anatomy, the Fontan operation remains a palliative procedure, which is characterized by abnormal hemodynamics (1, 2). In the long-term course, chronic venous congestion and low cardiac output lead to progressive clinical heart failure with limited treatment options (3, 4). The relative scarceness of effective pharmacological therapies and the limited applicability of mechanical circulatory support restrict end-stage therapeutic strategies to cardiac transplantation, which itself is associated with considerable morbidity and mortality (5, 6). The indications and optimal timing of cardiac transplantation in Fontan patients are still subject of ongoing debate. The urgency of addressing these issues is illustrated by the fact that within the next decades a significant increase in adult Fontan patients experiencing hemodynamic compromise and subsequently cardio-circulatory demise can be expected (7).

Liver-associated morbidity and mortality are well described in the adult Fontan population and constitute major risk factors significantly impacting survival rates after cardiac transplantation (8, 9). Additionally, the indication for a combined heart and liver transplantation is currently subject of ongoing debate. Therefore, reliable diagnostic modalities are required to monitor hepatic end-organ damage, determine the optimal timing for cardiac transplantation and define the indications for a combined heart-liver transplantation. The liver maximum capacity test (LiMAx®) has been developed to quantitatively determine metabolic liver function. Methacetin is exclusively metabolized by the cytochrome P4501A2 (CYP1A2) system, which exclusively exists in hepatocytes (10). Therefore, enzymatic cleavage of intravenously administrated ^{13}C-methacetin into $^{13}CO_2$, reliably correlates with hepatic parenchymal volume and metabolic function (10). Previously, we have demonstrated that structural hepatic alterations antecede functional hepatic impairment as assessed by LiMAx®, with maximum liver function capacity being well preserved in the majority of Fontan patients (11). However, the potential impacts of late Fontan failure and hemodynamics on metabolic liver function are unknown.

Herein, we aimed to analyze the potential associations between maximum liver function capacity and (I) Fontan hemodynamics by clinical, echocardiographic and invasive assessments and (II) late Fontan failure.

Methods

Study design and patients

From 2019 to 2022 58 adult Fontan patients, who successively presented in our outpatient clinic for follow-up, were included in our cross-sectional observational study. All patients received measurement of maximal liver function capacity using LiMAx® test as well as a detailed hemodynamic and hepatic assessment. Exclusion criteria were intolerance to methacetin or paracetamol and/or patient age below 18 years. The institutional review board and ethics committee approved the study (decision number: EA2/127/18). All individual participants consented to participate in the study prior to inclusion.

Hemodynamic assessment

Hemodynamic assessment included clinical evaluation, echocardiography, cardiopulmonary exercise testing (CPET) and cardiac catheterization. Systolic ventricular function was measured by echocardiography based on the modified Simpson's method (12). Atrioventricular valve incompetence (AVVI) was classified as absent/mild, moderate or severe by visual assessment of the regurgitation jet dimensions in color Doppler sonography. CPET was performed following a standardized institutional protocol using a cycle ergometer. Peak oxygen uptake (VO_2peak) was measured in ml/kg*min and normalized in % of age-, gender- and body dimension-adjusted reference values. Cardiac catheterization included measurements of mean pulmonary artery pressure (mPAP) and systemic ventricular end-diastolic pressure (SVEDP). Transpulmonary pressure gradient (TPG) was calculated as the difference between mPAP and pulmonary capillary wedge pressure. Cardiac output (CO) and pulmonary vascular

resistance (PVR) were determined by Fick's principle using oximetry (13). For comparability, CO and PVR are indexed to body-surface area (Cardiac index, CI, l/min/m²; pulmonary vascular resistance index, PVRi, WU*m²). Fontan failure was defined as severe dysfunction of the Fontan circulation caused by impaired ventricular function, moderate to severe atrioventricular valve incompetence, increased pulmonary vascular resistance, recurrent arrhythmia or therapy-refractory protein-losing enteropathy based on commonly applied clinical criteria (14) and our previously described Fontan failure score (15). Briefly, the score includes a set of 15 clinical, echocardiographic, invasive hemodynamic and laboratory parameters and is calculated by assigning one score point for each score item beyond the defined threshold with a range from 0 to 15 points. A score $\geq$ 8 score points detects late Fontan failure with a sensitivity of 99.3 % and a specificity of 53.9 % (15).

Hepatic assessment

Hepatic assessment was performed based on our previously published institutional protocol (16) and consisted of laboratory analyses, hepatic ultrasound and liver stiffness measurement by transient elastography (TE). FibroTest® was computed on Biopredictive website (Paris, France; www.biopredictive.com).

Maximal liver function capacity

The LiMAx® test was performed following the standardized protocol of Stockmann et al. (10).

Briefly, a body weight-adjusted solution (2 mg/kg) of ^{13}C-labeled methacetin was administered intravenously. The hepatozyte-specific CYP1A2 system metabolizes ^{13}C-labeled methacetin into paracetamol and $^{13}CO_2$, which is continuously measured in the exhaled air. The LiMAx test result is calculated based on the individually determined maximum delta-over-baseline ratio of $^{13}CO_2/^{12}CO_2$ (10).

Statistical analysis

Data were collected from medical records of the German Heart Centre Berlin. Data are expressed as median and interquartile range, which were calculated as the 75th minus 25th percentile. Fontan follow-up duration was defined as the interval between Fontan operation and last follow-up. Correlations between maximum liver capacity, echocardiographic, hemodynamic and hepatic parameters as well as the Fontan failure score were assessed using Spearman's correlation and Mann-Whitney U test. Statistical analyses were performed using SPSS statistical software (version 23, IBM Corp., NY, USA). A p-value <0.05 was considered statistically significant.

Results

Patient cohort

Patient characteristics of the entire cohort are provided in Table 1. Median patient age was 29.3 years (IQR 12.7) and median follow-up time after Fontan operation 23.2 (IQR 8.7). The most common underlying cardiac morphologies were tricuspid atresia (n = 18), double inlet left ventricle (n = 15) and unbalanced atrioventricular septal defect (n = 9). Fontan modifications consisted of extracardiac conduit in 22 patients, lateral tunnel in 17 patients and atriopulmonary/ atrioventricular connection (APC/AVC) in 19 patients. From the study cohort, 3 patients died during follow-up; 2 patients after cardiac transplantation and 1 patient on mechanical circulatory support. Two additional patients successfully underwent cardiac transplantation.

Hemodynamic assessment

Results of hemodynamic assessment are presented in Table 2. Systolic ventricular function was preserved/ mildly impaired in 47 patients, moderately impaired in 9 patients and severely impaired in 2 patients. AVVI was classified as absent/mild in 44 patients, moderate in 13 patients and severe in 1 patient. Median percentage of reference VO_2peak was 44.4 % (IQR 21.3) in the entire cohort. Invasive hemodynamic evaluation revealed mPAP, SVEDP and TPG to be within normal reference ranges (Table 1). Calculated median CI was 2.2 L/min/m² (IQR 0.8) and median PVRi 2.3 WU*m² (IQR 1.1). Late Fontan failure was diagnosed in 15 patients.

Hepatic assessment

Results of hepatic assessment are listed Table 3. The laboratory parameters Alanin-Aminotransferase (ALT), Aspartat-Aminotransferase (AST), bilirubin and thrombocytes did not significantly differ between patients with and without Fontan failure, whereas γ-glutamyl-transferase (γGT) was significantly increased in patients with a failing Fontan circulation (p = 0.017). Results from hepatic ultrasound revealed that surface nodularity, ascites and segmental atrophy/ hypertrophy were more frequently detected in patients with Fontan failure (Table 3). Additionally, liver stiffness values measured by TE were significantly higher in patients with a failing Fontan circulation (p = 0.001), whereas Fibrotest® fibrosis score did not differ between patients with and without Fontan failure.

TABLE 1 Patient characteristics.

	Entire cohort (n = 58)	No Fontan failure (n = 43)	Fontan failure (n = 15)	*P*-value
Patient age (years)	29.3 (12.7)	27.8 (10.9)	36.3 (22.0)	0.093
Age at Fontan operation (years)	5.7 (9.0)	4.6 (8.3)	11.4 (7.8)	**0.035**
Follow-up after Fontan (years)	23.2 (8.7)	23.0 (9.1)	24.6 (11.1)	0.214
Cardiac anatomy (n)				0.541
Tricuspid atresia	18 (31.0%)	14 (32.6%)	4 (26.7%)	
Double inlet left ventricle	15 (25.9%)	11 (26.2%)	4 (26.7%)	
Hypoplastic left heart syndrome	2 (3.5%)	1 (2.3%)	1 (6.7%)	
Complex TGA	3 (5.1%)	2 (4.7%)	1 (6.7%)	
Unbalanced AVSD	9 (15.5%)	5 (11.6%)	4 (26.7%)	
Other	11 (18.9%)	9 (20.9%)	2 (13.3%)	
Left ventricular morphology (n)	39 (67.2%)	31 (72.1%)	8 (53.3%)	0.213
Fontan type (n)				0.373
Extracardiac conduit	22 (37.9%)	16 (37.2%)	6 (40.0%)	
Intracardiac lateral tunnel	17 (29.3%)	12 (27.9%)	5 (33.3%)	
APC / AVC	19 (32.8%)	15 (34.9%)	4 (26.7%)	

Data are presented as median and interquartile range or frequencies and %. Statistically significant results are given in bold letters. APC, atriopulmonary connection; AVC, atrioventricular connection; AVSD, atrioventricular septal defect; TGA, transposition of the great arteries.

TABLE 2 Hemodynamic assessment.

	Entire cohort (n = 58)	No Fontan failure (n = 43)	Fontan failure (n = 15)	*P*-value
Ejection fraction (%)	48.0 (11.3)	50.0 (9.0)	40.0 (16.5)	**<0.001**
≤ 45% (n)	18/54 (33.3%)	9/41 (22.0%)	9/13 (69.2%)	**0.005**
AV valve regurgitation (n)				
Absent/mild	44/58 (75.9%)	36/43 (83.7%)	8/15 (53.3%)	0.056
Moderate	13/58 (22.4%)	7/43 (16.3%)	6/15 (40.0%)	
Severe	1/58 (1.7%)	0 (0.0%)	1 (6.7%)	
Cardiopulmonary exercise testing VO_2peak (% of reference)	44.4 (21.3)	46.0 (24.5)	30.4 (31.4)	**<0.001**
< 50% of reference (n)	31/50 (62.0%)	19/37 (51.4%)	12/13 (92.3%)	**0.008**
Transcutaneous oxygen saturation (%)				
at rest	93.0 (4.3)	95.0 (4.0)	92.0 (5.0)	**0.004**
at VO_2peak	92.0 (9.8)	92.0 (9.0)	88.0 (11.0)	0.222
mPAP (mmHg)	12.0 (6.3)	10.0 (4.0)	17.0 (6.0)	**<0.001**
≥ 15 mmHg (n)	16/58 (27.6%)	5/43 (11.6%)	11/15 (73.0%)	**<0.001**
SVEDP (mmHg)	10.0 (7.0)	9.0 (6.0)	14.5 (4.8)	**<0.001**
≥ 12 mmHg (n)	20/43 (46.5%)	8/29 (27.6%)	12/14 (85.7%)	**0.001**
TPG (mmHg)	3.5 (1.0)	4.0 (1.0)	3.0 (5.0)	0.551
CO (L/min)	3.9 (1.4)	3.9 (1.4)	4.1 (1.8)	0.664
CI (L/min*m^2)	2.2 (0.8)	2.3 (0.8)	2.1 (0.7)	0.18
PVR (WU)	0.9 (0.6)	0.8 (0.6)	1.1 (0.9)	0.117
PVRi (WU*m^2)	1.7 (1.1)	1.6 (1.0)	2.0 (1.9)	0.117
≥ 2.5 WU*m^2 (n)	10/55 (18.2%)	4/40 (10.0%)	6/15 (40.0%)	**0.018**

Data are presented as median and interquartile range or frequencies (%). Statistically significant results are given in bold letters. AV, atrioventricular; CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; SVEDP, systemic ventricular end-diastolic pressure; TPG, transpulmonary pressure gradient.

TABLE 3 Hepatic assessment.

	Entire cohort (n = 58)	No Fontan failure (n = 43)	Fontan failure (n = 15)	*P*-value
Laboratory parameters				
ALT (U/l)	30.1 (7.5)	30.6 (7.3)	30.0 (10.0)	0.901
AST (U/l)	31.0 (12.8)	31.4 (12.9)	27.5 (15.7)	0.189
γGT (U/l)	91.8 (60.5)	79.2 (61.0)	119.8 (51.4)	**0.017**
Total bilirubin (mg/dl)	1.0 (0.7)	1.0 (0.7)	1.0 (1.4)	0.195
Thrombocytes (K/μl)	164.5 (69.5)	165.0 (69.0)	155.0 (74.0)	0.683
Fibrotest® Fibrosis Score	0.6 (0.3)	0.6 (0.3)	0.7 (0.3)	0.434
TE (kPa)	19.4 (19.2)	16.2 (13.0)	33.7 (21.0)	**0.001**
Hepatic ultrasound findings (n)				
Hepatomegaly	11/54 (20.4 %)	8/40 (20.0 %)	3/14 (21.4 %)	1.0
Splenomegaly	13/54 (24.1 %)	6/40 (15.0 %)	7/14 (50.0 %)	**0.025**
Heterogeneous liver parenchyma	52/54 (96.3 %)	38/40 (95.0 %)	14/14 (100.0 %)	1.0
Segmental atrophy/hypertrophy	16/54 (29.6 %)	10/40 (25.0 %)	6/14 (42.9 %)	0.38
Hepatic vein dilatation	48/54 (88.9 %)	36/40 (90.0 %)	12/14 (85.7 %)	0.643
Abnormal hepatic vein architecture	38/54 (70.4 %)	26/40 (65.0 %)	11/14 (78.6 %)	0.507
Hyperechogenic lesions	10/54 (18.5 %)	7/40 (17.5 %)	3/14 (21.4 %)	0.708
Surface nodularity	8/54 (14.8 %)	3/40 (7.5 %)	5/14 (35.7 %)	**0.021**
Ascites	7/54 (13.0 %)	1/40 (2.5%)	6/14 (42.9%)	**0.001**
Maximum liver function capacity (μg/kg/h)	355.0 (160.8)	390.0 (162.0)	288.0 (140.0)	**0.007**

Data are presented as median and interquartile range or frequencies (%). Statistically significant results are given in bold letters. ALT, Alanin-Aminotransferase; AST, Aspartat-Aminotransferase; γGT, γ-glutamyl-transferase; kPA, Kilopascal; TE, transient elastography.

Maximal liver function capacity

Median maximum liver function capacity was 355.0 μg/kg*h (IQR 160.8), which corresponds to a normal hepatic function (≥ 315 μg/kg*h). In 18 patients maximum liver function capacity was moderately impaired (140–314 μg/kg*h), while no patient suffered from severe hepatic damage (≤ 139 μg/kg*h). No correlation was detected between systolic ventricular function or the extent of AVVI and maximum liver function capacity ($p = 0.178$, r = 0.186 and $p = 0.873$, r = −0.016, respectively). Additionally, no association was found between VO_2peak and LiMAx® test results ($p = 0.356$, r = 0.133). No correlation was detected between maximal liver function capacity and resting or peak oxygen saturation ($p_1 = 0.202$, r = 01.7; $p_2 = 0.056$, r = −0.267). In patients with mPAP ≥ 15 mmHg maximal liver function capacity was significantly reduced compared to patients with mPAP < 15 mmHg [294.0 μg/kg*h (IQR 126.0) vs. 388.5 μg/kg*h (IQR 177.0), $p = 0.019$, Figure 1A]. An SVEDP ≥ 12 mmHg was also associated with decreased maximum liver function capacity [331.5 μg/kg*h (IQR 136.5) vs. 401.0 μg/kg*h (IQR 173.0), $p = 0.029$; Figure 1B]. Finally, in patients with late Fontan failure, maximal liver function capacity was significantly impaired as compared to patients without evidence of Fontan failure [288.0 μg/kg/*h (IQR 140.0) vs. 390.0 μg/kg*h (IQR 162.0), $p = 0.007$; Figure 1C].

Discussion

This is the first study to describe the association between Fontan hemodynamics, Fontan failure and maximum liver function capacity assessed by LiMAx®. Briefly, no correlation was detected between echocardiographic parameters or CPET results and metabolic liver function. Additionally, hemodynamic parameters such as CI and PVRi also showed no association with results from the LiMAx® test. However, maximum liver function capacity was significantly decreased in patients with increased mPAP (≥15 mmHg), and those with increased SVEDP (≥12 mmHg) as well as in patients with Fontan failure. In these patients, hepatic functional impairment was graded as moderate whereas no severe hepatic failure was detected.

The LiMAx® test was introduced to accurately quantify metabolic liver function based on the hepatocyte-specific cytochrome P4501A2 (CYP1A2) system and was evaluated in several clinical settings (17–19). We previously described the missing correlation between maximum liver function capacity and results from other diagnostic modalities such as laboratory parameters, TE and hepatic ultrasound (11). The major finding of our previous study was that metabolic liver function was preserved in the majority of adult Fontan patients even in those with clear evidence of advanced FALD.

Due to the non-physiological hemodynamics, failure of the Fontan circulation is inevitable in the long term (20–22).

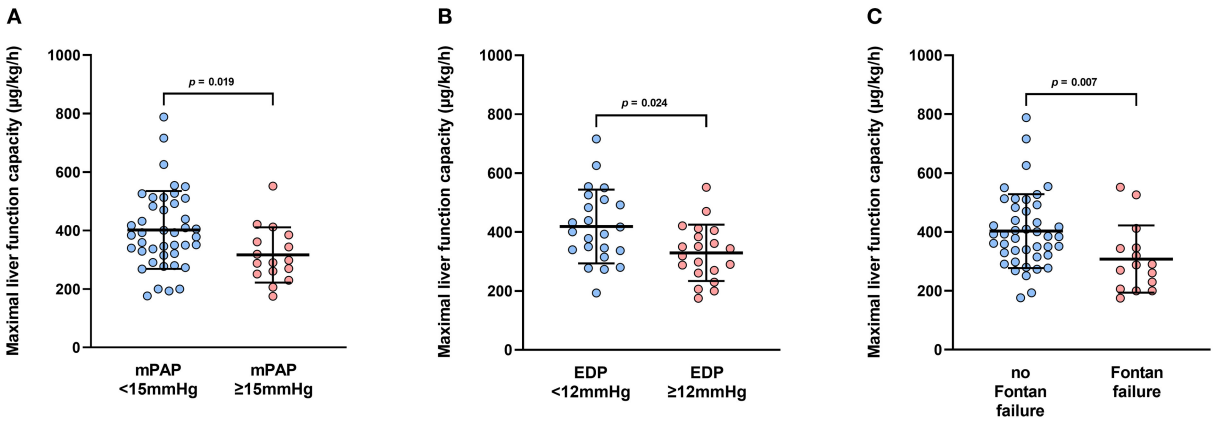

FIGURE 1
(A) Boxplots depict maximal liver function capacity according to mean pulmonary artery pressure (mPAP). mPAP < 15 mmHg: n = 42; mPAP <15 mmHg: n = 15. **(B)** Boxplots depict maximal liver function capacity according to systemic ventricular end-diastolic pressure (SVEDP). SVEDP < 12 mmHg: n = 23; SVEDP <12 mmHg: n = 19. **(C)** Boxplots depict maximum liver function capacity according to the presence of Fontan failure. Fontan failure; n = 15; no Fontan failure, n = 43.

Since therapeutic strategies are limited, cardiac transplantation remains the only viable end-stage treatment option but is associated with considerable mortality and morbidity (23). Additionally, guidelines for the timing of cardiac transplantation are missing and delayed listing may result in progressing secondary end-organ damage, which significantly contributes to post-transplant mortality (8, 9). Fontan-associated liver disease (FALD) is the most frequent end-organ dysfunction and encompasses all abnormalities in both liver structure and function with the end-stage being severe liver cirrhosis or hepatocellular carcinoma (24, 25). The indication for a combined heart and liver transplantation in failing Fontan patients is currently subject of ongoing debate. The decision whether a patient may benefit from single or multi-organ transplantation is challenging due to the lack of sound data to support or refute any given approach. Whereas successful isolated heart transplantation has been reported in the presence of hepatic cirrhosis (26), feasibility of combined heart and liver transplantation has also been demonstrated (27, 28). The most commonly encountered scenario in Fontan patients considered for cardiac transplantation is the inevitable presence of some degree of liver fibrosis with most patients demonstrating 'cirrhotic' alterations on imaging. However, it has been shown that cirrhosis on biopsy is less common and often does not correlate with imaging modalities such as ultrasound, magnetic resonance imaging or computed tomography (29). These discrepancies between imaging and biopsy findings complicate the interpretation and classification of FALD and its clinical significance for therapeutic decision making.

The LiMAx® test may represent a valuable complementary diagnostic modality in the hepatic assessment of Fontan patients and provides a reproducible quantitative measurement of hepatocyte function. Since a deterioration of maximum liver function capacity seems to occur relatively late during the disease course, when a significant impairment of Fontan hemodynamics and Fontan failure is already evident, its occurrence may prove as a valuable indicator for the requirement of a timely evaluation for cardiac transplantation. In our cohort, maximum liver function capacity was moderately reduced in patients who received cardiac transplantation [247.0 µg/kg*h (IQR 148.8) vs. 369.5 µg/kg*h (IQR 182.5), $p = 0.029$), however, none of these patients fulfilled the criteria for a combined heart and liver transplantation such as hepatocellular carcinoma or severe liver cirrhosis. In patients who survived cardiac transplantation, improvements in morphological and laboratory FALD parameters were detected. This observation has also been reported by other institutions and might underline the remarkable hepatic potential for regeneration (11, 30, 31). Therefore, patients with mild to moderate impairment of metabolic liver function might be appropriate candidates for isolated cardiac transplantation, whereas a severely impaired maximum liver function capacity may indicate the necessity of a combined heart and liver transplantation. Since both, FALD and Fontan failure, are characterized by a slow progress and are often clinically disguised by patient's adaptation to their chronically reduced output state and clinical deterioration, it seems advisable to perform repeated measurement of maximum liver function capacity during long-term follow-up, however, based on the currently available data, no precise intervals can be recommended. In patients with severe hemodynamic and hepatic impairment a yearly evaluation might be required followed by the consultation of an experienced hepatologist.

However, further well-conducted research efforts are warranted to address these questions, including additional studies, which compare maximum liver function capacity before and after cardiac transplantation as well as explore correlations of hepatic metabolic function with histologic findings of liver biopsies.

Limitations

This study has several limitations. Since this is a cross-sectional single center study with a comparably small patient cohort, future multi-institutional studies are necessary to evaluate metabolic liver function in larger patient cohorts. Additionally, the longitudinal relationship between Fontan hemodynamics and hepatic function was not addressed by this study. Since the parameters SVEDP and PAP are included in the calculation of the Fontan failure score, the association between LiMAx and Fontan failure might be confounded. However, considering that SVEDP and PAP are only 2 of 15 parameters used for score calculations, the confounding effect seems negligible. Additionally, all of the 15 Fontan failure patients fulfill the clinical consensus definition criteria of Fontan failure (14). Parts of the data of our current study cohort (n = 38/58, 65%) have previously been published in a study with a different scope focusing on morphologic hepatic assessment (11).

Conclusions

We herein demonstrate that maximum liver function capacity measured by the LiMAx® test is impaired in patients with impaired Fontan hemodynamics and Fontan failure. Hence, the LiMAx® test represents a valuable complementary diagnostic modality for FALD and might be useful in evaluating the indication for combined heart and liver transplantation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethikkommission der Charité, Berlin. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization and formal analysis: AS, PK, and SO. Data collection: AS, NJ, MP, and PK. Investigation: AS, PK, FD, H-PM, TM, and HS. Supervision: FB and FT. Writing original draft: AS. Writing review and editing: PK and SO. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Current state of the art in hypoplastic left heart syndrome

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Hypoplastic left heart syndrome (HLHS) is a complex congenital heart condition in which a neonate is born with an underdeveloped left ventricle and associated structures. Without palliative interventions, HLHS is fatal. Treatment typically includes medical management at the time of birth to maintain patency of the ductus arteriosus, followed by three palliative procedures: most commonly the Norwood procedure, bidirectional cavopulmonary shunt, and Fontan procedures. With recent advances in surgical management of HLHS patients, high survival rates are now obtained at tertiary treatment centers, though adverse neurodevelopmental outcomes remain a clinical challenge. While surgical management remains the standard of care for HLHS patients, innovative treatment strategies continue to be developing. Important for the development of new strategies for HLHS patients is an understanding of the genetic basis of this condition. Another investigational strategy being developed for HLHS patients is the injection of stem cells within the myocardium of the right ventricle. Recent innovations in tissue engineering and regenerative medicine promise to provide important tools to both understand the underlying basis of HLHS as well as provide new therapeutic strategies. In this review article, we provide an overview of HLHS, starting with a historical description and progressing through a discussion of the genetics, surgical management, post-surgical outcomes, stem cell therapy, hemodynamics and tissue engineering approaches.

KEYWORDS

stem cells, congenital heart defect (CHD), genetics, hemodynamic, regenerative medicine

Introduction

Hypoplastic left heart syndrome (HLHS) is a congenital heart condition in which a pediatric patient is born with an underdeveloped left ventricle and associated structures (1). This condition affects ∼1,000 patients annually in the US (1). If not aggressively treated and managed at the time of birth, HLHS is fatal (1). There have been excellent reviews in recent literature covering specific topics related to HLHS, to include stem cell therapy (2, 3), regenerative medicine approaches (4, 5), tissue engineering strategies (6), and treatment approaches (7). These review articles each provide an excellent overview of a very focused area related to HLHS. The current review serves to provide a comprehensive overview of HLHS, starting with a historical perspective, followed by a review of genetics, stem cell therapy, clinical outcomes, neurodevelopmental aspects, hemodynamics, and proposed tissue engineering therapies.

Surgical management of HLHS patients

Since the pioneering work by Dr. Norwood and the development of the staged palliative surgical approach (8), high survival rates are now accomplished in tertiary treatment centers (9). HLHS can be diagnosed *in utero* during a routine fetal echocardiography as early as the second trimester and allows for surgical planning at the time of birth (7). At the time of birth, a series of medical management strategies are used to stabilize the patient prior to surgical intervention, as described below.

One of the first tasks is stabilization with prostaglandins to maintain ductal patency. During fetal circulation, the placenta is the primary source of oxygen-exchange with the maternal circulation (10). Since the fetus does not rely on the lungs for oxygen, the ductus arteriosus shunts the blood away from the lungs and provides a flow pathway from the pulmonary artery directly to the descending aorta (10). After birth, this circulation changes and the ductus arteriosus rapidly begins and the pulmonary vascular resistance falls and the neonate now relies on the pulmonary circulation for oxygenation (10). However, in HLHS hearts, prograde aortic flow is minimal or absent and the right side of the heart delivers the majority of the cardiac output to the lungs and through the ductus arteriosus to the body (7). Pharmacologically maintaining patency of the ductus arteriosus with infusion of prostaglandin E1 (PGE-1), a naturally occurring prostaglandin and a known vasodilator, is required to maintain patency of the ductus arteriosus at the time of birth prior to surgical intervention (10).

Once the patient has been stabilized through the use of PGE-1, the next steps include three palliative interventions, the first stage palliation, the second stage palliation and the Fontan procedure (7). Surgical intervention was developed on the philosophy that the right side of the neonatal heart can support both systematic and pulmonary circulation. To achieve this surgically, the right side of the neonatal heart must deliver blood to the lungs for oxygenation and through the systematic circulation to the whole body. A series of staged palliative surgeries were developed to accomplish this task by Dr. Norwood; they were published in his landmark paper in 1983 (8) and were described in an earlier section of this review.

The characteristics of HLHS is underdeveloped left heart structures including the mitral valve, left ventricle, aortic valve, and ascending aorta and aortic arch (Figures 1A,B), all of which severely limit the ability of the neonatal heart to support systematic circulation (7). The most immediate need is to support both systematic and pulmonary circulation independent of the ductus arteriosus and develop a patent aorta for blood flow through the RV. The four basic objectives of first stage palliation are to: 1. Provide unobstructed systemic cardiac output; 2. Provide a controlled source of pulmonary blood flow; 3. Provide a reliable source of coronary blood flow; 4. Provide unobstructed egress of blood from the pulmonary veins (Figures 1C,D) (8). During the Norwood, the main pulmonary artery is divided amalgamated with the ascending aorta and the reconstructed aortic arch to provide cardiac output to the body and a reliable source of coronary circulation (8). The second objective achieved with the Norwood is to provide a controlled source of pulmonary blood flow which can be provided by a modified Blalock-Taussig-Thomas (mBTTS) shunt, which directs blood from the innominate artery to the pulmonary artery (Figure 1C) (11, 12). An alternative is the Sano shunt, which provides pulmonary blood flow through a conduit between the RV and the pulmonary artery (Figure 1D) (13). These steps result in a parallel circulation where the cardiac output is divided between the systemic and pulmonary circulations. During the Norwood procedure, the atrial septal defect is enlarged to ensure unobstructed egress of oxygenated blood from the left atrium to the right atrium. In addition, the atrial septal defect is enlarged to ensure unobstructed egress of oxygenated blood from the left atrium to the right atrium (14).

The second surgery, known as the bidirectional cavopulmonary shunt, is performed about 4–6 months after the Norwood procedure (15). The objective of the Glenn procedure is to reduce the load on the RV to support both the pulmonary and systematic circulation through the Norwood (15). During the Glenn procedure, the superior vena cava (SVC) is divided from the right atrium and anastomosed directly to the pulmonary artery (Figure 1E) (15). This provides a pathway for venous blood from the upper extremities and head to be directed to the pulmonary circulation directly, thereby unloading the RV of this burden achieved by converting an in-parallel circulation to an in-series circulation. The objective of the second stage procedure is to maintain oxygenation and to convert from an in-parallel to an in-series circulation as an interim step prior to a Fontan procedure.

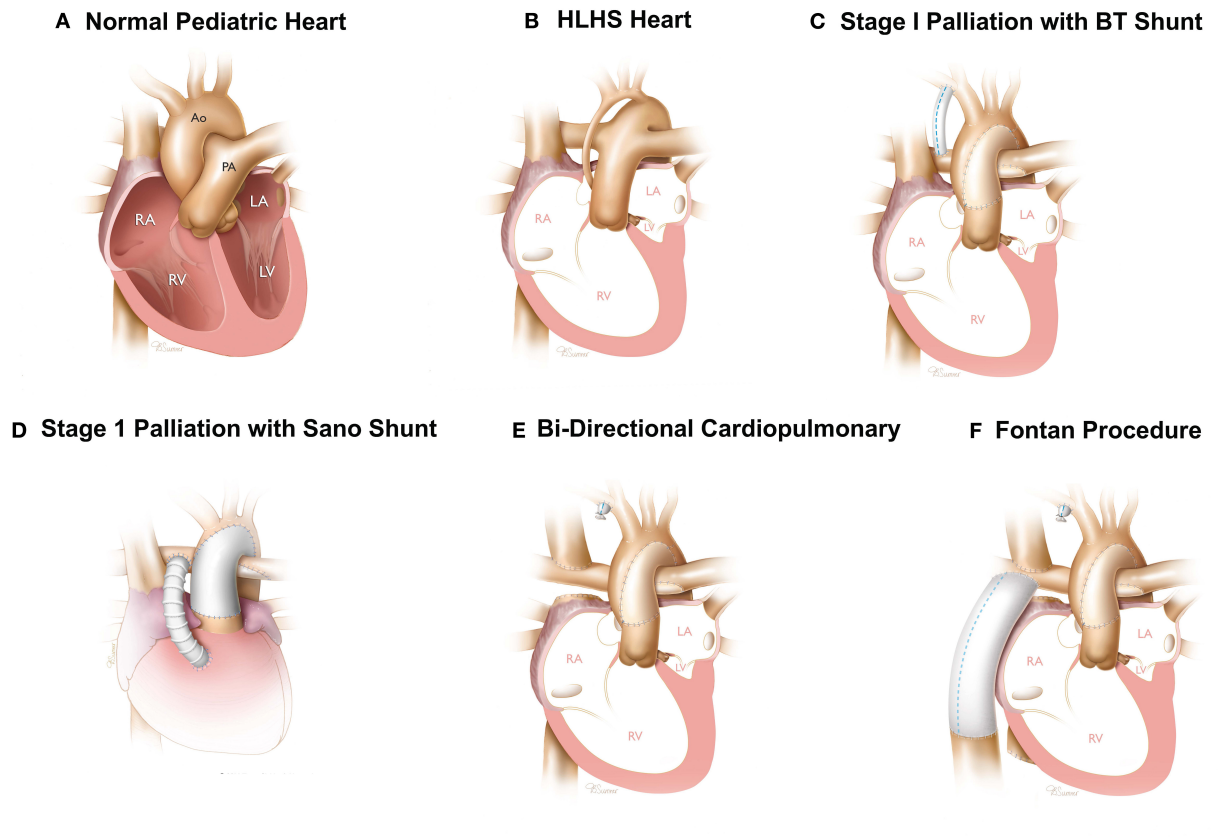

FIGURE 1
Surgical reconstruction of HLHS hearts—Normal **(A)** and HLHS pediatric heart **(B)**. Three stage surgical reconstruction starting with stage one palliation using a BT shunt **(C)** or sano-shunt **(D)**, bidirectional cavopulmonary shunt **(E)**, and Fontan procedure **(F)**. Images printed with permissions from Texas Children's Hospital.

The third surgery is known as the Fontan (16) and performed 3–4 years after the Glenn procedure. During the Fontan surgery, the inferior vena cava (IVC) is divided and anastomosed to the pulmonary artery using a conduit or a tunnel comprised of a patch and the lateral wall of the right atrium. In both configurations, the physiologic result is inclusion of venous blood flow from the IVC into the pulmonary circulation (Figure 1F) (16).

While the staged palliation surgical management approach is the most common, alternative strategies are also used. A hybrid approach has been used and, in some cases, HLHS patients are directly listed for a heart transplantation, though with the scarcity of donor organs, this strategy becomes challenging. Mechanical support devices have also been used as a bridge to transplantation.

Genetic basis of HLHS

Genetic studies can be grouped into three categories and are discussed in subsequent sections: (1) Linkage analysis and heritage analysis mapping HLHS to specific regions of the chromosomes. (2) Mutation analysis to identify individual genes responsible for HLHS. (3) Use of induced pluripotent stem cells to elucidate the genetic basis of HLHS.

Linkage analysis of HLHS patients

Linkage analysis is a powerful tool that identifies the chromosomal location of genes that are responsible for a particular disease (17). This technique has been used in the case of HLHS and several examples are presented here. In one study involving 353 patients, linkage analysis was used to connect the inheritance of bicuspid aortic valve (BAV) dysfunction, a common disorder observed in congenital heart patients, including HLHS, to chromosomes 18q, 5q, and 13q, suggesting the presence of genes whose mutations are responsible for BAV dysfunction (18). Another study, also relying on linkage analysis using 289 patients, demonstrated chromosomal linkage of HLHS abnormalities to chromosome 2p15 (19).

Additional studies provided evidence and demonstrated that HLHS was linked to mutations in chromosomes 10q22 and 6q (20) and 21q22.3 (21) and also 11q23 deletion (22). While there is no doubt that linkage analysis has provided valuable insights into the chromosomal locations of mutations related to HLHS, such a strategy has done little to develop a pathway for therapeutic approaches. This strategy was used during an earlier timeframe, prior to the recent and powerful advances in RNA-seq, single-cell seq, and other related strategies that can identify individual genes responsible for HLHS.

Mutation analysis to identify individual genes responsible for HLHS

Identifying individuals and families of genes responsible for the pathophysiology of HLHS is critical in developing effective therapeutic strategies to treat this patient population. While there is now an abundance of rich literature describing many different gene candidates, the molecular mechanisms leading to HLHS remain poorly studied and understood. One of the earliest reports observed in HLHS patients showed mutations in connexin43 (23). In this study, HLHS patients undergoing heart transplant were analyzed based on PCR analysis of tissue biopsies obtained at the time of transplant. In this group of patients, eight out of 14, or 57.1%, had mutation in connexin43 (23). Given the critical role of connexin43 in intercellular communication, this result was not surprising (24). In addition, NOTCH1 (25–28) and NKX2.5 mutations (29), deletion of ETS1 (30), impaired adrenergic signaling (31, 32), and upregulation of cTnI (33) have all been linked to HLHS. In another study, 87,355 chemically mutagenized mice were screened and whole exome sequencing was performed, identifying 91 recessive mutations in 61 genes that included 34 cilia-related genes and 16 genes involved in cilia transduced cell signaling (34), highlighting the role of the cilia mutations in congenital heart disorders. In yet another recent study, mouse forward genetics was used to link Sap130 and Pcdha9 in mediating left ventricle hypoplasia and increased penetrance of aortic valve abnormalities, both of which are associated with HLHS (35). Changes in micro-RNA expression has been implicated in HLHS (36), including upregulation of miR-486 in certain cases (37). In addition, one study performed a genome-wide exon array analysis to determine differentially expressed genes and alternatively spliced transcripts in the right ventricle (RV) of six neonates with HLHS, compared to the RV and left ventricle (LV) from non-diseased control subjects (38). In HLHS, more than 180 genes were differentially expressed and 1,800 were differentially spliced, leading to changes in a variety of biological processes involving cell metabolism, cytoskeleton, and cell adherence (38).

HLHS is caused by multiple genes

Recent literature suggests that HLHS is caused by mutations in multiple genes and is not the result of a single mutation only. Examples of genes shown to be cause HLHS include HAND1, GJA1, ZIC3, NKX2.5, NOTCH1, MCTP2, and MYH6 (39). The exact nature of the relative contribution of these genes and how they affect the etiologies observed in HLHS, it is becoming increasing evident that a multitude of genes acting in tanden lead to the anatomical abnormalities seen in HLHS (39).

Single cell analysis

More recent work has focused on single cell analysis and 3D patch engineering to decipher the role of various genes in HLHS (40). The single cell analysis showed significant changes in many pathways related to cardiomyocyte contraction, heart development, striated muscle differentiation, and cytoskeleton organization. Deficiencies in heart muscle contractility were shown based on work using 3D patches (40). Overall, this work provided a broader perspective of the genetic basis of HLHS showing that a family of genes are responsible, rather than a single gene mutation.

Induced pluripotent stem cells and genetics of HLHS

Induced pluripotent stem cell derived cardiomyocytes (iPSC-CMs) have been used extensively as a disease model in many cardiac disorders (41), though not extensively in the congenital space and much less so in the study of HLHS. In one study, iPSC-CMs were used to demonstrate the role of hypoxia in the development of HLHS through upregulation of the master regulator hypoxia inducible factor (HIF-1α), oncogene-associated cellular senescence, TGF-β1-associated fibrosis and impaired vasculogenesis (42). In a more recent study, whole genome sequencing of iPSC-CMs from three related individuals, identified LDL receptor-related protein LRP2 as a key modulator of cardiomyocyte proliferation and development during embryogenesis, mutagenesis of which could lead to HLHS (43).

Future studies

The genetic basis of HLHS has been an area of investigation, though a clear signaling pathway that leads to the anatomical malformations of the fetal heart is yet to be established. Understanding the genetic basis of HLHS and the role of hemodynamics is essential to develop effective therapeutic strategies. The current body of literature lacks a cohesive

understanding of the genetic basis of HLHS; rather, alterations in the expression of a few select genes are linked to HLHS. The current set of models used to study HLHS development will need to be expanded, and recent advances in bioengineering approaches related to iPSC-CMs and patch engineering will prove to be valuable in these studies.

iPSC-CMs technology has not been leveraged to its full potential as a tool to significantly understand the key modulators of HLHS. The main advantage of iPSC-CMs is the ability to obtain patient-specific information on the genetic modulators of HLHS. In addition, iPSC-CMs can be subjected to known master regulators of HLHS, like volume overload and cyanosis, and the responsiveness of these cells can be characterized in an isolated *in vitro* monolayer culture system. The ability to bioengineer three-dimensional heart muscle from these cells further adds to the advantages of this technology as the genetic modulators and response to external stimuli can now be investigated in three-dimensional tissue (44).

HLHS outcomes

Table 1 includes a list of reports describing 1-year mortality after the Norwood procedure (9, 45–57). Scanning Table 1 provides some insight into post-surgical outcomes for HLHS patients. A review of the data shows large variations in outcomes with no clear trends. The range of mortalities is broad, from a low of 15% from 157 patients during the period 1996–2007 at University Hospital Schleswig-Holstein in Germany (52) to a high of 60% from 129 patients during the period 1983–2004 at Royal Children's Hospital in Australia (50). Based on an analysis of the outcomes data presented in Table 1, the HLHS patient survival 1 year after stage one palliation surgery has improved significantly in the current decade compared with survival 1990–2010. Further advances in management of HLHS include stem cell therapies and bioengineering solutions, which have the potential to increase survival of HLHS patients. While surgical management will continue to be the standard of care for HLHS patients in the near-term, use of innovative therapies (stem cell therapy and bioengineering) are essential tools in increasing patient survival and improving outcomes.

HLHS cavopulmonary hemodynamics

The selection of the optimal shunt during the Norwood procedure and the construction of the optimal cavopulmonary connection configuration during the Glenn and Fontan surgeries rely on multiple patient-specific factors such as RV function, cardiac and vessel anatomies, inflow conditions and respiration rates, and their relations with the systemic and pulmonary flow dynamics generated at each surgical stage (58). Experimental approaches based on state-of-the-art *in vitro* flow diagnostic techniques, as well as computational fluid dynamics (CFD) strategies combining patient-specific flow models with lumped parameter networks have been successfully implemented to improve surgical planning in HLHS patients (59). As a result, the bulk of the literature published to date on HLHS hemodynamics has mostly focused on the extracardiac hemodynamics generated by the different palliative surgical stages and the use of this knowledge in surgical planning. In contrast, the pre- and post-surgical intracardiac hemodynamics of the single RV, which are key predictors of HLHS patient survival (60), remain largely unexplored. This section describes the important contributions made to the characterization of HLHS hemodynamics to date.

Norwood hemodynamics

While post-operative complications of the Norwood procedure may be linked to pre-operative patient characteristics (e.g., presence of non-cardiac/genetic abnormalities, weight <2.5 kg, right dominant single ventricle) (61), the specific hemodynamics and flow resistance of the systemic-pulmonary arterial shunt has also been suggested as an important prognostic factor for patient survival. As demonstrated in an early *in vitro* study, which evaluated pressure-flow relationships in systemic-to-pulmonary Blalock-Taussig shunts of different diameters, an increase in shunt diameter resulted in reduced pressure gradients at both the proximal and distal anastomoses (62). More recently, a computational parametric investigation conducted in an idealized Blalock-Taussig shunt geometry revealed that not only shunt diameter but also anastomosis placement was critical to oxygen delivery to both systemic and coronary circulations (63). Lastly, multiscale computational flow modeling has also been used to compare the hemodynamic performance of different shunt configurations. The simulations suggested that the Sano shunt consistently generated more favorable hemodynamics (i.e., lower RV systolic and diastolic pressures, lower pulmonary-to-systemic flow ratios, and higher coronary perfusion pressure).

The surgical management of HLHS consists of redirecting the venous deoxygenated blood toward the lungs while bypassing the RV *via* a staged surgical approach. A challenge raised by the construction of this bypass is the requirement to achieve a balanced flow split between both lungs while minimizing flow energy loss. The dominant objective in single ventricle management is to achieve the Fontan circulation, which depends upon kinetic energy to propel blood through the lungs without a sub-pulmonary ventricle. The concept of energy is critical to the success of this staged palliative surgery. In fact, the single RV must eject blood with sufficient kinetic energy to overcome energy losses caused by the viscous friction along the entire vasculature and the hemodynamic disturbances (e.g., mixing, collision, separation, and recirculation) generated at each stage of the surgical cardiac and vascular reconstructions

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TABLE 1 Outcomes table.

ID	Year published	Senior author	Country	Hospital	# of patients	Years	1-yr. mortality	References
1	1997	Quaegebeur	USA	Columbia University	53	1990–1996	40.0%	(45)
2	2001	Anderson	UK	Guy's Hospital	64	1995–2000	48.0%	(46)
3	2002	Klitzner	USA	Multicenter	1,986	1998–1997	40.9%	(47)
4	2005	Vogt	Germany	University Hospital Muenster	41	1992–2002	29.0%	(48)
5	2006	Ohye	USA	University of Michigan	111	2001–2003	21.0%	(9)
6	2006	Brawn	UK	Birmingham Children's Hospital	333	1992–2004	29.0%	(49)
7	2007	Wlikinson	Australia	Royal Children's Hospital	129	1983–2004	60.0%	(50)
8	2008	Ishino	Taiwan	National Taiwan University Hospital	62	1998–2007	20.0%	(51)
9	2009	Kramer	Germany	University Hospital of Schleswig-Holstein	157	1996–2007	15.0%	(52)
10	2011	Jennifer Li	USA	Multicenter	2,557	2000–2009	22.0%	(54)
11	2012	Latal	Switzerland	University Children's Hospital	31	2004–2008	36.0%	(53)
12	2014	Krasemann	UK	Evalina London Children's Hospital	138	2005–2011	41.4%	(55)
13	2018	Skalski	Poland	Jagiellonian University Children's Hospital	85	2007–2011	28.2%	(56)
14	2019	Spray	USA	Children's Hospital of Philadelphia (CHOP)	1,663	1984–2014	25.9%	(57)

(64). Therefore, optimization of the staged surgery is critical to produce efficient hemodynamics necessary for positive long-term clinical outcomes (65).

Glenn and Fontan hemodynamics

The hemodynamics of the Glenn and Fontan surgical reconstructions have been documented in many *in vitro* and CFD studies. *In vitro* measurements in realistic glass models mimicking a bidirectional Glenn cavopulmonary connection suggested the benefits of this connection over a dilated atriopulmonary connection by demonstrating its ability to reduce fluid energy dissipation, achieve physiologic distribution of total flow, and maintain some hepatic venous flow to each lung (66). Pulsatile flow simulations in hemi-Fontan and bidirectional Glenn geometries reconstructed from magnetic resonance, angiocardiogram, and echocardiogram anatomic data complemented the previous experimental findings by indicating no substantial difference in power loss and flow distribution to each lung (67).

However, the bulk of the literature published to date on Glenn and Fontan hemodynamics has focused on the identification of key geometrical parameters affecting the hydraulics of the Fontan total cavopulmonary connection (TCPC). Experimental particle image velocimetry measurements in realistic stereolithography intra-atrial connection models have revealed the existence of complex, unsteady, and highly three-dimensional flow structures, suggesting a substantial degree of energy loss in this type of connection (68). Those results are supported by 4D-flow MRI and patient-specific CFD studies, which have evidenced the existence of high vorticity magnitudes and atrial recirculation in the intra-atrial connection (69), and the hydraulic superiority of the lateral tunnel Fontan operation relative to any other method (67).

Another important finding suggested by the literature on TCPC hemodynamics is the stronger dependence of energy loss

on the TCPC topology and geometrical features than on the Fontan surgical option. In fact, a retrospective analysis of CFD and *in vitro* flow data revealed that the minimum cross-sectional area of the pulmonary arteries at the TCPC outlets was a stronger predictor of energy loss characteristics than the surgical procedure (extra- vs. intra-cardiac conduit) (70). Another CFD analysis using realistic pulsatile flow boundary conditions and TCPC geometries featuring extra- and intra-cardiac conduits demonstrated that power dissipation was primarily influenced by the actual cross-sectional area of the inferior vena cava anastomosis (71). Lastly, steady flow pressure measurements and flow visualization conducted in idealized TCPC glass models suggested that caval offsets and anastomotic flaring could reduce the hydraulic power loss by half relative to no offset and by at least 45% relative to no flaring, respectively (72, 73). Altogether, those studies suggest that patient-specific flow modeling could be an effective surgical planning tool toward the improvement of HLHS patient outcome and the reduction of surgical risks (74).

RV hemodynamics during staged palliation

While the re-engineering of the right side of the heart is a critical requirement to support both pulmonary and systematic circulations in HLHS patients (7), RV function is a key determinant of HLHS patient survival (60). Mathematical and computational approaches with various degrees of sophistication have been proposed to estimate RV hemodynamics and function in HLHS. Flow simulations in a post-Norwood RV geometry confirmed the hemodynamic superiority of the Sano shunt over the Blalock-Taussig shunt, as suggested by the predicted reduction in RV workload and no substantial difference in systemic blood flow (75). Another computational model based on patient-specific RV anatomies reconstructed from magnetic resonance imaging revealed the strong dependence of interventricular pressure gradients, filling dynamics and capacity on RV shape and temporal deformation patterns (76). To date, the only quantification of the native pre-surgical HLHS RV hemodynamics was performed numerically in a fetal heart in the context of cardiac development (77). This investigation, which assessed fetal blood flow using 4D spatiotemporal image correlation ultrasound and numerical modeling, revealed that despite a larger right-ventricular cavity size and a greater cardiac output, HLHS fetal hearts generated essentially the same global interventricular hemodynamics as a normal heart.

Future studies

The synergies suggested by previous RV studies between interventricular RV flow dynamics, cardiac function, and TCPC power loss suggest that the knowledge of pre- and post-surgical RV hemodynamics on a patient-specific basis could guide clinical decision making and promote patient survival (78). However, determining the exact role played by RV hemodynamics in the long-term outcome of the right heart surgical reconstruction requires the assessment of the hemodynamic alterations experienced by the RV during the course of the staged Fontan palliation. While this knowledge gap has not been addressed yet, computational strategies have been designed and successfully implemented to assess the potential mechanical changes of other cardiac defects such as discrete subaortic stenosis (DSS) (79–81). Cine-magnetic resonance imaging data was used in tandem with state-of-the-art fluid-structure interaction modeling to predict native blood flow patterns in patient-specific left-ventricular models featuring normal and DSS-prone outflow tract anatomies, and to characterize the resulting myocardial mechanical stresses. A similar modeling strategy could be deployed to elucidate RV hemodynamics in patient-specific post-Norwood RV anatomies, and to identify particular blood flow patterns and mechanical stresses associated with good clinical outcomes.

Stem cell therapy in HLHS patients

Stem cell therapy is conceptually based on the idea of delivery of isolated cells to the region of injury in an attempt to promote repair and/or regeneration (82). Stem cell therapy has been evaluated in many different fields, particularly in the realm of myocardial infarction in the adult population (83). In comparison, there is a much smaller, though growing body of literature, with varying degree of success, in the pediatric congenital heart field, particularly related to HLHS patients (84–89). Important considerations in stem cell therapy are the source of cells, bone marrow derived mesenchymal stem cells (BMMSCs) being a common choice, mode of delivery (intra-muscular vs. intra-coronary), the number of cells, and timing of stem cell delivery relative to disease progression. Our discussion on this topic is divided into the following sections: (1) lessons learnt from stem cell therapy in adult heart patients, (2) stem cell therapy for pediatric HLHS patients, (3) summary and future perspective.

Lessons learnt from stem cell therapy in the adult heart

Stem cell therapy for myocardial infarction in adult hearts is now a large and expansive field, with numerous lessons being learnt (82). However, our goal is to focus this discussion on the potential mode of action of injected cells. How are the injected cells acting on the host tissue to provide a functional benefit? Initially, it was hypothesized that injected cells would integrate with host myocardium, transform to become contracting cardiomyocytes, electromechanically couple with host cardiomyocytes, and provide direct functional improvement to an otherwise failing heart (82). Conceptually,

this was the basis of the field and if realized, would truly be revolutionary in the field of adult cardiac regeneration. However, this was not the case for many reasons, perhaps the most significant of which was the low rate of local cell retention: <5% of injected cells were retained at the site of injury (90). Irrespective of the challenges in the field, many lessons have been learnt regarding the potential mode of action of injected stem cells. It is now hypothesized that injected stem cells act through one of several mechanisms, including the release of paracrine signaling factors, promoting neovascularization and/or recruitment of resident or circulating stem cells, all of which serve to either increase the number of functional cardiomyocytes or promote neovascularization (90). With such a rich literature in the adult cardiac stem cell transplantation space, it provides a strong background to initiate similar studies in the pediatric congenital cardiac space, particularly related to HLHS.

Stem cell therapy for pediatric HLHS patients

Many of the factors discussed earlier apply to stem cell therapy for HLHS patients, to include the source and number of cells and mode of delivery. However, specific to HLHS patients is the timing of stem cell delivery. The surgical palliation of HLHS is a complex three-stage process, progressing through the Norwood, Glenn, and Fontan surgeries. Therefore, the timing of stem cell delivery becomes crucial and most studies making use of stem cell therapy have been at the time of stage two palliation.

Table 2 provides an overview of several studies describing stem cell therapy in HLHS patients, and these are discussed in subsequent sections. Table 2 is designed to serve as a survey of the recent literature on stem cell therapy in HLHS, rather than an exhaustive list of all published studies. Earlier studies in 2010 (89) and 2015 (87) were designed to provide safety of injected cells in single HLHS patients at the time of the Glenn surgery, followed by the Phase I TICAP trial in 2015 (87) and Phase II PERSEUS trial in 2017 (86), all of which are discussed below.

One of the earlier case studies was described in 2010, in which intracoronary injection of bone marrow mesenchymal stem cells (BMMSCs) during stage II procedure in a single pediatric HLHS patient proved to be safe (89). This was an initial proof of concept study to demonstrate the feasibility of BMMSCs at the time of Glenn, without much detail to any potential functional benefit and/or mode of action. While the results of this study demonstrated safety of BMMSCs delivery in a single HLHS patient at the time of Glenn, many unanswered questions remained. A second case study was published in 2015, using mononuclear cells from umbilical cord blood, again injected during stage II surgery, increasing RV ejection fraction from 30–35 to 50% (84).

Phase I results of the TICAP trial were published in 2015, making use of intracoronary infusion of cardiac progenitor cells (CPCs) in 14 patients, seven undergoing staged palliation with

TABLE 2 Stem cell therapy.

Year	Senior author	Cell type	Number of cells	Mode of delivery	Number of patients	Time of delivery	RV EF	References
2010	Schranz	BMMSCs	Not specified	Intracoronary	1	Glenn	44% after 14 months	(89)
2015	Nelson	UCB mononuclear cells	18 million cells	Intramyocardial	1	Glenn	35–50%	(84)
2015	Oh	CDCs	3.5×10^5 cells per kg of body weight	Intracoronary	14, 7 with cells, 7 controls	Glenn and Fontan	46.9%+/-4.6% to 52.1%+/-2.4%	(87)
2017	Oh	CDCs	3.5×10^5 cells per kg of body weight	Intracoronary	41	Glenn and Fontan	35.3%+/-9.2% to 41.7%+/-7.4%	(86)
2017	O'Leary	BMMNCs	2×10^6 cells per kg of body weight	Intracoronary	1	As an Adult	35–40% after 6 months	(88)
2019	Nelson	UCB mononuclear cells	0.1 ml per kg of body weight	Intramyocardial	10	Glenn	No change	(85)

CPCs infusion and an equal amount with only staged palliation (87). Patients treated with CPCs showed RV ejection fraction improvement from baseline to 3-month follow-up (46.9 ± 4.6% to 52.1 ± 2.4%; $P = 0.008$) (87). Compared with controls at 18 months, cardiac MRI analysis of CPC-treated patients showed a higher right ventricular ejection fraction (31.5 ± 6.8% vs. 40.4 ± 7.6%; $P = 0.049$) (87). This was followed up by a Phase II clinical trial, PERSEUS with 41 patients; at 3 months, the absolute changes in ventricular function were significantly greater in the CPC-treated group than in the controls (35.3%+/-9.2% to 41.7%+/-7.4%; $P = 0.0002$) (86).

Another recent study made use of autologous bone marrow derived mononuclear cells administered *via* cardiac catheterization to the coronary circulation in a single patient 23 years after the Fontan Surgery, showing decrease in ventricular size 3 months after cell injection (88).

A more recent study published in 2019 showed the feasibility of intramyocardial injections of mononuclear cells derived from umbilical cord bloods in a Phase I clinical trial with 10 patients, though there were no functional benefits resulting from this intervention (85).

Summary and future perspective

Stem cell therapy in HLHS patients is at a stage of infancy, and very few studies have been conducted in a very small patient population. The mode of delivery has been either intracoronary or intramyocardial, and the number and source of cells has varied. The time of delivery has been consistent, with most studies conducted at the time of the second stage palliation. Source and number of cells, along with the timing of delivery, must be optimized, and the modes of action must be elucidated. Furthermore, a combinational therapy consisting of stem cells coupled with growth factors to increase the contractile function of the RV may also prove to be beneficial.

Tissue engineering and regenerative medicine

Recent advances in bioengineered functional cardiovascular tissue have provided a novel opportunity for new technologies, both to increase our understanding of HLHS and to provide therapeutic options. The definition of tissue engineering has been very elegantly presented in a recent publication (91): Tissue engineering is a multidisciplinary field bringing together experts from engineering, life sciences and medicine, utilizing the building blocks of cells, biomaterials and bioreactors for the development of three-dimensional artificial tissue and organs which can be used to augment, repair and/or replace damaged and/or diseased tissue. Or in simpler terms, tissue engineering is the field focused on fabricating three-dimensional tissue, and applied to the cardiac space, this includes heart muscle (92), ventricles (93), Purkinje networks (94), and whole hearts (95).

The tissue fabrication process has been presented in a very methodological manner in a recent publication (96). In summary, iPSCs are generated from peripheral blood mononuclear cells, isolated from a routine blood draw and converted to cardiomyocytes (iPSC-CMs), using an established protocol (97). iPSC-CMs are cultured within a 3D matrix, resulting in the formation of contractile heart muscle tissue (92). Recent developments in the field of 3D bioprinting have provided a powerful tool to fabricate patient-specific tissue, to perfectly fit the geometry of the defect or to match the patient's anatomy (91). Electromechanical stimulation is used for the maturation and development of iPSC-CMs (98), and subsequent vascularization of the bioengineered tissue is required to support metabolic activity.

While presented in a very simple manner, fabricating cardiovascular tissue is not without its challenges. Some of the challenges include the inability to generate large numbers of mature iPSC-CMs, fabricating heart muscle with high contractility, and optimized bioreactors for electromechanical stimulation. Recent advances point to the development of highly functional 3D cardiac patches, though functional integration with host tissue remains a challenge.

There are two potential applications of bioengineered cardiovascular models in HLHS: (1) tools to understand the underlying molecular mechanisms and (2) potential therapeutic strategies, as detailed in a recent review (6).

Tools to understand the underlying molecular mechanisms in HLHS

As one example, there is a high incidence of progressive myocardial dysfunction after the Norwood surgery, as discussed in an earlier section. The goal is to identify molecular indicators responsible for myocardial dysfunction. To accomplish this, blood samples from patients at the time of Norwood can be used to generate iPSCs and cellular difference can be used to correlate with observed clinical outcomes. These iPSCs can further be used to bioengineer 3D patches and that can be used to model tissue level contractility in post-surgical response of HLHS patients. Bioengineered right ventricles (93) can be used to study the effect of volume overload on heart muscle function and subsequent myocardial dysfunction. iPSCs-CMs, patches and ventricles can be used as powerful tools to provide mechanistic information at the cell, tissue, and organ levels.

Potential therapeutic strategies

Bioengineered models may someday be used as potential therapies to support HLHS hearts. As an example, biological contractile pumps (99) can be used in the Fontan circuit

to provide pulsatile support for blood, as opposed to the inert grafts currently in use which only serve a passive role. These biological pumps can support the flow of blood through the Fontan circuit. Another example is the use of bioengineered heart muscle, which can be used to add musculature to the right ventricle, thereby augmenting contractile function to support the increased blood volume after the Norwood surgery. Heart transplantation is another important therapeutic approach, but the current scarcity of donor hearts precludes heart transplant as routine management strategy. However, in the future, if bioengineered hearts become available, heart transplantation may be expanded as a treatment option for all HLHS patients, or at minimum, expanded to patients considered high risk for palliative surgeries.

Summary

Our understanding of HLHS has increased over the past two decades, including recent advances in stem cell therapy, dissecting the genetic basis of HLHS, and management of progressive myocardial dysfunction using ventricular assist devices and heart transplantation. Recent advances in tissue engineering and regeneration provide promise to develop new therapies based on stem cell therapy and bioengineered cardiovascular tissue, including patches, ventricles, biological pumps, and whole hearts.

The goal of new therapies is to improve the survival of HLHS patients. This can be accomplished based on an understanding of the genetic basis of the disease, as the master regulator(s), once identified, can be blocked or chemically inhibited. Furthermore, based on an understanding of the molecular basis predictive tools can be developed to quantify the risk of mortality for HLHS patients. Tissue engineering tools, are very powerful, and can be used to increase our understanding of the basic mechanisms and can also be used for repair of the HLHS heart and in the future, bioengineered hearts can be used for HLHS patients and alleviate current shortage of donor hearts.

Author contributions

AB prepared the section on historical perspective, introduction, and abstract. WS, OO, and CC prepared the section on surgical management of HLHS. SL prepared the introduction. RB the prepared sections on genetic basis of HLHS, tissue engineering, regenerative medicine, and summary. SL and SK prepared section on HLHS outcomes. PS and JS prepared the section on hemodynamics. AP the prepared section on stem cell therapy in HLHS patients. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Is the six-minute walk test still reliable compared to cardiopulmonary exercise test for exercise capacity in children with congenital heart disease?

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Objectives: We aimed to assess the validity of the six-minute walk test (6MWT) to reflect the functional capacity of children with congenital heart disease (CHD), evaluate a possible correlation between the 6MWT distance with cardiopulmonary exercise test (CPET) variables, as well as to find a cutoff value to stratification the physical fitness in this population.

Methods: We enrolled 459 children with CHD, 6–18 years old, who performed a complete CPET and 6MWT on the same day in a cross-sectional observational study. Correlations between variables of CPET and six-minute walking distance (6MWD) were analyzed and cutoff values of 6MWD were identified for the classification of the physical fitness in the population.

Results: The mean distance ambulated during the 6MWT was 578 ± 65 m, 590 ± 65 m for boys, and 562 ± 62 m for girls ($p < 0.001$). Both VO_{2max} and %predicted VO_{2max} showed a correlation with the 6MWT distance ($r = 0.35$, $p < 0.001$ and $r = 0.51$, $p < 0.001$, respectively), and an inverse correlation was found between VE/VCO2 slope and the 6MWT distance ($r = -0.31$; $p < 0.001$). There appeared to be a linear association between 6MWD and VO_{2max} up to a 6MWD of approximately 600 m. We divided the population into 4 subgroups (boys <130 cm; boys ≥130 cm; girls <130 cm; girls ≥130 cm), and get the cutoff values (554 m, 617 m, 549 m, 587 m) respectively equivalent to 80% of predicted VO_{2max}. The 6MWT distances of another 102 patients were applied for external verification of the cutoff values.

Conclusions: Our study provided evidence on when a 6MWT should be considered as a convincing complementary test in the pediatric population with CHD and explored the classification of exercise tolerance

Abbreviations

CHD, congenital heart disease; CPET, cardiopulmonary exercise test; 6MWT, six-minute walk test; 6MWD, six-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; VO_2, Oxygen uptake; VCO_2, Carbon dioxide output; ACSM, American College of Sports Medicine; RER, respiratory exchange ratio; VAT, ventilatory threshold; VE, minute ventilation; BP, blood pressure; HR, heart rate; HRR, heart rate reserve; VSD, ventricular septal defect; PDA, patent ductus arteriosus; TGA, d-transposition of the great arteries; TOF, tetralogy of Fallot; ASD, atrial septal defect; AUC, Area under curve; BMI, body mass index; BSA, body surface area; OUES, oxygen uptake efficiency slope.

using a 6MWD value. The cut-off values for 6MWD may be qualified as an intervention target for exercise rehabilitation.

KEYWORDS

congenital heart diasease, six minute walk test, cardiopulmonary exercise test (CPET), children, six minute walk distance

Introduction

Although a significant increase in survival of children with congenital heart disease (CHD) has been observed with advances in cardiac surgical techniques and perioperative support in decades, decision-making of interventions or identifying deteriorating conditions in long-term follow-up are still critical issues for complex CHD patients (1, 2). Many studies recommended that physical activity should be assessed routinely as part of clinical follow-up in adult and young patients with CHD (3–5).

Objective assessment of the cardiopulmonary fitness is one of the most important factors affecting the quality of life of patients and prognosis after surgical correction (3, 6, 7), which remains difficult in pediatric clinical practice. The gold standard for cardiopulmonary fitness expression is the maximum oxygen uptake (VO_{2max}) obtained at peak exercise of cardiopulmonary exercise testing (CPET), which is an established and reliable indicator of physical fitness (8), but expensive, requiring sophisticated equipment and specialized personnel, cannot be widely conducted in the primary or community health care facilities, especially in developing countries. Moreover, CPET does not represent the usual physical activity level of these children. Therefore, CPET has not yet been used widely in the follow-up of patients with CHD, especially in children and adolescents.

As a simple, reproducible, negligible cost and safe exercise test (9), the six-minute walk test(6MWT) measures the distance a participant can walk within 6 min. It was more likely to be easily used to quantify the functional capacity of patients, which closely reflects the activities in daily life because of the submaximal nature of the test (9–11).

Previous studies in patients with pulmonary arterial hypertension (PAH), chronic heart failure and grown-up patients with CHD (12–16) provided the correlation between walking distance in 6 min and VO_{2max}. Despite widespread use, the role of the 6MWT in the evaluation of children with CHD remains lacking so far, and more data and research regarding the application in this population are required. In this article, we tried to assess the validity of 6MWT to reflect the functional capacity of children and adolescents with CHD, evaluate a possible correlation between the distance walked during the 6MWT with CPET variables in measuring exercise capacity, as well as to find a cutoff value to stratification the physical fitness in this population.

Methods

Study subjects

This cross-sectional observational study was carried out from October 2018 to March 2020 in our CPET laboratory, and a total of 459 children with congenital heart defects aged 6–18 years were included in this study and performed CPET assessment and 6MWT, as a part of routine pediatric cardiology outpatient follow-up. In addition to the majority of the subjects having previously undergone corrective surgical interventions, fewer preoperative patients were also included. Our study population was provided in **Table 1**. Of these, 76 patients underwent the surgery with Fontan physiology and 16 patients had no surgery. No CHD patients were in New York Heart Association (NYHA) class IV.

Participants were not included in the study if they had contraindications (fever, respiratory failure, uncontrolled asthma, acute myocarditis or pericarditis, uncontrolled severe arrhythmias, uncontrolled heart failure, and children suffering from genetic defects leading to inability to cooperate or noncompliance, or had any other chronic medical condition other than their known heart disease, or with obesity.

The study protocol was approved by the Medical Ethics Committee of Guangzhou Women and Children's Medical Center, and informed consent was provided by all patients before exercise testing.

Procedures

The clinical data collected included gender, date of birth, body mass (BM) (kg) and body height (cm), surgery or not, age at surgery, medical treatments, and type of cardiac surgery. Functional capacity was graded according to the NYHA class.

Plasma NT-proBNP for CHD patients was measured within 3 h before beginning the cardiopulmonary exercise test and the 6-min walk test, using a commercially available fluorescence immunoassay (competitive Enzyme Immuno Assay; ReLIA II, Shenzhen, China) by the Central Laboratory Institute, Guangzhou Women and Children's Medical Center.

All children underwent CPET and 6MWT without complications on the same day, and the interval between tests was more than 60 min.

TABLE 1 Primary diagnostic categories of the study population.

Classification of congenital heart disease	*N*
Left to right shunts corrected	
Septal defects	123 (26.8%)
PDA	9 (2.0%)
Fontan circulation	
Single ventricle	34 (7.4%)
ccTGA	26 (5.7%)
Pulmonary atresia	7 (1.5%)
Double outlet of right ventricle	4 (0.9%)
Ebstein anomaly	2 (0.4%)
Complex anatomy, biventricular corrected	
TOF	37 (8.1%)
TGA	26 (5.7%)
ccTGA	5 (1.1%)
Double outlet of right ventricle	16 (3.5%)
Coarctation of the aorta	5 (1.1%)
Total anomalous pulmonary venous connection	16 (3.5%)
Truncus arteriosus communis	4 (0.9%)
Anomalous coronary artery from the pulmonary artery	12 (2.6%)
Pulmonary atresia and extremely severe pulmonary stenosis	59 (12.9%)
Ebstein anomaly	2 (0.4%)
Severe valvular malformation	27 (5.9%)
Others[a]	45 (9.8%)
All cases	459

CHD, congenital heart disease; VSD, ventricular septal defect; ASD, atrial septal defect; TGA, d-transposition of the great artery; ccTGA, congenitally corrected transposition; TOF, Tetralogy of Fallot; PDA, Patent ductus arteriosus.
[a]Coronary anomalies, mild or moderate valvular defects, atrio-ventricular canal, left to right uncorrected, several congenital heart defects in the same patient.

Cardiopulmonary exercise testing

All participants underwent a symptom limited CPET after performing spirometry first, using a treadmill (GE Healthcare, Little Chalfont, UK) with a breath-by-breath respiratory gas exchange analysis (MasterScreen CPX, Jaeger, Vyaire, Germany) according to the ramped Bruce protocol, as suggested by the American College of Sports Medicine (ACSM). The test was terminated when the participants demonstrated subjective unbearable symptoms, or when they attained maximal exertion despite intense verbal encouragement. An incremental overall duration between 6 and 12 min was obtained with this protocol.

Blood pressure (BP), pulse oximetry and heart rate (HR) were monitored and recorded for the duration of the test. Oxygen uptake (VO_2), carbon dioxide consumption (VCO_2) and minute ventilation (VE) were measured through the respiratory gas exchange analysis. The ventilatory threshold (VAT) was derived during maximal exercise testing, and determined by use of the modified V-slope method and reinforced by the VE/VO_2 curve.

The following criteria for reaching VO_{2max} were used: (1) respiratory exchange ratio (RER) > 1.1(2) peak HR > 85% of age-predicted maximum; (3) plateau of VO_2 can be seen despite increasing the exercise intensity, or the peak VO_2 defined as the highest mean VO_2 of any 30 s interval during exercise was informed without a VO_2 plateau (17). VO_{2max} and VAT values were normalized in a percentage of the predicted VO_{2max} according to normal values from Wasserman and Cooper (18).

The 6-minute walking test

The 6MWT was performed following a standard protocol proposed by the American Thoracic Society guidelines (19). The subjects were instructed to walk back and forth along a flat, 30-m long corridor as much as possible for 6 min. The total distance walked in 6 min was measured, with interruption or slowing down the rhythm if necessary. All children and adolescents received the same instructions before undertaking the walk test. The heart rate, pulse oximetry, blood pressure and respiratory rate were measured at the beginning and end of the test, as the modified BORG scale, used to assess the subjective sensation of dyspnea and fatigue of the lower limbs. The walked distance during the test was compared with reference values with the equation proposed by Li (20).

Data statistics

The study population was described with means and standard deviations (SD) for quantitative variables and with frequencies for qualitative variables. Categorical data were analyzed using the chi-square or Fisher's exact test, however continuous data used the independent samples *t*-test or Wilcoxon rank-sum test where appropriate.

Locally weighted regression (LOWESS smoothing) was used to further determine the relationship between 6MWT distance and VO_{2max}.

Additionally, we performed Receiver Operating Characteristic (ROC) analysis to determine a cutoff value for the 6MWT that corresponds to 80% of predicted $VO_{2\ max}$, as VO_{2max} ≥80% of predicted value were regarded to have a preserved exercise capacity (21, 22). Since our study showed that 6MWT was associated with gender and height, we divided the population into four subgroups (boys with a height of <130 cm; boys with a height of ≥130 cm; girls with a height of <130 cm; girls with a height ≥130 cm) and performed separate ROC analyses for the different subgroups. We then derived cutoff values for the four different subgroups

to improve practical applicability, and finally validated the results using external validation.

Results

Patient's baseline characteristics

Baseline characteristics of all patients ($n = 459$) are shown in Table 2. In total, 56.2% were male and 43.8% were female, and the median age was 8.76 years old (range 7–11 years). In our subjects 76.3% of the patients were NYHA class I and only 0.3% were NYHA class III.

Correlations between variables of CEPT and 6MWT

The cardiopulmonary responses during CPET and 6MWT distance are summarized in Table 3. The mean VO_{2max} and VO_{2max} (%pred) were 36.23 ± 6.87 ml/min/kg and 0.81 ± 0.17 respectively. There were 270 (58.8%) patients who had VO_{2max} more than 80% of predictive value. No complications occurred during maximal exercise testing and all tests were terminated because of dyspnoea (38%) or fatigue (62%). The mean distance ambulated during the 6MWT was 578 ± 65 m (range from 390 to 762 m), with no patient requiring a rest stop, which represents approximately 83% of the mean value of predicted distance (695 ± 59 m) by the formula.

TABLE 2 Patient's baseline characteristics.

	All case ($n = 459$)
Age (year)	8.8 (7.0-10.8)
Gender (%)	
Male	258 (56.2%)
Female	201 (43.8%)
Height (cm)	127.0 (118.0-141.5)
Weight (kg)	24.5 (20.3-31.7)
BMI (kg/m^2)	15.2 (14.0-16.6)
BSA (m^2)	0.9 (0.8-1.1)
NYHA (%)	
I	350 (76.3%)
II	106 (23.1%)
III	3 (0.7%)
NT-proBNP	246.7 (130.4–677.7)
Therapy	
Surgery	431 (93.9%)
Without surgery	28 (6.1%)

BMI, Body Mass Index; BSA, body surface area; NYHA, New York Heart Association; Values are presented as interquartile range (IQR).

TABLE 3 Exercise performance and the relationship between peak oxygen uptake and the 6-min walk test.

Variables	Value	6MWT
Cardiopulmonary exercise testing		
VO_{2max} (%pred)	0.81 ± 0.17	$r = 0.35^b$
VO_{2max} (ml/min/kg)	36.2 ± 6.9	$r = 0.51^b$
VO_2/kg @ AT (ml/min/kg)	25.1 ± 4.8	$r = 0.14^a$
O_2/HR (ml/beat)	5.5 ± 1.9	$r = 0.57^b$
VE/VCO_2 slope	34.7 ± 8.0	$r = -0.31^b$
RER	1.14 ± 0.98	$r = 0.16^b$
OUES	1051.52 ± 358.06	$r = 0.56^b$
6MWT distance (m)	578 ± 65	—

Data are presented as means ± SD.
[a]<0.05.
[b]<0.001.
VO_{2max}, peak oxygen uptake; AT, anaerobic threshold; VE/VCO_2, ventilatory equivalent of carbon dioxide; HR, heart rate; O2/HR, O2 pulse; OUES, oxygen uptake efficiency slope; 6MWT, The 6-minute walking test; RER, respiratory exchange ratio.

Univariate correlation between 6MWD and the various demographic in Supplementary Tables S1. The mean 6MWT distance of boys was 590 ± 65 m, higher than girls (562 ± 62 m, $p < 0.001$). Height has the best correlation with 6MWT distance on univariate analysis (all cases, $r = 0.460$, $p < 0.001$; boys, $r = 0.424$, $p < 0.001$; girls, $r = 0.499$, $p < 0.001$). The distribution of 6MWD by gender is shown in Figure 1. The association between height and 6MWD is shown in Figure 2.

Both VO_{2max} and VO_{2max} (%pred) showed a correlation with the 6MWT distance ($r = 0.35$; $p < 0.001$ and $r = 0.51$, $p < 0.001$, respectively), and an inverse correlation was found between VE/VCO_2 slope and the 6MWT distance ($r = -0.31$; $p < 0.001$).

However, when the relationship between the 6MWT distance and VO_{2max} was investigated further using locally weighted polynomial regression (lowess), it became apparent that a linear correlation between 6MWT distance and VO_{2max} existed only at low levels of exercise capacity. As illustrated in Figure 3A, there appeared to be a close to a linear association between 6MWT distance and VO_{2max} up to a 6MWT distance of approximately 600 m. A similar phenomenon is also reflected in the relationship between 6MWT distance and VO_{2max} (%pred), see Figure 3B.

We further analyzed the correlation between CPET variables and 6MWT distance in participants with VO_{2max} (%pred) ≥ 80% and <80% separately (Supplementary Table S3). VO_{2max} was 39.7 ± 5.2 ml/min/kg in the group with higher VO_{2max} (%pred) as compared to a VO_{2max} of 31.2 ± 5.8 ml/min/kg in the other group. In children with VO_{2max} (%pred) < 80%, the 6MWT distance correlated more strongly with VO_{2max} [VO_{2max} (%pred): $r = 0.17$, $p = 0.035$; VO_{2max} (ml/min/kg): $r = 0.34$, $p = 0.001$], whereas for the subgroup with VO_{2max} (%pred) ≥ 80%, the correlation

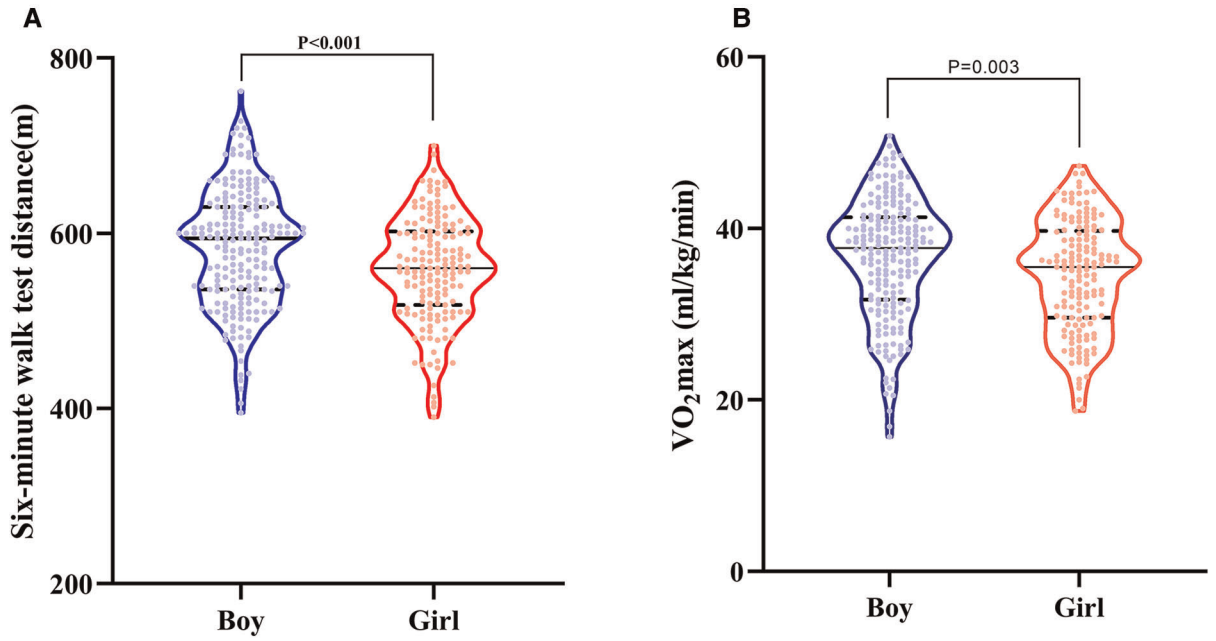

FIGURE 1
Violin diagrams of the distribution of six-minute walk test (6MWT) distance by gender (A); violin diagrams of the distribution of VO_2 max by gender (B). The upper and lower dashed lines represent the first and third quartiles, and the solid line in the middle represents the median.

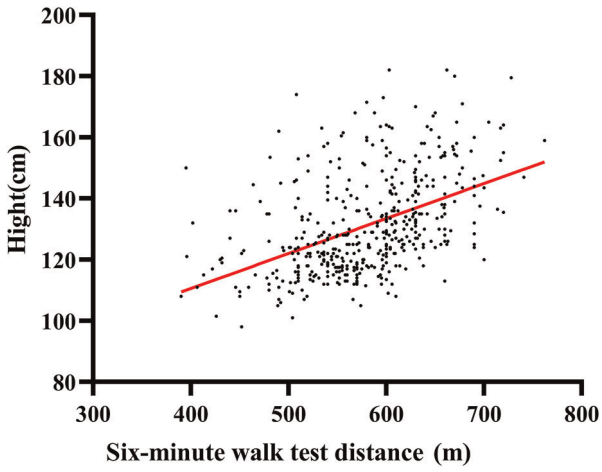

FIGURE 2
Scatter plots of the relationship between the six-minute walk test (6MWT) distance and height of children and adolescents with congenital heart disease. The red straight line in the scatter plots is linear regression fits.

between VO_{2max} and 6MWT seemed to be negligible. Similarly, we fitted a plot of the relationship between VO_{2max} and 6MWT distance for both groups using lowess, and the results were consistent with those without grouping, both indicating 600 m as the turning point (**Supplementary Figure S1**).

Cutoff values of 6MWT distance for the exercise tolerance

To evaluate the diagnostic potential of 6MWT for the cardiopulmonary exercise capacity, we performed ROC analysis according to VO_{2max}(%pred) ≥80%, as mentioned in the methodology. We analyzed and calculated Area Under Curve (AUC) for four subgroups, and these four subgroups have AUCs of 0.86, 0.80, 0.87, and 0.87, respectively (**Figure 4**). The cutoff values regarding sensitivity and specificity were calculated with Youden's index, and the cutoff values of 6MWT for four subgroups were 554 m, 617 m, 549 m, 587 m respectively (**Table 3**).

External validation

The external validation was performed using data from this hospital that is representative of the external validation set. The confusion matrix applying the cutoff values of the 102 test sets was shown in **Supplementary Table S2**. Our final showed an overall accuracy of 81.2%, sensitivity (recall) of 75.5%, and specificity of 76.8%. The positive predictive value (PPV), which indicates "precision," was 78.2%, and the negative predictive value (NPV) was 72.4%. The above results indicated acceptable performance.

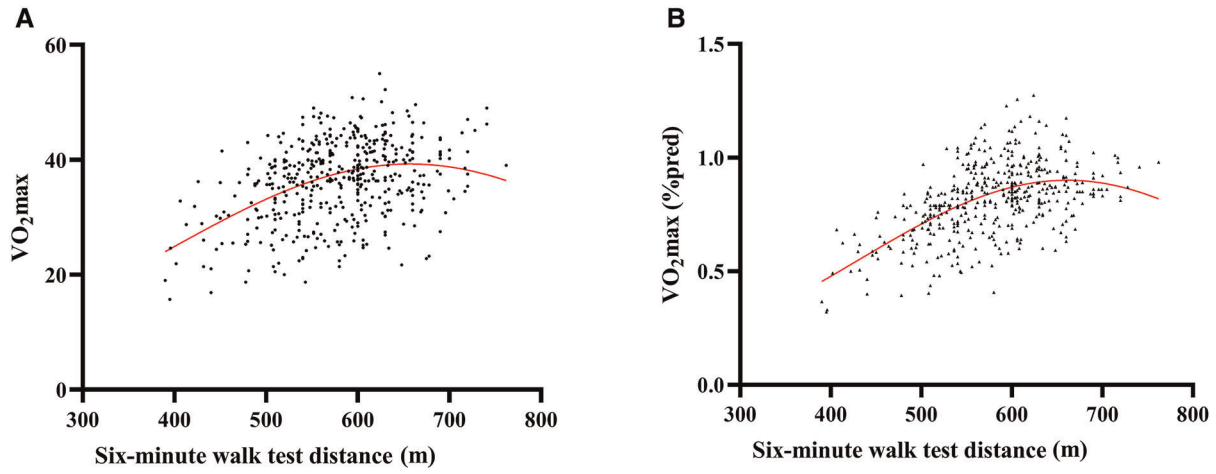

FIGURE 3
Scatter plots of the relationship between the six-minute walk test (6MWT) distance and VO2max of children and adolescents with congenital heart disease(A); scatter plots of the relationship between the six-minute walk test (6MWT) distance and VO_{2max} (%pred) of children and adolescents with congenital heart disease (B). The red curvy lines in the scatter plots are nonparametric regression fits.

Discussion

The main objectives of this study were to determine the reliability of the 6MWT in assessing the functional capacity of children with CHD and to investigate any potential relationships between the 6MWT distance and CPET characteristics.

In this study, we investigated the 6MWT and CPET-derived variables in the prognostic assessment of children and adolescents with CHD. Our result showed the patients with CHD had a mean VO_{2max} of 81% of predicted value, which is consistent with the fact that most patients self-perceived their exercise endurance was not significantly inferior to their peers since VO_{2max} above 80% of the predicted value was considered approximate or equal to a normal quality of life. Whereas, from a purely data analysis point of view, children with CHD can still be considered to have depressed VO_{2max} or exercise capacity to some extent compared with healthy children. Our previous study (23) also demonstrated that even for children undergoing simple CHD surgery, their mean value of VO_{2max} was only 91% of the predicted value, compared with 101% for the healthy controls.

Compared with the healthy children of the same age, the 6MWT distance as a submaximal exercise test showed a similar downward trend as $VO_{2\ max}$ for children with CHD, given that both accounted for approximately 82% and 81% of the predicted values, respectively. Nevertheless, the criteria for the descending level of the 6MWT distance to evaluate the degree of exercise capacity was controversial and unclear. Dourado (24) and Sperandio (25) et al. verified that a 6MWT distance below 96% is a critical point for identifying physically inactive adults with cardiorespiratory fitness levels below the normal range. Although there are differences in the subjects and statistical methods, it also indicates that the aerobic capacity of children with CHD is distinct from that of the general adult population.

We can expect that the results will be convincing in clinical practice for screening and monitoring the cardiorespiratory risk in children and adolescents with CHD if the 6MWT distance is reported as a percentage of the predicted value. The analyses of 6MWT distance cutoff values have been established to predict outcomes according to the literature (11, 13, 24, 26) on adults with cardiovascular disorders, including chronic heart failure and pulmonary hypertension, and others. In an earlier study by Kehmeier et al. (14) involving 102 grown-up patients with congenital heart disease, a cutoff value of 482 m by 6MWT was shown to be the optimal for identifying a VO_{2max} of ≤15.5 ml/kg/min. However, it is not reasonable for children to utilize a single value of walking distance for the threshold of inadequate cardiopulmonary fitness since 6MWT distance was more likely to be influenced by height and gender for children. We performed the analysis of 6MWT in the children with CHD in comparison with VO_{2max}, defined a cutoff value equivalent to 80% of predicted $VO_{2max,}$ and performed external validation further using additional data. To the best of our knowledge, this is the first study to obtain the cutoff value of 6MWT distance in children with CHD by sex and body height. Meanwhile, we also identified that 130 cm as an inflection point of the correlation between height and other variables, had excellent sensitivity and specificity for metrics of grouping.

We observed that the correlation between the 6MWT distance and VO_{2max} was not linear when the average walking distances of the subjects in 6 min were more than 600 m,

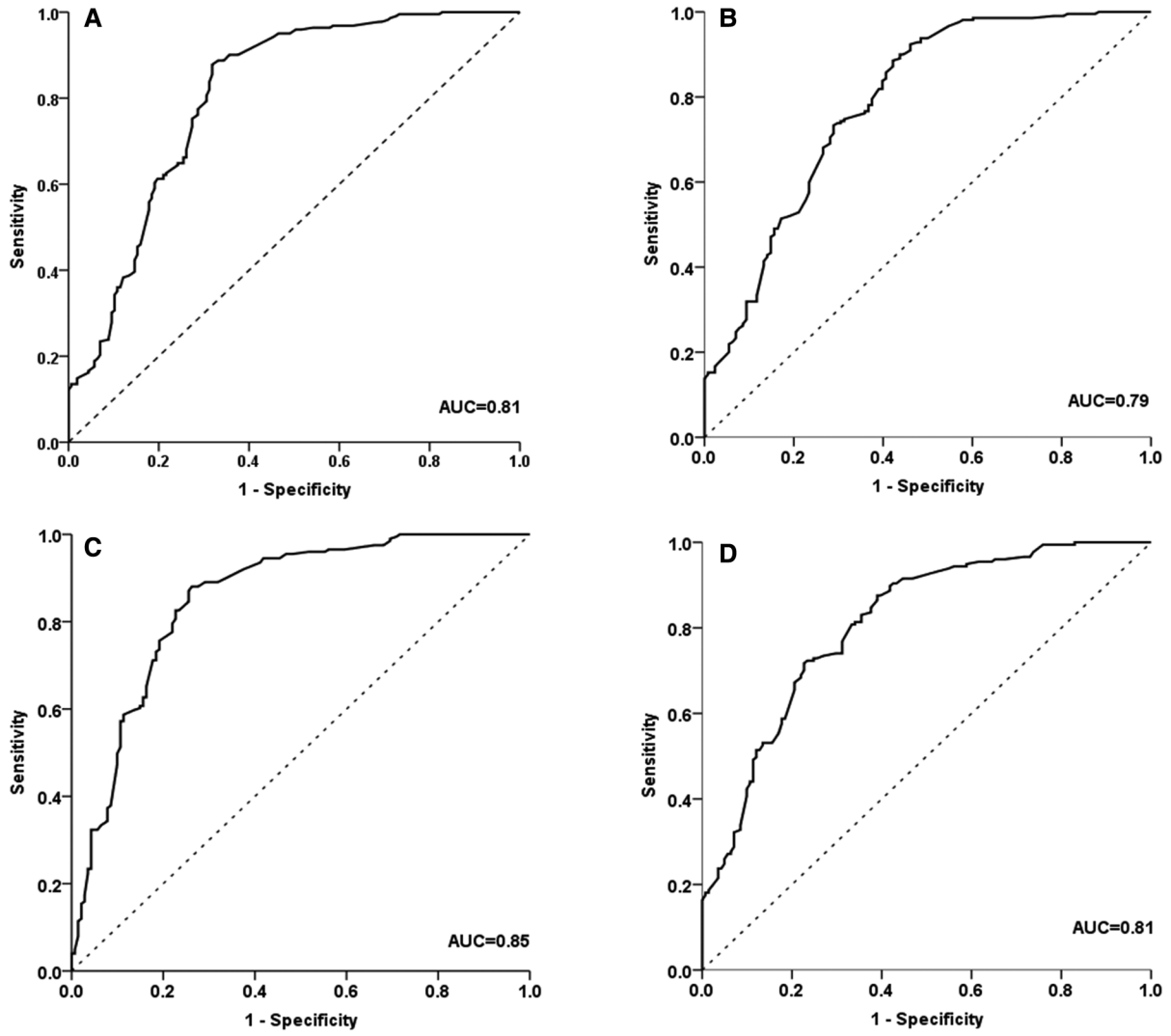

FIGURE 4
ROC curve analysis for determining six-minute walk test (6MWT) distance cut-off values in boys with a height of <130 cm (A); in boys with a height of ≥130 cm (B); in girls with a height of <130 cm (C); girls with a height ≥130 cm (D). ROC, receiver operating characteristic.

consisted with Lammers et al. (13) that VO_{2max} is closely related to the 6MWT distance in children with PAH who have a poor exercise capacity (ie, a 6MWT distance below 300 m). Previous studies in adults with cardiovascular problems (14, 15, 27) have shown similar findings, with some deviation in cutoff values. Additionally, when we divided the subjects according to VO_{2max}, we identified that the 6MWT did not demonstrate significant importance in the group with higher VO_{2max}, or in other words, individuals with a better exercise capacity. This result again supported the earlier finding that submaximal exercise testing is not very effective for this population (13, 28). On the other hand, 6MWT distance and both of the VE/VCO_2 slope and OUES linearly correlate with no influence of walking distance, probably due to the fact that these two parameters have no certain association with the degree of effort. Therefore, a 6MWT should not be considered the preferred exercise testing modality or a reliable substitute for CPET when assessing the outcome of medical intervention in pediatric patients with relatively mild functional impairment.

In accordance with studies (27–30) it is advised not to conduct the 6MWT in participants younger than 5 years old because of the lack of concentration during 6 min and questionable results in these children. CPET cannot also provide reliable predictive value for participants under 6 years old (31), so there is still a large space for further exploring

how to evaluate the exercise capacity of children of this age more objectively.

Limitations

There were few patients with NYHA III who participated in our study and the population of patients with NYHA IV was not represented in the subjects. As observed in studies including more advanced heart failure, the predictive power of the 6MWT would likely portend additional clinical assessment and prognostic value in these patients. Thus a high sample number of patients with cyanosis or undergone palliative surgery is necessary for this affirmation to be finally consolidated.

This was a cross-sectional analysis and further longitudinal studies are required to assess whether serial CPET or 6MWT represent efficacy endpoints and functional capacity for an individual with CHD.

Conclusion

Our study confirmed the linear correlation between 6MWT distance and CPET-derived variables in functional impaired pediatric patients with CHD, therefore providing evidence on when a 6MWT should be considered as a convincing complementary test in the pediatric population with CHD. The cutoff values for 6MWT distance may be qualified as one of the intervention targets for exercise rehabilitation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Guangzhou Women and Children's Medical Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JQ: concept, data acquisition, data interpretation, drafting article, approval of the final version of this manuscript. HS: data interpretation, statistics, critical revision, approval of the final version of this manuscript. YG, XC, XX, XZ: data acquisition, approval of the final version of this manuscript. YC: concept, data interpretation, drafting article, approval of the final version of this manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at https://www.frontiersin.org/articles/10.3389/fped.2022.965739/full#supplementary-material.

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Clinical significance of right ventricular–pulmonary arterial coupling in patients with tricuspid regurgitation before closure of atrial septal defect

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Background: Functional tricuspid regurgitation (TR) usually decreases after atrial septal defect (ASD) closure; however, it may persist and cause heart failure that requires treatment. We aimed to investigate clinical and echocardiographic factors predicting persistent TR after ASD closure.

Methods: Among 348 adults who underwent isolated ASD closure between January 2010 and September 2020, 91 (26.1%) patients with significant TR (at least moderate degree) before ASD closure were included. Persistent TR was defined as significant TR on echocardiography at 6 months to 1 year after ASD correction. We comprehensively analyzed the echocardiogram before ASD closure, including speckle-tracking imaging. Right ventricular (RV)–pulmonary arterial (PA) (RV–PA) coupling was assessed by the ratio of RV global longitudinal strain (RV GLS) and tricuspid annular S′ velocity to PA systolic pressure (PASP).

Results: Persistent TR was observed in 22 (24.2%) patients. Patients with persistent TR were significantly older and had larger TR jet areas and lower RV–PA coupling parameters than those without persistent TR. On multivariable regression, persistent TR was independently associated with age [odds ratio (OR) 1.07, 95% confidence interval (CI) 1.01–1.14, $p = 0.030$) and |RV GLS|/PASP (OR 0.001, 95% CI 0.00–0.017, $p = 0.012$). ROC curves analysis showed that |RV GLS|/PASP's best cut-off for persistent TR was 0.46 (cut-off 0.46, the area under the curve 0.789, $p < 0.001$).

Conclusion: Persistent TR after ASD closure is not rare. Old age and RV–PA uncoupling could be associated with persistent TR after ASD closure. In older patients with abnormal RV–PA coupling, careful evaluation and concomitant or subsequent TR intervention may be considered.

KEYWORDS

atrial septal defect, tricuspid regurgitation (TR), right ventricular-pulmonary artery coupling, echocardiography, old age

Introduction

Atrial septal defect (ASD) is a relatively common congenital heart disease in adults. The left-to-right shunt causes right ventricular (RV) volume overload and changes in pulmonary vasculature resulting in RV pressure overload (1). Finally, if ASD is not corrected, pulmonary hypertension can be induced. Functional tricuspid regurgitation (TR) is the result of RV volume overload and frequently occurs in adult patients with ASD (2, 3). Significant TR has been associated with cardiovascular morbidity and mortality (4, 5). Previous studies have addressed the effects of percutaneous and isolated surgical ASD closures in patients with significant TR (6, 7). In patients with ASD combined with significant TR, ASD closure is associated with a significant reduction in functional TR, over the long term (6, 8). However, a few studies reported that residual functional TR is common after device closure (2, 7). Understanding the regression of functional TR after ASD closure is important to determine the optimal therapeutic strategy for ASD [i.e., ASD occlusion alone or combined corrected tricuspid valve (TV) surgery].

Non-invasive estimation of RV–pulmonary arterial (PA) coupling, a load-independent measure of RV performance, using a ratio of RV systolic functional parameters and RV afterload (PA systolic pressure), has been validated as a prognostic marker in patients with PA hypertension, heart failure, and adult congenital heart disease (9, 10). In the present study, we aimed to examine the clinical and echocardiographic factors associated with persistent TR after ASD closure and whether RV–PA coupling and persistent TR after ASD closure are related.

Methods

Study population

This study included a total of 348 adults who underwent isolated ASD (primum and secondum) surgical or percutaneous closures without combined structural abnormality between January 2010 and September 2020 at a single tertiary hospital. In patients with ASD closure, echocardiography was routinely performed at baseline, before ASD closure, and at 6 months or 1 year after ASD closure. The exclusion criteria included the following: (1) no or mild TR at baseline echocardiography (n = 222); (2) concomitant valve surgery or congenital cardiac defects (n = 21); (3) severe pulmonary hypertension [right ventricular systolic pressure (RVSP) $\geq$ 70 mmHg] (n = 8); (4) ASD closure with fenestration type (n = 6); and (5) absence of echocardiography between 6 months and 1 year after ASD closure (n = 78). Finally, 91 (26.1%) patients with significant TR (at least moderate degree) before ASD closure were included (Figure 1). Patients' clinical data recorded before ASD closure were obtained from hospital records. The study protocol was developed according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital.

Abbreviations: TR, Tricuspid regurgitation; ASD, Atrial septal defect; RV, Right ventricular; RA, Pulmonary arterial; GLS, Global longitudinal strain; PASP, Pulmonary artery systolic pressure.

Echocardiography

Transthoracic echocardiography was performed using a standard ultrasound machine (Vivid E9; GE Medical Systems; Wauwatosa, WI, Philips iE33; Philips Healthcare; Netherlands) with a 2.5–3.5 MHz probe. Standard echocardiographic measurements were performed according to the recommendations from the American Society of Echocardiography guidelines (11). Assessment of the right side of the heart included the measurements of RV basal and mid-cavity at the end-diastole and end-systolic and diastolic area of the right ventricle on a four-chamber view. Dimension of the tricuspid annulus was measured at end-diastole on an RV-focused four-chamber view (11). For a comprehensive assessment of RV systolic function, RV end-systolic and end-diastolic areas were traced in a focused RV apical view, and RV fractional area change (FAC) was calculated using the following formula: FAC = [(diastolic area–systolic area)/diastolic area] × 100%. Tissue Doppler tricuspid lateral annular peak systolic velocity (S') was measured from the RV-focused apical view. The severity of TR was evaluated using multiple parameters (12). TR jet area was measured at the time of mid-systole in the apical four-chamber view using the area trace method. The vena contracta width of TR was measured at its narrowest point as it passes through the orifice. Estimated PA systolic pressure (PASP) was calculated from peak TV flow velocity using the modified Bernoulli equation, and right atrial pressure was estimated using the respiratory index of the inferior vena cava (13).

Speckle tracking echocardiography

Speckle tracking echocardiography was performed by an experienced cardiologist blinded to clinical data, using a vendor-independent software package (TomTec software; Image Arena 4.6, Munich, Germany). All echocardiograms were uploaded in the Digital Imaging and Communications in Medicine format to the software package. For myocardial deformation analysis,

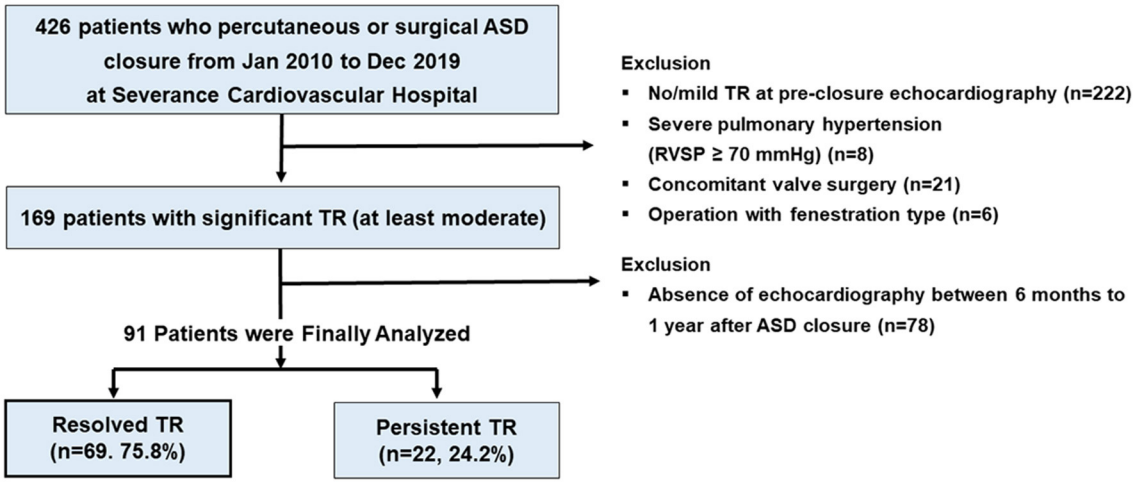

FIGURE 1
Graphical representation of the patient selection process.

the endocardial border was traced on the end-systolic frame in each selected image. The end-systolic frame (≥ 50 frames per second) was defined by the QRS complex or based on the smallest ventricular volume during a cardiac cycle. The software automatically tracked speckles along the endocardial border and myocardium throughout the cardiac cycle. The myocardium of the right ventricle was divided into six segments (basal, mid, and apical segments) of the RV free wall and septum. For the assessment of RV strain, we evaluated the average value of the longitudinal peak systolic strain from all segments of the free and septal walls of the right ventricle (RV GLS) in the RV-focused apical view. For the assessment of left ventricular global longitudinal strain (LV GLS), the value for LV GLS was obtained by averaging all segmental strain values from the 18 LV segments in the apical four-, three-, and two-chamber views. The absolute value of RV GLS and LV GLS was expressed as |RV GLS| and |LV GLS|, respectively.

Assessment of RV–PA coupling

RV–PA coupling was estimated non-invasively using the conventional echocardiographic parameters and RV strain. Conceptually, RV–PA uncoupling occurs when RV contractility cannot rise further to match RV afterload (9–11). RV contractility was assessed by RV FAC, TV annular S', and |RV GLS|. Furthermore, PASP was used as a parameter of RV afterload. Finally, RV–PA coupling parameters were derived using the formula: RV FAC/PASP ratio, TV annular S'/PASP ratio, and |RV GLS| /PASP ratio.

Follow-up

Echocardiography was routinely performed at 6 months to 1 year after ASD closure. Persistent TR was defined as a significant TR (at least moderate degree) even after ASD correction on echocardiography. Clinical outcomes were defined as a composite of cardiovascular death, HF admission, urgent hospital visits due to HF aggravation, and up-titrated diuretics.

Statistical analysis

Continuous variables are presented as a mean ± standard deviation (SD) or median (interquartile range) and were compared using paired Student's *t*-test (for normally distributed data) or the Mann–Whitney U-test (for non-normally distributed data). Categorical variables are presented as absolute numbers and percentages and were analyzed using the chi-square or Fisher's exact test. Kaplan-Meier survival analyses and log-rank tests were used to compare the clinical outcomes between patients with persistent TR and those with resolved TR during the follow-up period. The cut-off values for parameters were determined as the values that maximized the sum of the sensitivity and specificity for persistent TR after ASD closure in the receiver operating characteristic (ROC) curve analysis. Logistic regression analysis was performed to determine the relationships between clinical and echocardiographic variables and persistent TR after ASD closure. The variables selected for entry into the multivariate analyses were those with a $p < 0.10$ in the logistic univariate analysis. The multivariate analyses focusing on RV function

TABLE 1 Baseline characteristics of the study population.

	Total ($n = 91$)	Resolved TR ($n = 69$)	Persistent TR ($n = 22$)	*P*-value
Age, years	55 ± 14	52 ± 14	66 ± 10	<0.001
Female sex, *n* (%)	62 (68.1)	49 (71.0)	13 (59.0)	0.168
Body mass index, kg/m^2	23.6 ± 4.3	23.4 ± 2.6	23.7 ± 3.3	0.445
Hypertension, *n* (%)	25 (27.5)	14 (14.4)	11 (50.0)	0.040
Diabetes mellitus, *n* (%)	8 (8.8)	5 (7.2)	3 (13.6)	0.234
Atrial fibrillation, *n* (%)	27 (29.7)	16 (23.1)	11 (50.0)	0.008
Systolic BP, mmHg	122 ± 18	123 ± 16	121 ± 17	0.353
Diastolic BP, mmHg	75 ± 13	75 ± 15	76 ± 11	0.490
Heart rate, bpm	71 ±14	71 ± 13	73 ± 13	0.432
ASD size, cm	2.43 ± 0.87	2.44 ± 0.72	2.43 ± 0.93	0.236
Qp/Qs ratio	2.44 ± 0.81	2.46 ± 1.82	2.24 ± 0.79	0.597
Type of closure, *n* (%)				
Percutaneous	56 (61.5)	39 (56.5)	17 (77.2)	
				0.461
Surgical	35 (38.5)	30 (43.4)	5 (22.7)	
Type of ASD, *n* (%)				
Secondum ASD	82 (90.1)	65 (94.2)	17 (77.1)	
				0.078
Primum ASD	9 (9.8)	4 (5.8)	5 (22.7)	

TR, tricuspid regurgitation; BP, blood pressure; ASD, atrial septal defect; QP/Qs; pulmonary blood flow/systemic blood flow.

were performed in model 1. In model 2, the analyses including RV–PA coupling parameters were performed. A two-sided $p < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk NY, USA).

Results

Baseline characteristics

The baseline characteristics of the study population, according to the presence of persistent TR, are presented in Table 1. The mean age was 55 ± 14 years and 62 (68.1%) patients were women. The average size of ASD was 2.43 ± 0.87 mm and the mean pulmonary-systemic flow ratio (Qp/Qs) was 2.44 ± 0.81. In total, 56 (61.5%) patients in our study population underwent percutaneous ASD closure and 35 (38.5%) patients underwent surgical ASD closure. Echocardiography performed at 6 months to 1 year after ASD closure revealed 22 (24.1%) patients with persistent TR (Figure 2). Patients who had persistent TR were significantly older (66 ± 10 vs. 52 ± 14 years, $p < 0.001$), had more hypertension (50.0 vs. 14.4%, $p = 0.040$), and had a higher prevalence of atrial fibrillation (AF) (50.0 vs. 23.1%, $p = 0.008$) compared to patients with resolved TR. There were no significant differences in ASD size, Qp/Qs, and type of intervention between patients with persistent TR and those with resolved TR.

Cardiac remodeling and change in TR after ASD closure

Transthoracic echocardiography was performed at a median of 195 days (range 174–245 days) after ASD closure. The echocardiographic parameters were significantly changed after ASD closure (Table 2). Compared with baseline echocardiography, there was a significant reduction in the RV and right atrial (RA) sizes by reducing RV volume overload, along with an increase in the two-dimensional diameters of LV. In the RV systolic functional parameters, RV FAC decreased after ASD closure. Additionally, Tricuspid annular S' as an indicator of RV longitudinal function decreased significantly, but these parameters were within the normal range. There was a significant reduction in TR severity. Several parameters evaluating the TR severity, such as TR jet area, TR vena contracta, and end-diastolic TV annulus diameter, were significantly reduced after ASD closure. Furthermore, PASP decreased with a reduction in peak TR velocity.

Comparison of echocardiographic parameters between patients with resolved TR and those with persistent TR

Echocardiographic parameters of the resolved TR and persistent TR groups after ASD closure are described in Table 3. LV chamber size and *E*/*e*' were not different between the two

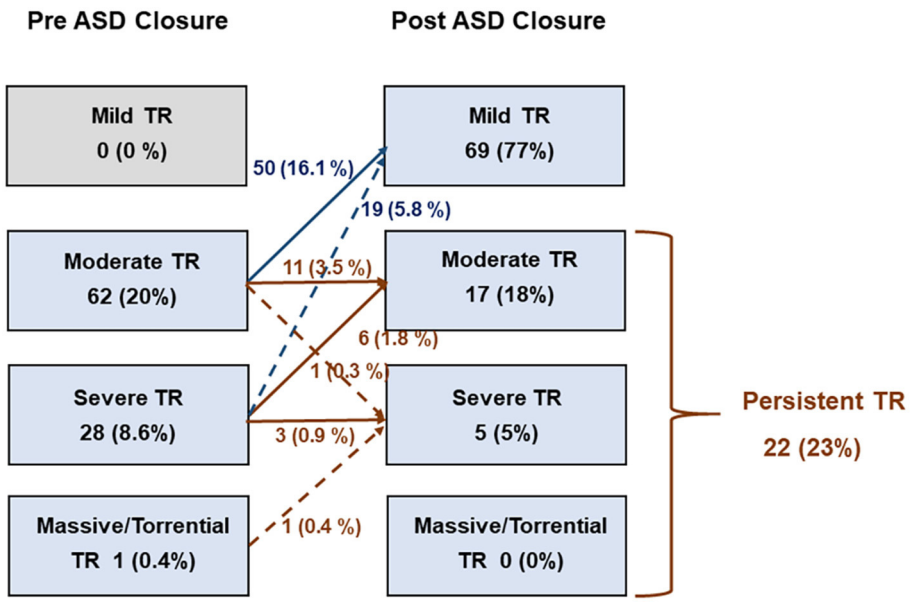

FIGURE 2
Changes in tricuspid regurgitation after closure of atrial septal defect.

groups. Right cardiac chamber size was similar between the two groups. In RV functional parameters, TV annular S' and |RV GLS| were significantly lower in patients with persistent TR than in those with resolved TR, but RV FAC was not different. In terms of RV–PA coupling, both TV annular S'/PASP ratio and |RV GLS|/PASP ratio illustrated significantly lower values in patients with persistent TR compared with those with resolved TR. TR jet area was significantly larger in patients with persistent TR, but other TV parameters were not significantly different between the two groups.

Clinical outcomes between patients with resolved TR and those with persistent TR

During the follow-up duration (median: 22 months), there were no cardiovascular death and HF admission in patients with resolved TR and those with persistent TR. One (1.4%) of the 69 patients with resolved TR and 2 (9.0%) of the 22 patients with persistent TR were urgent visits due to HF aggravation. The diuretics dose was up-titrated in four (18.1%) patients with persistent TR and one (1.4%) patient with resolved TR. There was no significant difference in diuretics (furosemide) dose in patients with resolved TR and persistent TR (32 vs. 35 mg, $p = 0.116$). During follow-up, the diuretics dose was significantly higher in patients with persistent TR compared to the patients with resolved TR (34 vs. 20 mg, $p = 0.023$). Kaplan-Meier analysis showed that the event-free survival rate was worse in patients with persistent TR than in those with resolved TR (log-rank test; $p < 0.001$) (Supplementary Figure 1).

Associating factors with persistent TR

Persistent TR after ASD closure was observed in 22 (24.1%), including 17 (19%) with moderate TR and 5 (5%) with severe TR (Figure 2). In univariate logistic regression analysis, age, hypertension, AF, TV annulus diameter, TR jet area, TV annulus S', |RV GLS|, and RV–PA coupling parameters were significantly associated with persistent TR after ASD closure. A multivariate logistic regression analysis was performed in two models. In model 1, only age remained an independent predictor for persistent TR after ASD closure. In model 2, age and |RV GLS|/PASP as an RV–PA coupling index were significant factors for persistent TR after ASD closure (Table 4).

Associations between RV–PA coupling and persistent TR after ASD closure

ROC was performed to evaluate the associations between RV–PA coupling and persistent TR after ASD closure. Parameters of RV–PA coupling demonstrated good predictive value (Tricuspid annular S' /PASP: area under the curve = 0.684, $p = 0.003$; cut-off value: 0.32; |RV GLS|/PASP: area under the curve = 0.789; $p < 0.003$, cut-off value: 0.46) (Figure 3). In a comparison of ROC in the RV–PA coupling index, the area under the ROC curve value of |RV GLS|/PASP was statistically significantly higher than that of tricuspid annular S' /PASP ($p < 0.012$). |RV GLS| was also a good cut-off value, but the area under the ROC curve value of |RV GLS|/PASP was statistically significantly higher than that of |RV GLS| [area under the curve:

TABLE 2 Echocardiographic parameters before and after ASD closure.

	Pre ASD closure	Post ASD closure	*P*-value
Left chamber parameters			
LVEDD, mm	40.4 ± 6.0	47.0 ± 4.2	<0.001
LVESD, mm	26.8 ± 5.0	30.2 ± 4.2	<0.001
LVEF, %	62.8 ± 9.0	66.9 ± 7.3	<0.001
LA volume index, ml/m^2	40.2 ± 15	40.5 ± 16	0.848
E velocity, m/s	0.78 ± 0.21	0.77 ± 0.24	0.719
A velocity, m/s	0.66 ± 0.17	0.62 ± 0.16	0.046
e' velocity, cm/s	0.76 ± 0.22	0.79 ± 0.17	0.499
E/e'	10.3 ± 3.0	11.6 ± 4.5	0.007
Right chamber parameters			
PASP, mmHg	45.7 ± 9.0	30.3 ± 8.1	<0.001
RV end-systolic area, cm^2	18.8 ± 4.9	13.2 ± 3.9	<0.001
RV end-diastolic area, cm^2	31.2 ± 7.2	21.2 ± 5.6	<0.001
RV basal diameter, mm	50.0 ± 6.3	40.9 ± 6.2	<0.001
RV mid diameter, mm	42.9 ± 6.6	31.4 ± 5.6	<0.001
RA area, cm^2	26.8 ± 7.2	17.5 ± 5.1	<0.001
RA major dimension, mm	63.1 ± 8.7	52.2 ± 8.8	<0.001
RA minor dimension, mm	46.5 ± 8.2	36.7 ± 5.8	<0.001
Tricuspid annular S', cm/s	13.9 ± 4.5	10.9 ± 2.8	<0.001
RV FAC, %	40.0 ± 8.2	38.1 ± 7.2	0.040
Tricuspid valve parameters			
Significant TR, n (%)	91 (100)	22 (24.1)	
TR jet area, cm^2	6.4 ± 4.2	2.5 ± 3.0	<0.001
TR vena contracta, mm	5.7 ± 1.5	2.9 ± 2.3	<0.001
TR velocity, m/sec	3.0 ± 0.4	2.4 ± 0.4	<0.001
TV annulus diameter, mm	40.6 ± 4.1	32.1 ± 6.8	<0.001

ASD, atrial septal defect; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LA, left atrial; E, early diastolic mitral inflow; A, late diastolic mitral inflow; e', early diastolic mitral annular tissue Doppler; E/e', ratio of early diastolic mitral inflow to early diastolic mitral annular tissue Doppler velocity; PASP, pulmonary arterial systolic pressure; RV, right ventricle; RA, right atrium; FAC, fractional area change; TR, tricuspid regurgitation.

0.729 (0.607–0.81)] (*p*-value: 0.043) (Supplementary Figure 2). TR jet area was not a significant factor in predicting persistent TR after ASD closure. Figure 4 displays a representative case of persistent TR after ASD closure, which showed that |RV GLS|/PASP ratio before ASD closure was lower than 0.46.

Discussion

The principal findings of this study are as follows: (1) Persistent TR after ASD closure is not uncommon; (2) Old age and abnormal RV–PA coupling are associated with persistent TR after ASD closure; (3) Among the RV–PA coupling parameters, |RV GLS|/PASP < 0.46 depicts the most satisfactory predictive performance for persistent TR after ASD closure.

There is a growing interest in functional TR, which is associated with poor prognosis (4, 14). Dilatation of the tricuspid annulus secondary to RV enlargement, RA enlargement, tethering of tricuspid leaflets, and papillary muscle displacement are the main mechanisms of functional TR. As functional TR frequently occurs in adult patients with ASD, a few studies were focused on the change in functional TR after the closure of ASD (2, 6, 15). Functional TR was ameliorated after percutaneous and isolated surgical ASD closures, although half of the persistent TR cases remained in short-term follow-ups (2). Furthermore, pulmonary hypertension before ASD closure was associated with persistent TR after ASD closure (2). In a long-term follow-up study, significant TR decreased during the long-term follow-up period after transcatheter ASD closure, along with an improvement in heart failure symptoms (6, 15). However, even in long-term follow-up studies, significant TR persisted in approximately 20% of patients (6, 15). In our study, we followed up for 6 months to 1 year after ASD closure (surgical or percutaneous). Similar to the findings of previous studies, in our study, significant TR persisted in 22% of the patients after ASD

TABLE 3 Comparison of two groups based on the resolution or persistence of TR.

	Resolved TR ($n = 69$)	Persistent TR ($n = 22$)	*P*-value
Left chamber parameters			
LVEDD, mm	40.9 ± 6.0	41.6 ± 5.8	0.643
LVESD, mm	27.2 ± 4.6	27.8 ± 4.9	0.581
LVEF, %	62.6 ± 9.1	63.6 ± 8.5	0.581
|LV GLS|, %	20.24 ± 3.43	19.61 ± 5.17	0.631
E velocity, m/s	0.79 ± 0.22	0.76 ± 0.17	0.571
E/e'	10.1 ± 3.1	11.3 ± 2.6	0.142
Right chamber parameters			
PASP, mmHg	45.7 ± 9.9	49.1 ± 8.8	0.157
RV End-systolic area, cm^2	19.1 ± 4.9	18.2 ± 4.5	0.469
RV End-diastolic area, cm^2	32.2 ± 7.9	30.1 ± 7.1	0.307
RA area, cm^2	26.2 ± 7.3	29.1 ± 6.0	0.118
RV FAC, %	39.8 ± 8.2	39.1 ± 6.4	0.732
Tricuspid annular S', cm/s	13.4 ± 4.6	11.2 ± 3.0	0.042
|RV GLS|, %	20.6 ± 4.8	17.6 ± 6.4	0.032
RV FAC/ PASP, %/mmHg	0.86 ± 0.33	0.83 ± 0.21	0.623
TV annulus S' / PASP, cm/s*mmHg	0.31 ± 0.10	0.24 ± 0.08	0.011
|RV GLS| / PASP ratio, %/mmHg	0.46 ± 0.14	0.37 ± 0.13	0.013
Tricuspid valve parameters			
TR jet area, cm^2	5.9 ± 3.6	8.1 ± 5.6	0.047
TR vena contracta, mm	5.7 ± 1.5	5.9 ± 1.5	0.457
TR velocity, m/sec	3.0 ± 0.3	3.1 ± 0.4	0.356
TV annulus diameter, mm	40.2 ± 4.0	41.8 ± 4.2	0.116

GLS, global longitudinal strain; ASD, atrial septal defect; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LA, left atrial; E, early diastolic mitral inflow; A, late diastolic mitral inflow; e', early diastolic mitral annular tissue Doppler; E/e', ratio of early diastolic mitral inflow to early diastolic mitral annular tissue Doppler velocity; PASP, pulmonary arterial systolic pressure; RV, right ventricle; RA, right atrium; FAC, fractional area change; TR, tricuspid regurgitation.

closure. In patients with persistent TR, the urgent visit due to HF aggravation and up-titrated diuretics were significantly higher than those with resolved TR in this study.

With regard to the factors associated with persistent TR after ASD closure, previous studies showed varied results (6, 15). The left-to-right shunt of ASD causes volume overload of the right atrium and right ventricle. Accompanied by the enlargement of the right heart, functional TR was influenced by the changes in the atrial and ventricular geometry and function (16). Thus, preprocedural factors of the right side of the heart affect persistent TR after ASD closure. In previous studies, baseline RA size was the only parameter associated with persistent TR after ASD closure (6). However, in our data, we found no differences in the RA and RV sizes between those with and without persistent TR after ASD closure. This may be because not only the geometry of the right side of the heart but also RV function and remodeling of TV can affect persistent TR after ASD closure. In other studies, the presence of pulmonary hypertension before ASD closure predicted persistent TR (2). Patients with ASD and left-to-right shunts had a risk of PA hypertension (17). Chronic exposure of the pulmonary vasculature to increased blood flow in patients with ASD may produce histological changes in the pulmonary arteries, causing luminal narrowing leading, to high pulmonary vascular resistance with pulmonary hypertension (18). Pulmonary hypertension in patients with ASD influences outcomes and is associated with increased morbidity and mortality (19, 20). In our study, PASP before ASD closure was not associated with persistent TR after ASD closure. This may be because of the 6-month to 1-year follow-up after ASD closure in our study, instead of the short-term follow-up of previous studies (15). Consistent with other studies with long-term follow-up after ASD closure, in this study, the PASP showed normalization during the follow-up period.

Interestingly, in this study, RV–PA coupling parameters were independent factors of persistent TR after ASD closure. Chronic volume overload of the right side of the heart leads to dilatation of the right atrium and right ventricle and effects such as right heart failure and pulmonary hypertension (21). Furthermore, secondary TR imposes a chronic volume overload on the right ventricle that can increase RV wall tension leading to myocardial fibrosis and changed RV geometry, directly contributing to impaired RV contractility (22).

TABLE 4 Pre-procedural factors associated with persistent TR after ASD closure.

	Univariate analysis		Multivariate analysis			
			Model 1: |RV GLS|		Model 2: |RV GLS| /PASP	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Age	1.099 (1.045–1.157)	<0.001	1.075 (1.010–1.144)	0.022	1.071 (1.007–1.140)	0.030
Female sex	0.456 (0.169–1.229)	0.121				
HTN	5.169 (1.839–14.532)	0.002	2.595 (0.683–9.865)	0.162	2.594 (0.645–10.434)	0.179
DM	3.611 (0.821–15.879)	0.089	0.739 (0.126–4.346)	0.738	0.537 (0.087–3.304)	0.502
Atrial fibrillation	3.312 (1.212–9.054)	0.020	0.503 (0.126–4.346)	0.410	0.554 (0.121–2.540)	0.447
ASD size	0.715 (0.436–1.176)	0.186				
Qp/Qs ratio	1.202 (0.816–1.771)	0.353				
TV annulus diameter	0.998 (0.952–1.046)	0.943				
TR jet area	1.123 (0.003–1.257)	0.043	1.152 (0.981–1.362)	0.084	1.133 (0.961–1.336)	0.136
TR vena contracta	1.204 (0.919–1.578)	0.178				
PASP	1.038 (0.988–1.091)	0.136				
LVEF	1.019 (0.961–1.079)	0.534				
E/e'	1.080 (0.943–1.237)	0.267				
|LV GLS|	1.007 (0.947–1.072)	0.815				
Tricuspid annular S'	0.840 (0.711–0.993)	0.041				
RV FAC	1.004 (0.957–1.054)	0.870				
|RV GLS|	0.853 (0.766–0.950)	0.004	0.877 (0.760–1.012)	0.072		
Tricuspid annular S' /PASP	0.000 (0.000–0.0124)	0.009				
RV FAC/PASP	0.337 (0.072–1,566)	0.165				
|RV GLS| /PASP	0.000 (0.000–0.018)	0.001			0.001 (0.000–0.175)	0.012

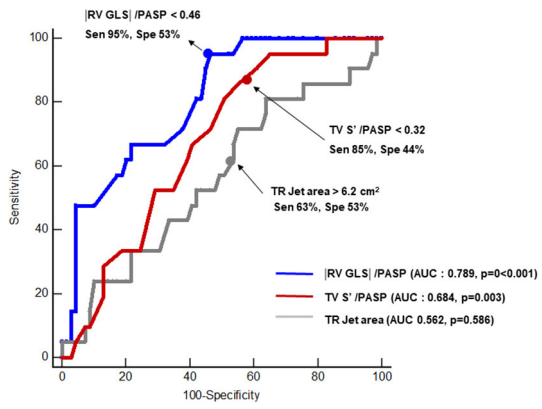

FIGURE 3
Receiver operating characteristic analysis comparing predictive values of tricuspid annular S' /PASP, |RV GLS|/PASP and TR jet area for predicting persistent TR after closure of ASD. AUC, area under the curve; Sen, sensitivity; Spe, specificity; RV GLS, right ventricular global longitudinal strain; PASP, pulmonary arterial systolic pressure; TR, tricuspid regurgitation.

RV remodeling is frequently associated with secondary TR, which may accelerate RV–PA uncoupling (23). RV–PA coupling is a comprehensive parameter for both RV contractility and RV afterload (9, 24). Noninvasively measured RV–PA coupling, using a ratio of RV systolic function and RV afterload, is of superior prognostic value compared with RV systolic function and has proven clinical implications in acquired heart disease and PA hypertension (9, 25). Recently, in the field of congenital heart disease, abnormal RV–PA coupling in chronic PR, even in the setting of normal RV ejection fraction, was correlated with exercise capacity. In the present study, we used non-invasively measured TV annular S'/PASP and RV GLS/PASP as a marker of RV–PA coupling. A previous study demonstrated that TV annular S'/RVSP and RV free wall strain /RVSP as RV–PA coupling was used as parameters for predicting successful weaning from ECMO compared with conventional criteria in patients with refractory cardiogenic shock (26). In the present study, TV annular S'/RVSP <0.32 and |RV GLS|/PASP <0.46 exhibited a good predictive value of persistent TR after ASD closure. The hemodynamic changes in ASD patients can be considered a combination of RV myocardial damage and pulmonary vasculopathy. Thus, it is important to evaluate the comprehensive RV function and pulmonary circulation in patients with ASD as RV–PA coupling.

Moreover, in our study, the included patients were relatively old. Old age was a significant factor contributing

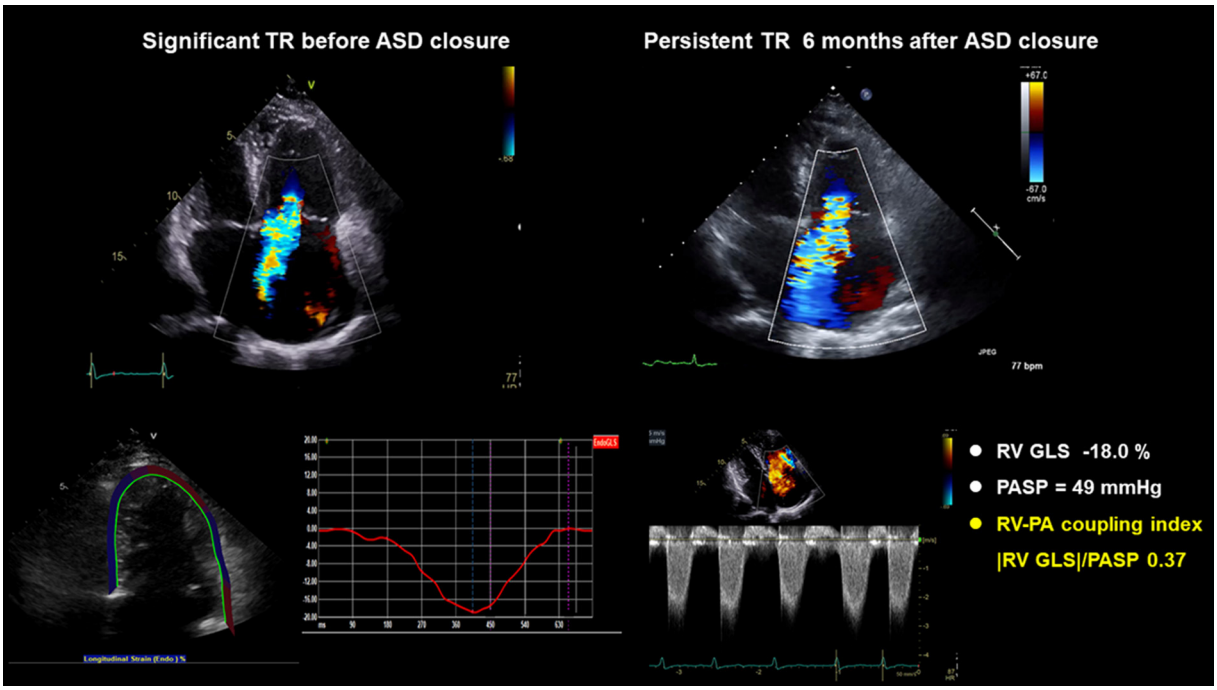

FIGURE 4
A representative case: A 72-year-old woman with hypertension, diabetes, atrial fibrillation, and |RV GLS|/PASP ratio before ASD closure < 0.46, had persistent TR after ASD closure. ASD, atrial septal defect; RV GLS, right ventricle global longitudinal strain; PASP, pulmonary arterial systolic pressure; TR, tricuspid regurgitation.

to persistent TR after ASD closure. This may suggest that long-standing remodeling of the right heart and pulmonary vasculature affects RV myocardial function and pulmonary circulation. Therefore, it may be suggested that concurrent or subsequent TR interventions should be considered in elderly patients and patients with RV–PA uncoupling. TR interventions could reduce RV volume overload (27); therefore, could have a positive effect on RV–PA coupling in patients with ASD.

Study limitation

There are several limitations to this study. First, this was a single-center, retrospective study with small sample size. Furthermore, the number of patients with persistent TR after ASD closure was small. Second, the severity of TR was evaluated using the semi-quantitative method in this study. Recent guidelines of TR showed that the grading of TR using quantitative methods, such as the PISA method or volumetric method, to evaluate the severity of TR. Third, we did not evaluate invasive hemodynamic data of RV–PA coupling. Thus, further validation of non-invasively measured RV–PA coupling parameters is needed. Last, TAPSE/PASP, the most validated parameter of RV–PA coupling, could not be analyzed due to small numbers ($n = 52$) in this study.

Conclusion

Persistent TR after ASD closure is not uncommon. Old age and RV–PA uncoupling could be associated with persistent TR after ASD closure. These findings suggest that concomitant or subsequent TR treatment should be considered in older patients with abnormal RV–PA coupling.

Synopsis

- Echocardiographic parameters of RV–PA coupling were reduced in patients with persistent TR after ASD closure.
- Old age and abnormal RV–PA coupling are associated with persistent TR after ASD closure.
- In elderly patients with abnormal RV–PA coupling, concomitant or subsequent TR intervention may be considered.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Severance Hospital. The Ethics Committee waived the requirement of written informed consent for participation.

Author contributions

SHL and CS: planning, conducting the study, and drafting the manuscript. SHL, YS, JK, SaL, JS, IC, D-YK, G-RH, J-WH, and CS: collecting and interpreting data. YS and CS: guarantor of the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.896711/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Kaplan-Meier survival curve according to presence of TR after the closure of ASD.

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Myocardial fibrosis in congenital heart disease

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Myocardial fibrosis resulting from the excessive deposition of collagen fibers through the myocardium is a common histopathologic finding in a wide range of cardiovascular diseases, including congenital anomalies. Interstitial fibrosis has been identified as a major cause of myocardial dysfunction since it distorts the normal architecture of the myocardium and impairs the biological function and properties of the interstitium. This review summarizes current knowledge on the mechanisms and detrimental consequences of myocardial fibrosis in heart failure and arrhythmias, discusses the usefulness of available imaging techniques and circulating biomarkers to assess this entity and reviews the current body of evidence regarding myocardial fibrosis in the different subsets of congenital heart diseases with implications in research and treatment.

KEYWORDS

myocardial fibrosis, fibrosis, congenital heart disease, cardiac magnetic resonance (CMR), collagen biomarkers, tetralogy of Fallot, systemic right ventricle, myocardial interstitial fibrosis

Introduction

The history of congenital heart disease (CHD) is a history of hope and success. Since the first ligation of a patent ductus arteriosus accomplished by Gross and Hubbard on August 8, 1938 (1), an unstoppable flow of innovative and creative surgical and interventional techniques has dealt with the most unimaginable cardiac malformations. Thousands of children destined to die soon after birth have been able to reach adulthood and, in most cases, develop a near-normal life. But the history of CHD is also paved with uncertainties. These repaired hearts are frequently afflicted with long-term complications, predominantly heart failure (HF) and arrhythmias. Our understanding of the mechanisms behind these complications and the available treatment options is based on the knowledge borrowed from acquired heart diseases and raises more questions than answers. The singularities of CHD should compel us to look beyond the ordinary and seek personalized, precision medicine for our patients.

During the last years, the myocardial interstitium (MI) has gone from the role of innocent bystander to a preeminent position in the pathogenesis of long-term cardiovascular complications, mainly HF. The MI is not a passive entity, but rather a complex and dynamic microenvironment that undergoes constant turnover: it ensures structural myocardial integrity, executes the repair response after injury, provides the means for force transmission throughout the cardiac

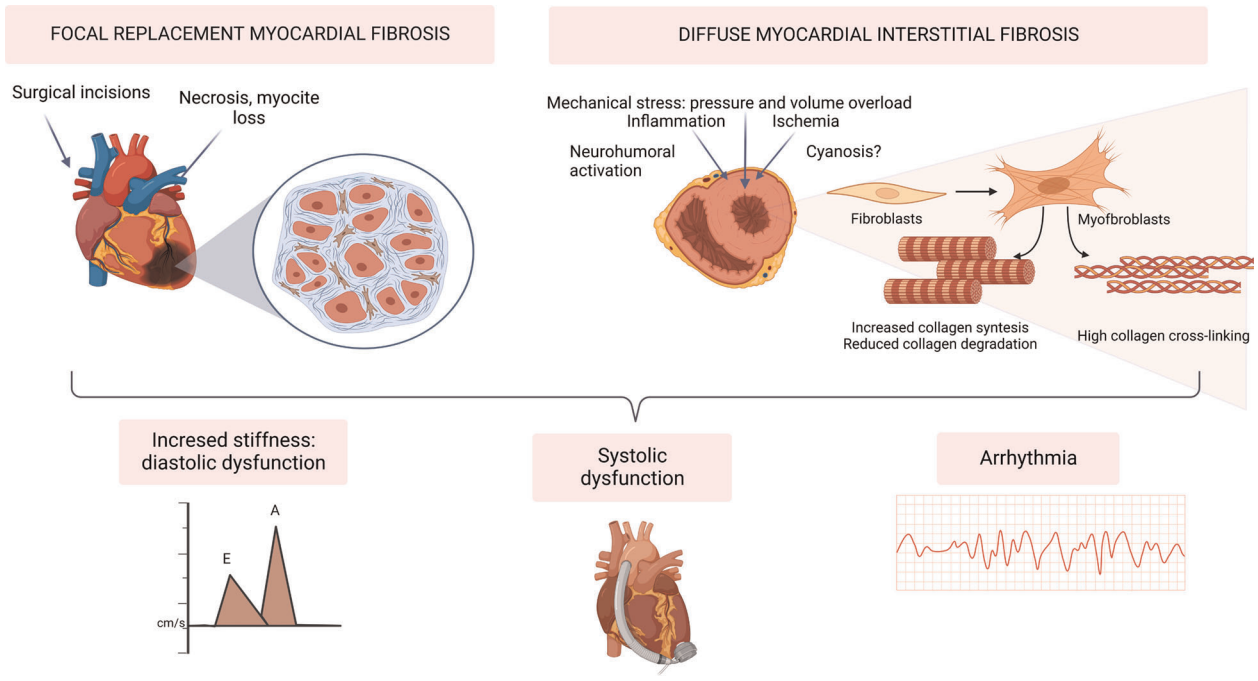

FIGURE 1
Myocardial fibrosis in the development of heart failure and arrhythmia in congenital heart disease. Created with BioRender.com.

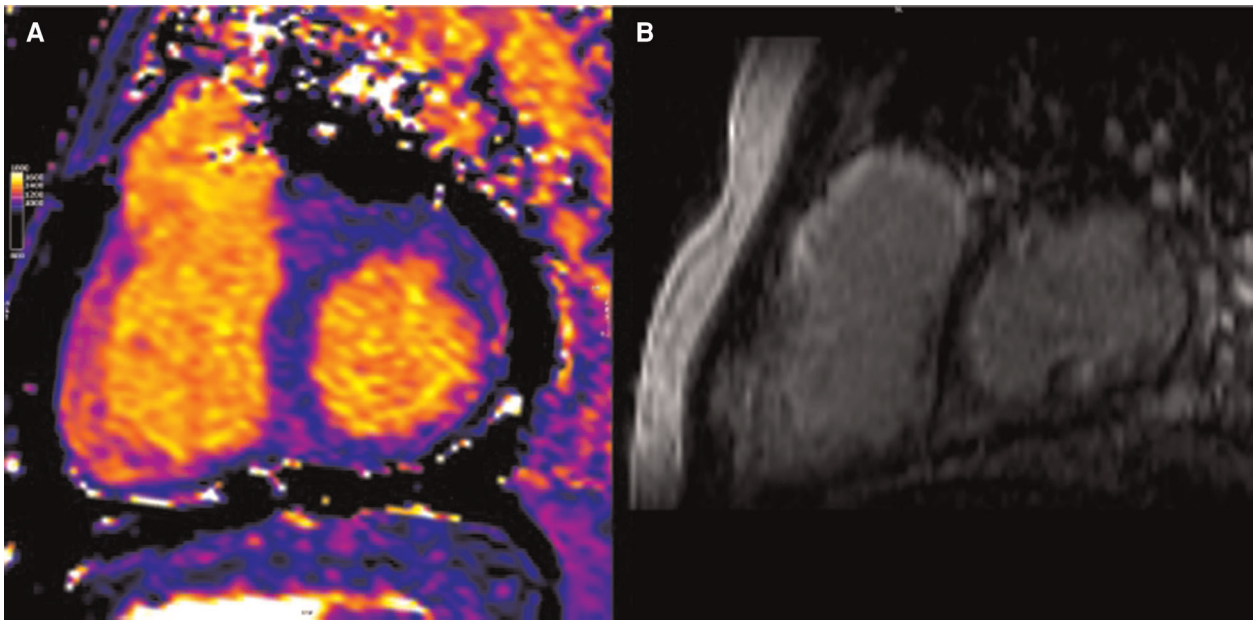

FIGURE 2
CMR of patient with repaired tetralogy of Fallot. (**A**) Precontrast T1 mapping of 1,091 ms (normal range of 950–1,050 ms) (**B**) Extent LGE, especially anterior wall of RVOT and anterior wall of RV.

cycle, translates myocyte shortening into overall ventricular pump function and facilitates communication between cells (2).

The accumulation of fibrillar collagen in the interstitial space, the so-called myocardial interstitial fibrosis, has been identified as a major cause of myocardial dysfunction. It not

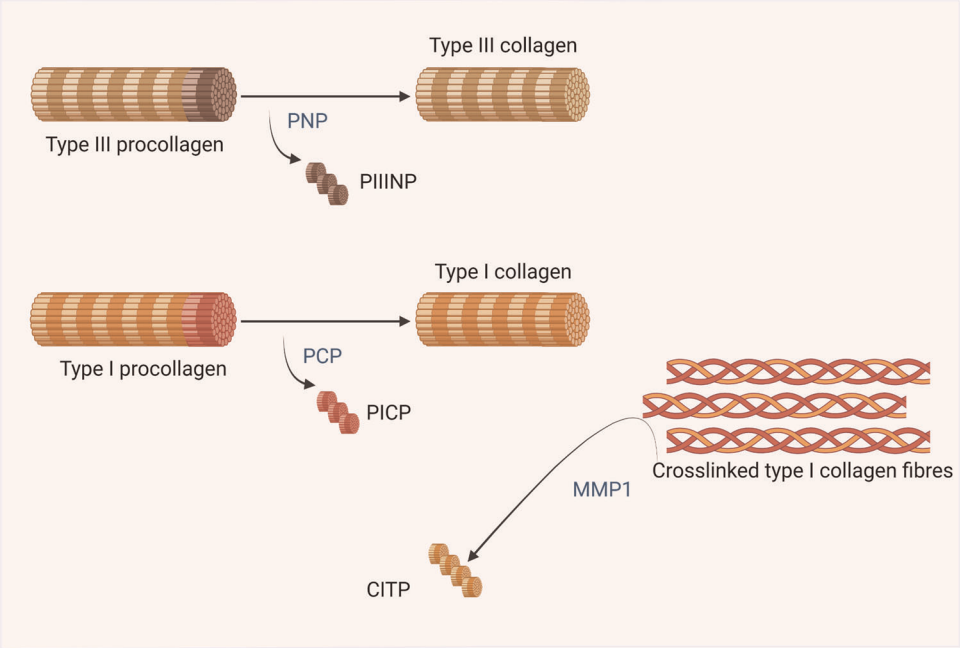

FIGURE 3
Biomarkers of collagen metabolism. Created with BioRender.com.

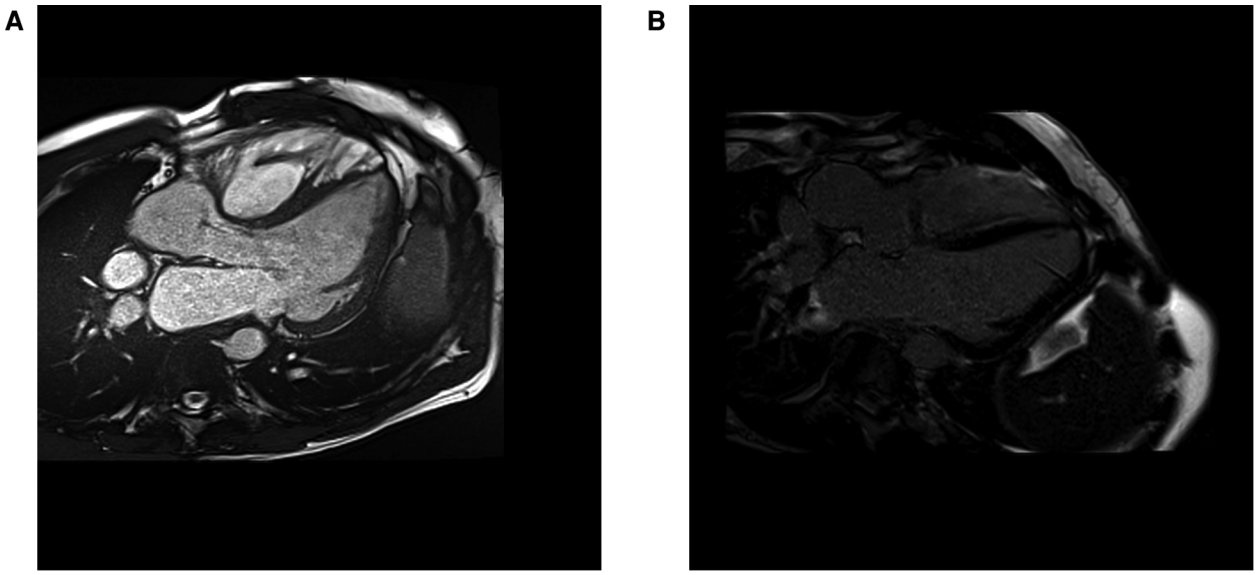

FIGURE 4
CMR cine 3 chamber view (**A**) and LGE image (**B**) from a 39 years old patient with a repaired tetralogy of Fallot, showing focal fibrosis in the anterior wall of the right ventricle.

only distorts this normal architecture but also impairs its biological function and properties.

The term "interstitial myocardial disease" was first coined in 1989 by Weber (3) in reference to maladaptive effects on interstitial remodeling in response to altered hemodynamic loading conditions and/or myocardial damage. These changes, including fibroblast activation, formation of myofibroblasts, inflammation and altered expression of

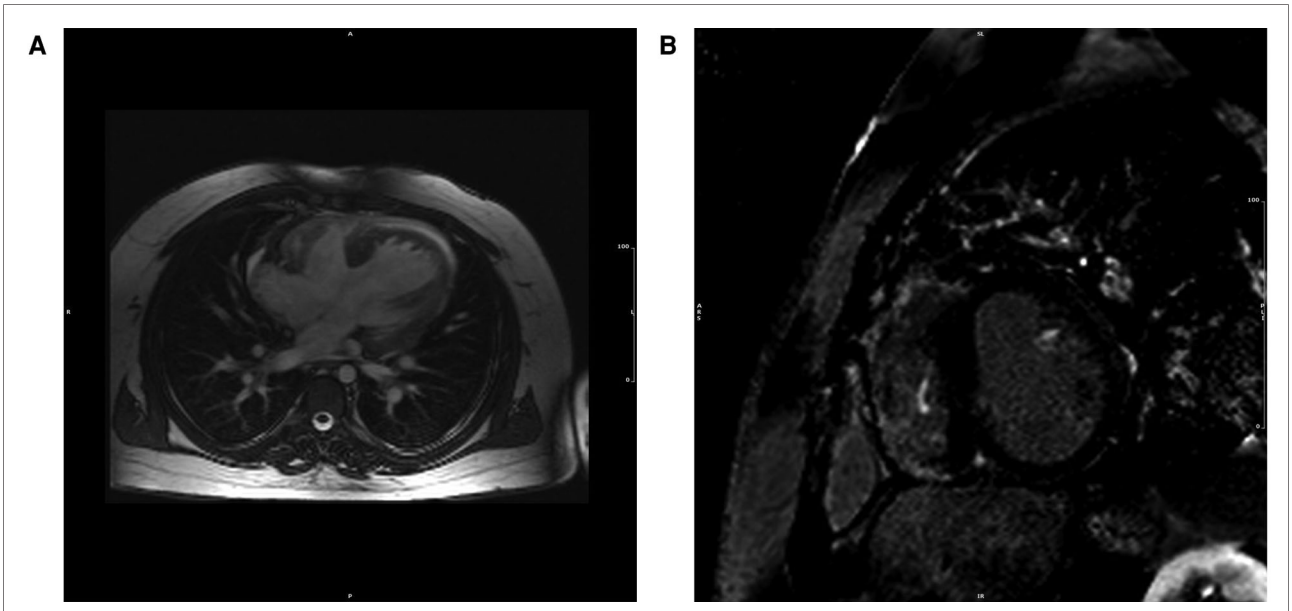

FIGURE 5
CMR cine (A) and LGE (B) image from 27-year-old patient Eisenmenger syndrome because of an untreated ventricular septal defect, showing extent in right ventricular free wall, as well as in the insertion points and in the left ventricle's papillary muscles. The patient developed ventricular arrhythmias in the follow-up and died suddenly at the age of 33.

TABLE 1 Most relevant studies characterizing myocardial interstitial fibrosis with cardiac magnetic resonance and collagen turnover biomarkers in patients with repaired tetralogy of Fallot.

	Reference	Year	Population	Characterization of fibrosis	Key clinical findings
CMR with LGE	Babu-Narayan, et al. (74)	2006	*N* = 92 32.2 ± 11 years	RV LGE was present in all patients at surgical sites, and common in the inferior RV insertion point (79%) and trabeculated myocardium (24%). LV LGE (53%) was located at site of the apical vent insertion (49%), in the inferior or lateral wall consistent with infarction (5%), or in other areas (8%)	Patients with supramedian RV LGE score were older and more symptomatic. A greater extent of RV LGE correlated with higher levels of BNP, exercise intolerance, RV dysfunction and clinical arrhythmia. Non–apical vent LV LGE also correlated with markers of adverse outcome.
CMR with ECV	Chen, et al. (73)	2016	*N* = 84 23.3 years (16.3–32.8)	LV ECV above the upper limit of normal was observed in 11 patients and for RV ECV in 9 patients	Greater RV ECV was associated with having volume overload as the predominant hemodynamic burden (in contraposition to pressure-overload or mixed lesions) Increased LV ECV was independently associated with arrhythmia,
	Broberg, et al. (75)	2016	*N* = 52 40 ± 14 years.	LV ECV was greater in TOF than in control subjects	LV ECV associated with adverse clinical markers and outcomes (arrhythmia, cardiovascular death)
	Hanneman, et al. (76)	2018	*N* = 44. 32.9 ± 13.6 years.	RV ECV was higher in patients compared with the controls.	RVECV correlated with adverse events (death, cardiac arrest, heart failure and ventricular tachycardia). LVECV was not associated with adverse events
	Cochet, et al. (77)	2019	*N* = 103. 28 ± 15 years	Higher T1 and ECV in both ventricles.	LV native T1 was independent correlate of ventricular arrhythmia Patients with a history of pulmonary valve replacement showed larger scars on RV out-flow tract but shorter LV and RV native T1.
Collagen turnover biomarkers	Lai, et al. (78)	2011	*N* = 39 17.7 ± 4.1 years	High PICP and PIIINP levels	PICP and PIIINP levels correlated with age, body mass index and parameters of RV and LV systolic function.
	Chen, et al. (79)	2013	*N* = 70	Higher PICP levels, PICP:CITP ratios and TIMP-1 concentrations	PICP levels correlated with higher RV LGE scores, lower VO2max and larger RV volumes.

TABLE 2 Most relevant studies characterizing myocardial interstitial fibrosis with cardiac magnetic resonance and collagen turnover biomarkers in patients with systemic right ventricle.

	Reference	Year	Population	Characterization of fibrosis	Key clinical findings.
CMR studies with LGE	Babu-Narayan et al. (94)	2005	36 d-TGA patients. 27 ± 7 years old.	61% of patients showed LGE in the sRV.	Patients with LGE were older, had increased RVESV, decreased SRV EF, increased QRS duration and increased QT dispersion. Arrhythmias were more prevalent in the LGE group.
	Giardini et al. (95)	2006	34 patients with sRV (23 d-TGA; 11 cc-TGA;) 25 ± 8 years old	41% of patients showed LGE in the sRV.	LGE was associated with older age, a lower sRV EF, higher RV wall stress, reduced peak oxygen uptake and history of arrhythmia
	Fratz et al. (96)	2006	27 sRV patients (18 atrial switch, 9 ccTGA) 23.4 ± 5.3 years old.	Only one subendocardial scar in a patient with cc-TGA.	
	Rydman et al. (97)	2015	55 patients 27 ± 7 years old.	RV LGE was present in 56% of patients..	Followed for a median 7.8 years; LGE was strongly associated with adverse clinical outcome, mainly atrial arrhythmia
	Babu-Narayan et al. (98)	2016	22 d-TGA patients 28 ± 8 years of age	LGE was found in 59% of the patients.	LGE was related to sRV dyssynchrony, reduced systolic function, lower exercise capacity, more severe tricuspid regurgitation and more previous arrhythmia
	Ladouceur et al. (99)	2018	48 patients with d-TGA. 32 ± 3 years old.	LGE was found in 35% of patients	Correlated with sRV wall stress
CMR studies with ECV	Plymen et al. (56)	2013	14 D-TGA patients. 33.7 + 6.5 years old.	Higher ECV at the mean septal level in comparison with healthy controls. This sRV population did not have areas of LGE and had normal EDV and systolic function.	ECV correlated with NT-proBNP levels
	Broberg et al. (100)	2018	53 subjects with sRV (43 d-TGA, 10 ccTGA). Age 34.6 ± 10.3 years,	28% had an elevated ECV for the sRV.	Those with an elevated ECV had higher BNP levels. After a median follow up of 4.2 ± 1.9 years those with elevated ECV presented more cardiovascular events (new arrhythmia, arrhythmia device, HF hospitalisation, listing for transplantation, mechanical support or cardiovascular death)
	Shehu et al. (101)	2018	10 d-TGA patients. 36.8 ± 5.3 years old	ECV of the inferior wall of the LV was significantly increased compared to the ECV of the sRV.	
Collagen turnover biomarkers	Dos et al. (102)	2013	26 patients with atrial switch, randomised to eplerenone or placebo. 26.4 ± 6.4 years old.	The whole cohort showed higher levels of CICP, ICTP than healthy controls. Galectin 3 and TIMP1 lower than controls.	In patients under eplerenone, a trend toward a reduction in CICP, NTproMMP1,TIMP1 and galectin 3 levels and a lower increase in ICTP
	Lipczynska et al. (103)	2017	56 patients with D-TGA 25.6 ± 4.8 years old.	Finding elevated levels of several biomarkers (TIMP1,PIIINP,CITP,PINP) when compared with healthy controls	PIIINP: good marker of sRV remodelling. MMP-9and TIMP-1 predicted adverse clinical outcomes.
	Ladouceur et al. (99)	2018	48 patients with D-TGA	Increased MMP1/TIMP1 ratio	MMP1/TIMP1 correlated with higher sRV wall stress and lower sRV EF

TABLE 3 Most relevant studies characterizing myocardial fibrosis in patients with arterial switch operation.

	Reference	Year	Population	Characterization of fibrosis	Key clinical findings
CMR with LGE	Shepard, et al. (115)	2016	220 patients (mean age of 15.4 years)	Myocardial scarring characterized by LGE was found in only 1.8% of patients.	LGE was not common even when 26% of patients had some degree of left ventricular dilatation and 21.5% of patients had some degree of left ventricular dysfunction.
CMR with ECV	Grotenhuis, et al. (116)	2019	30 patients (mean age 15.4 years)	No LGE was found. LV native T1 times were prolonged in ASO patients and correlated with the LV mass/volume ratio. No differences were found in ECV.	Neither ECV nor T1 times correlated with LV function.
	Suther, et al. (117)	2019	30 patients (mean age 11.7 years)	No LGE was found. Slight increase in ECV compared with healthy controls in all coronary territories	

TABLE 4 Most relevant studies characterizing myocardial fibrosis in patients with chronic cyanosis, Eisenmenger syndrome and Fontan circulation.

	Reference	Year	Population	Characterization of fibrosis	Key clinical findings
CMR with LGE	Rathod, et al. (121)	2010	$N = 90$ Fontan patients 23.1 ± 10.9 years	LGE was present in 28% of this population, the vast majority in the free wall of the predominant ventricle	LGE presence correlated with lower ejection fraction, increased ventricular volumes and mass. Patients showing LGE had more non-sustained ventricular tachycardia (36% vs. 11%; $p = 0.01$).
	Broberg, et al. (122)	2014	$N = 45$ Eisenmenger syndrome patients. Age: 43 ± 13 years	73% showed LGE in the right ventricular myocardium (70%) but also in the left ventricle (33%)	LGE could not be correlated with age, arrhythmia, oxygen saturation, haemoglobin levels, ventricular performance or exercise capacity.
CMR with ECV	Broberg, et al. (55)	2010	$N = 50$ CHD patients (10 cyanotic) Age: 37 ± 12 years	Among the entire cohort, ECV values were higher in patients with systemic RV and cyanotic patients	There was a strong correlation between ECV and systemic indexed EDV and EF. No correlation between the fibrosis index and resting oxygen saturation or age.
	Kato, et al. (123)	2017	$N = 21$ Fontan patients. Age: 9.7 ± 4.6 years	Higher ECV and prolonged native T1 times in patients with a morphologically right single ventricle compared to those with a morphologically left single ventricle.	Age at bidirectional cavopulmonary connection was correlated with T1
	Pisesky et al. (124).	2021	$N = 55$ Fontan patients Mean age: 14 years	Higher ECV and prolonged native T1.	Correlation between native T1 and the composite end point of cardiac readmission, cardiac reintervention, Fontan failure or any clinically significant arrhythmia

metalloproteinases, ultimately lead to myocardial fibrosis (MF) (4).

Altered hemodynamic conditions are a common feature of most CHDs, both before and after palliation or complete repair. Therefore, MF is expected to be one of the main maladaptative mechanisms behind the progressive deterioration of ventricular function in our patients and a potential therapeutic target.

This paper aims to summarize current knowledge about MF in terms of pathophysiology, diagnostic tools and potential treatments, focusing on the CHD population.

Histopathology, mechanisms and types of myocardial fibrosis

For a simplified description, the myocardium can be dichotomized into two components. The cellular component is mainly represented by cardiomyocytes, occupying 75% of the myocardium but only conforming one-third of the cell population. The rest is constituted of endothelial cells, vascular smooth muscle cells, fibroblasts, macrophages and mast cells.. The non-cellular component of the myocardium is also located in the interstitial space and mainly comprises fibrillar collagen (95% of the extracellular matrix) but has also other constituents: proteoglycans, glycosaminoglycans and different bioactive signaling molecules (2, 5).

Among the cellular constituents, fibroblasts are responsible for the synthesis and maintenance of cardiac connective tissue. Fibroblasts can migrate to areas of damaged myocardium (i.e., surgical injury or myocardial infarction) where they trans-differentiate into myofibroblasts, which are crucial cells for cardiac remodeling and fibrosis (6). A myriad of chemokines, cytokines and growth factors are secreted in the injured myocardium and stimulate the activation and differentiation of fibroblasts. These bioactive elements are produced in response to different stimuli, including mechanical stress (7). The healing process includes degradation of the damaged tissue and subsequent production, cross-linking and maturation of a new extracellular matrix (ECM). Although myofibroblasts are the major source of ECM, other cells, like monocytes, macrophages, cardiomyocytes and non-differentiated fibroblasts contribute to the process by secreting pro-fibrotic growth factors (8).

As for non-cellular components, fibrillar collagen is the cornerstone, with five isoforms in the myocardial interstitium: collagen type I, III, IV, V and VI. Type I collagen is the predominant, representing 80% of the total. It offers the greatest tensile strength (comparable to steel) and represents the major determinant of myocardial stiffness. Type III collagen has more elastic characteristics, representing 10% of collagens, and the other types(IV, V and VI) constitute the remaining 10% (9, 10).

From a histopathological point of view, two types of MF should be distinguished. The *reparative*, replacement or focal myocardial fibrosis (FMF) develops as a healing mechanism at the site of a previous myocardial injury (infarction or surgical scar). The necrotic tissue is replaced by collagen fibrils that are cross-linked to provide mechanical stability in response to cardiomyocyte loss. On the other hand, *reactive* diffuse myocardial fibrosis (DMF) is characterized by a diffuse deposition of excess fibrous tissue relative to the mass of cardiomyocytes. In this case, MF appears as an accumulation of collagen fibers between individual cardiomyocytes and cardiomyocyte fascicles and around the intramyocardial vessels. As a result, the highly organized architecture of the myocardial interstitium is replaced with a thickened, poorly organized structure (11, 12) that alters the mechanical

properties of the myocardium, thus impairing cardiac function and electrical activity, and contributing to the development of HF and the poor outcomes that characterize this condition.

Both types of MF can concur in the same individual, as seen in patients with ischemic cardiomyopathy that exhibit FMF at the necrotic site and DMF in the distant myocardium of both ventricles (13). Indeed, DMF can be facilitated by systemic factors activated secondarily to the loss of cardiac function (such as neurohormonal activation) (14) or related to extracardiac comorbidities (such as inflammation associated with metabolic syndrome or chronic kidney disease (15).

Beyond the quantity of fibrous tissue, the composition and physicochemical properties of the fibers are important in DMF. As previously mentioned, type I collagen fibers exhibit the highest stiffness, therefore, the ratio between type I and type III collagen will have an impact on overall myocardial stiffness. On the other hand, the type of intermolecular covalent bonding among collagen fibrils mediated by enzymes such as lysyl oxidases (LOXs), the so-called collagen cross-linking, will influence the resistance to degradation by matrix metalloproteinases (MMPs) and will also have an impact on myocardial stiffness.

Finally, it is well known that, coming from different embryonic origins, the left ventricle (LV) and the right ventricle (RV) respond distinctly to normal and abnormal loading conditions (16). Therefore, differences in the pattern and type of MF developed by both ventricles are also expected. The collagen content of a healthy RV is higher than that of the LV (17) and the RV and LV have different matrix metalloproteinase and ECM protein-expression patterns (18). Under the same overloading conditions, the RV exhibits less ability to develop adaptative remodeling (19, 20) leading to dilatation and dysfunction. This is particularly relevant in CHD, where morphologically RVs are exposed to extreme overloading conditions such as sustaining the systemic circulation, sometimes as a single ventricle, severe pulmonary hypertension or chronic pulmonary regurgitation as in repaired tetralogy of Fallot.

Role of myocardial fibrosis in the development of heart failure and arrhythmia

Diastolic dysfunction

Interstitial MF has classically been related to the development of diastolic impairment since an excessive accumulation of insoluble collagen in the ECM leads to an abnormally stiff myocardium (see **Figure 1**).

In a physiological state, collagen fibers form a deformable elastic structure that stores energy when deformed from its neutral position during systolic contraction. Lengthening of the myocardium during diastole is then facilitated by the release of potential energy stored during systolic compression of these fibers, generating a suction effect that allows early diastolic filling (21).

When extracellular viscoelastic properties are impaired this suction effect is compromised. This leads to a higher dependence on atrial contraction and elevated filling pressures to maintain the stroke volume, which can also cause venous congestion and ultimately result in congestive heart failure.

Aside from the absolute amount of collagen, myocardial stiffness also depends on the characteristics of the fibers in the extracellular matrix. Thus, a higher fiber linkage and a higher proportion of type I collagen have also been correlated with impaired diastolic parameters in echocardiography, elevated peptides or elevated filling pressures in right heart catheterization (22–27).

Systolic dysfunction

In this setting, MF might just be part of the reparative response to the loss of contractile mass, becoming a marker of more advanced cardiomyopathy (28). However, the architecture of myocardial fibrillar collagen is also important in systolic performance, as it facilitates transduction of cardiomyocyte contraction (29, 30). Furthermore, the reduced stretching of the fibers in diastole can also compromise systolic function by altering the length-dependent cardiac muscle fiber shortening related to the Frank-Starling law.

Arrhythmias

Both FMF and DMF impair myocardial electrophysiology *via* several mechanisms, constituting an important arrhythmic substrate. Beyond re-entry tachycardias around macroscopic scars (e.g., surgical incisions), DMF interferes with myocardial electrophysiology by slowing down action potential propagation, initiating re-entry, promoting after-depolarizations, and increasing ectopic automaticity (31, 32).

Interestingly, some studies have shown that tachyarrhythmias can initiate or exacerbate MF by activation of profibrotic and proinflammatory signaling. This mechanism would perpetuate electric disturbances while contributing to the impairment of ventricular function (33–35).

Diagnosing myocardial fibrosis

Endomyocardial biopsy with histopathological analysis is the gold standard for MF diagnosis, but it presents several limitations as it is an invasive procedure and a difficult option in clinical practice (7, 36). Fortunately, currently available

circulating and imaging biomarkers provide indirect MF diagnosis.

Imaging tests

Cardiac magnetic resonance (CMR) methodologies for the detection of MF are based on the concept that fibrosis increases the extracellular space (37). As previously mentioned, MF can be divided into FMF, with dense macroscopic "replacement" fibrosis (scar) located to a specific, definable area; and DMF, which is more microscopic and uniform, with a global distribution and typically in response to chronic abnormal loading conditions (38–40).

There are two major CMR techniques used for MF assessment: late gadolinium enhancement (LGE) imaging and T1 mapping/extracellular volume (ECV) fraction calculation.

Late gadolinium enhancement

LGE is a CMR technique that identifies areas of discrete replacement fibrosis. Image acquisition is typically performed 10–20 min after administration of a gadolinium-based contrast agent. In damaged myocardial tissue, where there has been a significant localized expansion of the extracellular matrix, the distribution volume of the contrast agent is increased and the wash-out delayed (41).

LGE requires spatial heterogeneity to detect focal fibrosis, being a dichotomous method. It has the advantage that it analyzes the entire cardiac image, without focusing on a specific area, so it could be more sensitive for overall fibrosis burden, even though it requires a greater amount of fibrosis to be detectable visually (37).

Extracellular volume and T1 mapping

ECV mapping quantifies MF by measuring the extracellular compartment depicted by the myocardial uptake of contrast relative to plasma (42). ECV represents the ratio of the interstitium relative to the total myocardial mass.

ECV has advantages over LGE, being intrinsically quantitative and able to assess both focal and diffuse fibrosis. However, although fibrosis is certainly a cause of increased ECV, it is not the only one, as extracellular space expansion may be due to other causes (myocardial vasculature, nonfibrillar proteins, edema, amyloidosis, etc.,) (7, 42, 43).

Even so, ECV is the most widely used imaging biomarker for interstitial fibrosis (41) as it has been extensively validated against the collagen volume fraction (44, 45), it is highly reproducible across different CMR scans (46), it can predict outcomes (47, 48) and histologic validation data show overall the best agreement with ECV compared with other T1 based metrics (46, 49). While native (precontrast) T1 increases and postcontrast T1 decreases with MF, they are inferior MF measures compared with ECV (42, 50). Native T1 reflects changes involving the whole myocardium (intracellular and extracellular compartments) and several confounders affect postcontrast T1 (clearance, body weight, anemia …). Despite this, some studies found a good correlation between native and post-contrast T1 and myocardial fibrosis (51, 52).

Both ECV and T1 are quantitative measures that can allow us to grade disease activity, monitor progress and guide treatment (53). However, the measurements are sensitive to many scanner parameters, with no consensus regarding a vendor-neutral standard approach to image acquisition and postprocessing, so standardization against healthy volunteers is recommended for each CMR scanner and each specific protocol (51, 54). The wide variety of technical and methodological bias-causing confounders makes it difficult to both directly compare native T1 and ECV values between studies.

Characterization of fibrosis with CMR in CHD

MF is the final common pathway of a variety of congenital lesions. It is found in both the right and left ventricles and is not limited to areas of surgical scarring or within a coronary distribution (38) (FMF), but it also occurs more diffusely (DMF) in the setting of volume and/or pressure overload (49).

Several studies have characterized MF by CMR in CHD (39, 55); however, there are several limitations. RV disease is hard to assess due to the small thickness of the RV wall, approaching the T1 mapping spatial resolution limit (49). Even in patients with RVs that support systemic circulation, the RV free wall has been deemed difficult to measure by T1 mapping (56) (see **Figure 2**). Some studies focus on a single mid-ventricular plane, which may not be representative of the entire ventricle, and many CHD patients have limitations for CMR scanning (device electrodes and young age or syndromic problems (38, 57).

CHD patients present certain peculiarities and common challenges to CMR when studying MF, such as wide and abnormally shaped QRS complexes, breath-holding difficulties, metallic artifacts from sternal wires and transcatheter devices, as well as pathology focused on the thin-walled RV (39).

Circulating biomarkers

Multiple circulating biomarkers of collagen metabolism have been described, but only a few molecules have demonstrated an association between the biomarker levels and histologically assessed myocardial collagen deposition or collagen cross-linking (58–61) (see **Figure 3**). A positive gradient has been found from the concentration of some of these biomarkers in coronary sinus blood toward the concentration in peripheral vein blood in patients with different types of cardiac disease (58); however, none were cardiac-specific (7).

The biomarkers that have shown more consistent results and a higher pathological correlation with MF upon biopsy are the carboxy-terminal propeptide of type I procollagen (PICP), the amino-terminal propeptide of type III procollagen (PIIINP) and the ratio of serum carboxy-terminal telopeptide of type I collagen to serum matrix metalloproteinase-1 (CITP: MMP-1ratio) (7, 40). The first two are biomarkers of collagen synthesis that directly correlate with the deposition of collagen fibers in the myocardium in different heart diseases. The CITP:MMP-1 ratio inversely correlates with myocardial collagen cross-linking (59, 62). Therefore, low levels of the CITP:MMP-1 ratio and high levels of PICP and PIIINP would indicate DMF.

Carboxy-terminal propeptide of type I procollagen

PICP is generated during the extracellular maturation of the collagen molecule by conversion of procollagen type I into collagen type I by the enzyme bone morphogenetic protein-1 or procollagen carboxy-terminal proteinase (63).

Serum levels of PICP have been associated with various findings: myocardial deposition of collagen type I fibers in HF patients (23); correlation with severity of HFrEF; with mortality in HFpEF and HFrEF (64, 65) and changes after treatment with torasemide and spironolactone in heart failure (66, 67).

Amino-terminal propeptide of procollagen type III

Most serum PIIINP is generated during the extracellular conversion of procollagen type III to collagen type III by the enzyme procollagen amino-terminal proteinase (63). An association has been found between serum PIIINP and myocardial deposition of collagen type III fibers in HF patients and with severity and outcomes in HF of different causes, regardless of the ejection fraction (64, 68).

Carboxy-terminal telopeptide of type I collagen to matrix metalloproteinase-1 ratio

Once the collagen molecule is mature, the spontaneous self-assembling of molecules results in the formation of collagen fibrils. In a second step, the formation of intra- and intermolecular covalent bonds, cross-links, between lysine residues ensues.

Collagen cross-linking determines the resistance of collagen fibers to MMP degradation; therefore, the highly cross-linked type I collagen fibers have increased resistance to degradation by MMP1, producing a reduction in collagen type I telopeptide (CITP) levels and, thereby, a decreased CITP: MMP1 ratio. Thus, the serum CITP:MMP-1 ratio inversely correlates with myocardial collagen cross-linking (59).

A low CITP:MMP-1 ratio has been associated with a higher risk of hospitalization for HF and cardiovascular mortality in hypertensive patients (59, 69). It also identifies HFpEF patients resistant to the beneficial effects of spironolactone (70).

Relevance of myocardial fibrosis in congenital heart disease

Myocardial fibrosis is the final common pathway of a variety of CHDs due to the multiple procedures and situations of volume and pressure overload to which these hearts are subjected throughout their lives. The current evidence regarding myocardial fibrosis in specific congenital heart conditions will be reviewed in this chapter, focusing on the most common congenital cardiac disorders.

Tetralogy of Fallot

There is histological evidence of increased interstitial collagen deposition in patients with tetralogy of Fallot (TOF). Existing data suggest that chronic exposure to cyanosis and pressure overload play a role in the development of MF before repair (71). Unloading the RV with a complete repair seems to have a beneficial effect; necropsy studies show a greater extent of MF in unrepaired than repaired TOF (72). However, even after reparative surgery, MF seems to progress in both ventricles and is associated with worse outcomes (72, 73), probably due to residual overloading conditions, usually severe pulmonary regurgitation (see **Figure 4**).

In 2006, Babu-Narayan et al. (74), published the first study to detect FMF in repaired TOF using LGE. FMF was not only found in areas with patch repair but also distant areas of the RV and even the LV. The extent of LGE was related to age, functional class, neurohormonal activation, ventricular dysfunction and clinical events, including exercise intolerance and clinical arrhythmias. Several studies have since followed, collectively confirming that a greater degree of fibrosis is associated with adverse clinical outcomes (80–82). Additional studies have shown that the presence of fibrosis is not limited to the RV but is also seen in the LV (37), with a positive correlation between LV and RV ECV values, thus indicating various coupling mechanisms and an adverse ventricular-ventricular interaction at the tissue level (73, 75).

RV LGE has been related to RV diastolic dysfunction (83) and fragmentation of the QRS complex, a marker of ventricular arrhythmias in this patient population (84). In a recent study (85), the extent of RV LGE and presence of LV LGE were included in a score that integrated multiple, appropriately weighted, risk factors and which identified the subgroup of patients at the highest annual risk of death.

DMF has also been studied in patients with TOF. Chen and colleagues (73) found a correlation between RV and LV ECVs and an association between predominant volume overloading

hemodynamic burden and RV ECV, in contrast with previous evidence supporting pressure overload as the main driver of MF. Since ECV represents the ratio of interstitium relative to total myocardial mass, the authors attributed this finding to a potential myocyte loss as a maladaptative mechanism of cellular remodeling in repaired TOF patients with chronic pulmonary regurgitation. Subsequent studies have also found prolonged RV native T1 times in repaired TOF with volume overload, both in pediatric (86) and adult cohorts (77), which would indicate the presence of DMF. Interestingly, a shorter native T1 was observed in patients with pulmonary valve replacement. This finding, together with histological evidence that patients with repaired TOF and residual pulmonary regurgitation, but reasonably preserved RV volumes and function, show no significant differences in collagen content and LOX activity when compared to healthy controls (87) suggests that DMF might be reversible and even have an oscillating behaviour according to the adaptative capacity of the myocardium to successive overloading conditions.

Elevated RV and LV ECVs have been associated with older age, age at TOF repair, neurohormonal activation, longer QRS duration, shorter six-minute walk distance, larger left atrial volume and adverse outcomes, including death, congestive heart failure and arrhythmias (73, 75, 76).

There are some studies with negative results. Using native T1 mapping, Yigit et al. (88), found focal fibrosis at the RV insertion points and the LV walls in a population of 35 patients with repaired TOF. However, it was not possible to detect RV outflow tract fibrosis with this technique, possibly due to the aforementioned technical limitations of the RV (88).

As for circulating biomarkers, patients with repaired TOF exhibit a pattern of excessive collagen synthesis and dysregulated degradation, with elevated circulating PICP and PIIINP levels and PICP:CITP ratio, a positive correlation between collagen synthesis biomarkers (PICP and PIIINP) and RV end-diastolic volumes (EDV) and a negative correlation with RV systolic function (78, 79).

Systemic right ventricle

Atrial switch operation in patients with D-transposition leaves the RV as the systemic pump (89, 90), as it happens naturally in patients born with congenitally corrected transposition of the great arteries (ccTGA) In both situations, a progressive systemic right ventricle (sRV) dilatation and dysfunction are the norm, leading to reduced exercise capacity, HF and arrhythmia (91–93) (see **table 2**).

The first cross-sectional studies characterizing sRV fibrosis *via* MRI (94–96, 98, 99) showed that the presence of late gadolinium enhancement is common in sRV, ranging from 5% to 60% of patients, probably reflecting methodological differences and heterogenic cohorts. These studies correlated the presence and extent of LGE with functional parameters such as higher sRV end-systolic volume index and lower sRV ejection fraction (EF). Furthermore, the patients more commonly presenting LGE had a prior history of arrhythmia and a lower exercise capacity.

Subsequently, the presence of LGE was validated as a prognostic marker in longitudinal studies. LGE was found to be a good predictor of new onset arrhythmia and heart failure in this population (97).

Lipczynska and colleagues (103) proved that collagen turnover biomarkers were also valuable as prognostic markers in patients with sRV. PIIINP was postulated as a good marker of sRV remodeling, as it correlated with higher sRV mass, higher sRV EDV and worse global longitudinal strain. Furthermore, MMP-9 and tissue inhibitor of metalloproteinase 1(TIMP-1) predicted adverse clinical outcomes in this cohort.

Different mechanisms are postulated to explain late sRV failure and the presence of scarring, which are probably multifactorial. Preoperative hypoxemia and deficient myocardial protection in older cohorts may play a role since more extensive fibrosis has been found in older patients and patients with a late repair (94, 95, 98, 99). A deficient coronary supply for a thickened sRV may be another explanation. Ladouceur and co-workers (99) found that sRV fibrosis was related to increased RV wall stress. Initially, the increased pressure overload for a morphological RV in the systemic position would be compensated by an adaptive hypertrophy to preserve RV function and normalize RV wall stress. However, with time, sRV maladaptation would lead to excessive hypertrophy, which would present demand-supply mismatch ischemia, resulting in the presence of patchy fibrosis and ultimately sRV systolic and diastolic dysfunction. Some studies correlated LGE with QRS duration and QT dispersion (94, 95) and, in the study by Babu-Narayan and colleagues, LGE correlated with echocardiographic parameters of electromechanical delay and dyssynchrony (98), this being another possible mechanism for the deterioration of myocardial function and arrhythmia development.

Recently, CMR studies with T1 mapping techniques for DMF characterization yielded interesting results. Plymen and colleagues (56) found a higher ECV at the mean septal level in a small cohort of 14 patients with sRV in comparison with healthy controls. Interestingly enough, this sRV population did not have areas of LGE and had normal EDV and systolic function (mean RVEDV 79 ml/m^2 and mean sRV EF 59%). This could imply that DMF is present in the early stages of the disease and even in the absence of macroscopic scars.

Broberg and co-workers (100) studied 53 subjects with sRV (43 D-TGA, 10 ccTGA);of these, 28% had an elevated ECV value based on gender-specific cut-offs for the systemic LV of healthy controls. No differences were found in sRV volume or EF, but patients with elevated ECV had higher levels of serum

brain natriuretic peptide (BNP) and presented more cardiovascular events (new arrhythmia, arrhythmia device, HF hospitalization, listing for transplantation, mechanical support or cardiovascular death)after a median follow up of 4.2 ± 1.9 years. Events in those with elevated ECV tended to occur early and be more related to HF, whereas events in the normal ECV group occurred later and were more often atrial arrhythmias.

More intriguing results focusing on the subpulmonic LV were published recently (101, 104). As in previous studies, a greater native T1 and ECV were found in the sRV, but the authors also found elevated ECV in the subpulmonic LV compared with healthy controls. Moreover, a greater segment and average ECV from the LV was found than in the sRV. The cause of these findings remains poorly understood, although there are several theories, including chronic volume unloading of the eccentrically compressed left ventricle, prevalent postcapillary pulmonary hypertension or ventricular-ventricular interaction at the extracellular matrix level. It also remains unclear whether fibrosis in the subpulmonic LV may play a role in prognosis, but it warrants further research as adverse remodeling with an overt increase in systolic and diastolic volumes of the subpulmonic LV is associated with a worse clinical outcome (105, 106).

Arterial switch operation

The arterial switch operation (ASO) is the current procedure of choice for patients born with D-TGA. In this population, the systemic LV is usually believed to be normal (107–110). However, several factors might impair its myocardial function in the long-term, such as neonatal cyanosis, neonatal cardiopulmonary bypass, impaired coronary perfusion, myocardial denervation, aortic regurgitation or increased aortic stiffness (111) (see **Table 3**).

Indeed, in the last few years, data with speckle tracking echocardiography have emerged suggesting that a mild impairment of LV function may be more common than previously thought (112–114).

A single-center CMR cohort study (115) in 220 patients (mean age of 15.4 years) found that 26% of patients had some degree of left ventricular dilatation, while 20% had right ventricular dilatation. Left ventricular dysfunction was present in 21.5% of patients (mild in most cases), and only 5.1% of patients had mild right ventricular dysfunction; however, myocardial scarring characterized by LGE was found in only 1.8% of patients.

Diastolic function may also be impaired. Some studies found slight differences in terms of ventricular stiffness and diastolic parameters when compared with healthy controls, but still within the normal range, and in the absence of an established LV hypertrophy (118). This could be explained by an intrinsic stiff myocardium with some degree of fibrotic remodeling, suggested by increased fibrosis markers in CMR studies. Grotenhuis and colleagues (116) studied a cohort of patients without myocardial scarring or perfusion defects and with a normal LV ejection fraction. However, compared with healthy controls, end-diastolic and end-systolic volumes were increased and an altered contraction pattern was observed, the longitudinal strain being lower while the circumferential strain was higher at all short-axis levels, maybe reflecting subclinical compensated systolic dysfunction. LV native T1 times were prolonged in ASO patients and correlated with the LV mass/volume ratio, suggesting the presence of a certain degree of myocardial fibrosis. However, no differences were found in ECV, and neither ECV nor T1 times correlated with LV function. On the other hand, Suther and co-workers detected a slight increase in ECV in a small cohort of adolescents with ASO and normal coronary arteries compared with healthy controls (117). Whether these findings precede the development of overt LV dysfunction over time remains speculative and multicentric longitudinal studies will be required to clarify their prevalence and their prognostic significance.

Chronic cyanosis

The assumption that cyanosis causes diffuse intramyocardial fibrosis has been accepted for decades, justified by the findings of fibrosis in specimens from autopsies of patients with unrepaired cyanotic heart disease (see **Figure 5** and **Table 1**). Nevertheless, it remains unclear whether these findings could be related to the presence of adverse hemodynamic loading conditions, the cyanotic condition itself *via* activation of hypoxia-inducible factors (119, 120) or both.

In the last few years, this hypothesis has been challenged by some MRI studies mainly focused on patients with Eisenmenger syndrome. However, data are scarce and there are some discrepant results (see **Table 4**).

Broberg and collaborators (55, 122) quantified ECV in a cohort of 50 CHD patients, 10 of which were cyanotic. Among the entire CHD cohort, cyanotic patients was the group with the second highest ECV, after patients with systemic right ventricle. There was a strong correlation between ECV and systemic indexed EDV and EF. In a larger study from the same group (122) in 45 subjects with Eisenmenger syndrome, LGE was present in 22/30 (73%) patients, specially in the right but also in the left ventricular myocardium. In none of those works fibrosis could be correlated with age, history of arrhythmia, oxygen saturation, hemoglobin levels, exercise capacity or mortality.

On the other hand, Kharabish et al. (125), performed contrast CMR in a very small cohort of patients with repaired and unrepaired cyanotic heart disease. Surprisingly, untreated patients had a significantly lower left ventricular ECV percentage than the repaired patients, and no significant

differences were found between cyanotic patients and normal controls.

Both studies were limited by the small cohort size and the heterogeneity of the underlying anatomy, age and physiological state of the patients. Larger multicenter studies are required to unravel the relevance of MF in the pathophysiology of chronic cyanosis and its role in sudden cardiac death and HF, the two leading causes of mortality in this patient population (126).

Fontan circulation

Myocardial fibrosis has been less studied in this patient population but new techniques for detecting diffuse fibrosis have increased the interest in univentricular patients.

Rathod and colleagues (121) detected FMF in 28% of a population of 90 patients with Fontan circulation. As expected, FMF was found at the surgical sites but the vast majority of LGE distribution was found in the free wall of the predominant ventricle. LGE presence correlated with adverse ventricular mechanics and was associated with non-sustained ventricular tachycardia. Likewise, LGE has been associated with time to death or transplant in this patient population (127).

DMF has also been evaluated in Fontan patients; compared with healthy controls, they presented higher ECV and native T1. Additionally, there was a correlation between native T1 and aortopulmonary collateral flow and an association with the composite end point of cardiac readmission, cardiac reintervention, Fontan failure or any clinically significant arrhythmia (124). However, Kato and colleagues could only find higher ECV in Fontan patients with morphologically right single ventricles. In these cohort, no difference was found regarding T1 or ECV between healthy controls and Fontan patients with morphologically left single ventricles (123).

A recent study using circulating biomarkers in 25 Fontan patients observed a significant correlation between ECV and systemic ventricular end-diastolic pressure and between ECV and liver stiffness. Furthermore, patients with elevated ECV had elevated MMPs and TIMPs, and these patients presented greater liver stiffness (128).

Whether all these findings are related to the intrinsic peculiarities of Fontan circulation, the previous cyanotic phase or both remains to be determined.

Therapeutic options and future directions

As previously mentioned, fibrosis is a highly dynamic process that typically involves the recruitment of fibroblasts and their conversion into myofibroblasts, excessive ECM synthesis and secretion, ECM protein cross-linking, dysregulation of ECM production and breakdown by MMPs and their endogenous inhibitors. Therefore, multiple targets or therapeutic opportunities may exist. In addition, different types of fibrosis (FMF vs. DMF) and different stages of the fibrotic process (more static vs. more dynamic) may coexist in the same individual and identification of the specific or dominant type of fibrosis would be important for the selection of the anti-fibrotic approach. Timely detection of fibrosis and determination of its state could potentially help diagnose and halt HF progression.

Targeting the fibrotic process

There are several potential novel therapeutic strategies for MF coming from the idiopathic pulmonary fibrosis armamentarium (Transforming growth factor beta inhibitor pirfenidone; tyrosine kinase inhibitor nintedanib; pamrevlumab, a human monoclonal antibody that inhibits connective tissue growth factoractivity; simtuzumab, a humanized monoclonal antibody to block lysyl oxidase like 2), some of them showing promising results in preliminary studies (7). However, we still have limited knowledge of the diverse and heterogeneous mechanisms involved in the pathophysiology of the complex process of fibrosis and the different factors (setting, timing or etiology) that might jeopardize the final effectiveness of a given treatment. Also, the therapeutical target should be the excessive fibrous tissue without affecting the physiological collagen scaffold (12); the complexity of this is illustrated by a murine model of myocardial infarction developed by Clarke and colleagues (129). In this experimental model, MMP inhibition proved to be less effective than initially presumed. The authors postulated that early during the remodeling phase, MMP inhibition might be less effective because, although MMP levels are at their highest, there is scant collagen to degrade, while at later fibrotic phases it is less effective because, although collagen concentrations are high, MMP levels have fallen to low levels. On the other hand, MMPs have a full range of functions and myriad targets. All these factors may convey unpredictable and counterintuitive results when targeting the fibrotic process once it has been initiated.

Targeting the triggers

While current experimental studies and even clinical trials [pirfenidone is currently being tested in the PIROUETTE (130) phase II trial] are underway to unravel these riddles, targeting the stimulus that triggered the maladaptative fibrotic process seems to be effective. There is evidence that some HF therapies (targeting neurohormonal activation) have antifibrotic effects (26, 67, 131, 132). However, in CHD, where clinical trials for

HF therapy are extremely scarce, those focusing on MF as an endpoint are anecdotal. Our group developed a clinical trial evaluating the effect of the mineralocorticoid-receptor antagonist eplerenone on MF in patients with systemic RV (transposition of the great arteries repaired with the atrial switch procedure) (102). The study found an increased collagen turnover in this patient population compared with age- and gender-matched controls but was underpowered to show a reduction in ventricular mass after one year of treatment. The interpretation of the trend toward a reduction in CICP, MMP1, TIMP1 and galectin 3 levels observed in patients under eplerenone remains elusive as no T1 mapping was available at the time of the study to assess changes in DMF.

While the prognostic role of preoperative myocardial fibrosis in patient outcomes after valvular replacement has been extensively studied (133, 134), there is little information regarding MF reversibility after valvular replacement. However, recent data support the hypothesis DMF may reverse after unloading the ventricles both under volume and pressure overloading conditions (135, 136). The limited data on this topic focuses mainly on mitral and aortic valvular disease with no information, to the best of our knowledge, on right-sided valves. However, experimental studies (artery banding mouse models) suggest that reversibility of RV fibrosis after cessation of the overloading stimulus can also be achieved (137). On the other hand, preliminary and indirect data suggest that DMF in TOF might be reversible and even have an oscillating behavior according to the adaptative capacity of the myocardium to successive overloading conditions (77, 87).

Differences between right and left ventricles

The RV and LV have distinct fibrotic responses and, therefore, may require different therapeutical approaches (138). Pirfenidone does not reverse RV fibrosis or enhance RV function in pulmonary artery-banded rats (139), but it does reduce RV fibrosis and remodeling in a murine model of non-severe pulmonary arterial hypertension (PAH) (140). In turn, eplerenone does not reverse RV fibrosis in Sugen-hypoxia and pulmonary artery-banded mice after PAH was established (141). On the other hand, whereas the microRNA miR-21, a known profibrotic agent currently studied as a target for the treatment of Alport Syndrome, seems to be crucially involved in the fibrotic response to mechanical and hormonal stimuli in isolated RV fibroblasts from dogs, this is not the case for dog LV fibroblasts (19). Whether these discrepant findings are related to the intrinsic different responses of both ventricles to overloading conditions or other determinants of the fibrotic process, such as timing or etiology, remain to be determined.

Additional diagnostic methods

Wider availability of diagnostic methods to evaluate MF is needed. In recent years, cardiac computed tomography angiography (CTA) has yielded good results for MF assessment. An excellent correlation between ECV evaluated by CTA and by CMR has been shown in animal models, healthy volunteers and HF patients (142, 143). CTA-based quantification of ECV has also been validated against a histological assessment of myocardial fibrosis (142) and presented an association with adverse clinical outcomes after percutaneous aortic valve implant (144, 145). This technique may be of particular interest in patients with CHD since it overcomes some important caveats of CMR in this population: the shorter acquisition times make it easier for patients with cognitive impairment and patients with claustrophobia and it can be used in patients with paramagnetic metal implants.

On the other hand, new targeted approaches that have shown promising results for collagen detection in other organs, such as the novel molecular magnetic resonance contrast agents utilized in liver studies, might be applicable in heart diseases (146).

In summary, understanding HF pathophysiology lies beyond the mere assessment of cardiac function. In-depth consideration of myocardial structure and function at the tissue level, particularly of the myocardial interstitium, provides additional and crucial insight and may drive the development of new therapies. MF, particularly diffuse interstitial fibrosis, constitutes an emerging and promising therapeutic target in HF secondary to acquired heart conditions. Due to intrinsic particularities (preeminent involvement of overloaded morphologically RV, chronic cyanosis, etc.,), MF seems to play a determinant role in the development of HF and arrhythmias in CHD. Further studies in the field are needed to shed light on this exciting and promising area of research in CHD.

Author contributions

All the authors contributed equally to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Pulmonary artery debanding in the cath lab: Lessons learned!

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Background: Although primary definitive repair of congenital heart disease has become the preferred management approach, pulmonary artery banding (PAB) remains a valuable palliative procedure used to restrict pulmonary blood flow in certain conditions. However, when the band is to be removed, another surgical intervention is usually required.

Methods: To describe percutaneous removal of pulmonary artery band, the medical records of patients who underwent this procedure were reviewed.

Results: Between 2000 and 2020, 143 patients underwent PAB. Of these, we attempted balloon debanding of the pulmonary artery in four patients. At the time of the procedure, the average age of patients was 36 ± 6.24 months, and their average weight was 12.37 kg. Band removal *via* catheter was successful in three cases and was associated with an adequate reduction in pressure gradient across the pulmonary artery band site (average of 71.67 ± 12.58 to 23.67 ± 2.89 mm Hg). None of the patients experienced complications during or after the procedure. Follow-up data after discharge (3–10 years) provides reassuring and satisfactory results.

Conclusion: Based on our findings, we suggest that percutaneous removal of the pulmonary artery band might be a safe and effective alternative to surgical debanding. However, studies with a larger sample are required for further clinical implementation of the technique.

KEYWORDS

congenital heart disease—cardiac, pulmonary artery banding, pulmonary artery debanding, balloon debanding, interventional cardiac catheterization (ICC)

1 Introduction

The use of pulmonary artery banding (PAB) in the management of congenital heart disease (CHD) dates to the 1950s. The first PAB surgery was performed in 1952 on a 5 months old infant with a large ventricular septal defect (VSD) (1). The goal of banding was to limit excessive blood flow to the lungs in young infants. This would delay the corrective surgery until a desirable age or weight is achieved. Since its introduction, the use of PAB has allowed a significant increase in the survival rate of several congenital heart lesions that are associated with neonatal heart failure such as tricuspid atresia (2, 3). Although the use of PAB has been widely replaced by primary surgical repair of the cardiac anomaly, PAB continues to be a valuable technique employed in managing both simple and complex CHDs. It offers palliative treatment for children with left to right shunts and excessive pulmonary blood flow (4). Similarly, in complex CHD requiring a staged-approach, PAB serves as a bridge for definitive correction (4).

Indeed, around 2% of congenital heart lesions still require banding of the pulmonary artery (5). The advancement in prenatal detection techniques and management strategies of neonates admitted to the neonatal intensive care units have allowed an increased number of neonates with CHD requiring early surgical intervention. Ultimately, PAB has been increasingly useful in early management of such critically ill neonates (5, 6).

Nevertheless, the mortality and morbidity associated with this procedure, although improved over the years, remain significant (7). Besides, a noteworthy concern in PAB is that it becomes restrictive and limiting pulmonary blood flow as the patient grows and eventually requires dilation or complete removal (8). This usually entails another surgical intervention and cardiopulmonary bypass to remove or adjust the band, which carries a risk of mortality and morbidity.

To avoid surgical re-intervention, several research groups discussed the possibility of catheter-based band removal or dilation. Early studies were performed *in vitro* and on animal models and have yielded promising results. However, they were limited by the technical difficulties (9, 10). Clinical efforts to replace surgical debanding with balloon-based technique started as early as 1990. Nevertheless, the need for advanced equipment and materials has thwarted the implementation of this technique. As medicine advanced, with significant advancements in techniques and medical resources, some studies reported successful cases of catheter-based PA band removal or dilation (11–15).

To explore the significance of percutaneous pulmonary artery band removal, this article aims to describe and assess this technique along with its short- and long-term outcomes. It was performed at the Children's Heart Center (CHC) at the American University of Beirut Medical Center (AUBMC), one of the leading tertiary referral centers in Lebanon and the Middle East.

2 Materials and methods

After securing Institutional Review Board (IRB) approval, we conducted a retrospective review of the medical records of patients who underwent PAB for various congenital heart conditions in the last 20 years at our institution. We explored those who had subsequent percutaneous removal of the band. The medical records of these patients including the pre- and post-procedure echocardiography reports, progress notes, surgical report, post-procedure notes, discharge summary, and catheterization reports were reviewed.

2.1 Procedures

2.1.1 Banding technique

The banding procedure, as described in **Figure 1**, may be performed through thoracotomy (anterior, lateral), or through a partial or full sternotomy. Any patent ductus arteriosus is ligated. The pulmonary artery is encircled with a 3 mm band, taking care to position it a few mm proximal to the right pulmonary artery, and distal the pulmonary valve. The band is tightened progressively with 1 or more sutures, and/or with metal clips, until the distal measured PAP is decreased to 50–30% of the systemic pressure, according to the cardiac lesion, as well as the patient's age and weight at the time of the

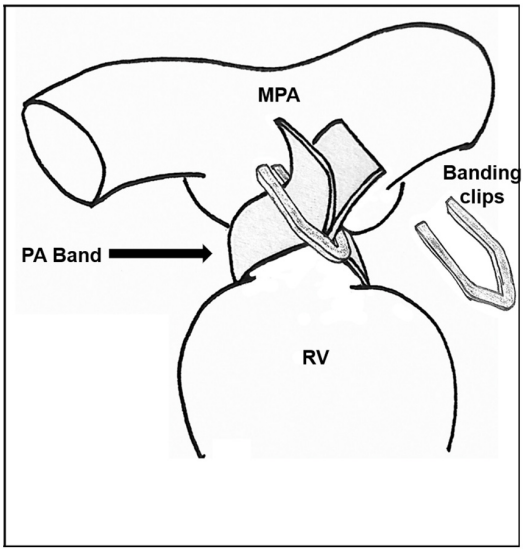

FIGURE 1
Pulmonary artery banding technique. RV, right ventricle; MPA, Main pulmonary artery; PA, Pulmonary artery.

procedure. Alternatively, Trusler's rule can be followed, adding the necessary fine tuning to reach the required PAP. The band is fixed to the adventicia of the main pulmonary artery to prevent its migration toward the pulmonary arteries. The band material is chosen (absorbable or durable) according to the cardiac lesion and planned treatment strategy.

2.1.2 Surgical debanding

Surgical debanding, when needed, is achieved during the cardiac procedure performed to repair the initial heart defect for which the patient was banded. The band is removed usually at the end of the procedure. The main pulmonary artery can be progressively dilated with Heggar dilators until the appropriate size is reached. Alternatively, it can also be dilated using an appropriately sized balloon. Surgical options for the restoration of an adequate main pulmonary artery include the use of an autologous fresh or bovine pericardial patch to enlarge the narrowed area. Alternatively, the pulmonary artery may be transacted at its narrowest diameter; the narrowed and fibrotic area is then totally resected, and the main pulmonary artery reconstructed by end-to-end anastomosis, with or without the use of a patch. Any narrowing of the right or left pulmonary arteries is usually enlarged with a patch.

2.1.3 Catheter-based debanding

Catheterization procedures may be performed under sedation. Vascular access is secured percutaneously, and the sheath is advanced through the vein. Initially, hemodynamic evaluation is performed to measure the right heart, left heart and pulmonary circulation pressures. The guidewire reaches the main pulmonary artery proximal to the PA band. The size of the balloon is selected to be 1–1.2 times the size of the pulmonary valve annulus. An appropriately sized high-pressure balloon is advanced over the guidewire and is positioned across the PA band site. Under fluoroscopic guidance, the balloon is inflated until the inner clip is slipped, and the desired gradient is achieved (**Figure 2**). After dilation, the balloon is pulled back, the saturation and pressure are measured and the angiogram is repeated.

2.2 Statistical analysis

All analysis was conducted and represented using Microsoft Office Excel 2020, and GraphPad Prism 5.00.288. Discrete variables were represented as absolute numbers or percentages of the total. Standard deviations were calculated and included for all normally distributed continuous variables and were reported as mean ± standard error of the mean (SEM).

3 Results

During the period 2000–2020, a total of 143 patients underwent PAB. The mean age of the patients at the time of PAB was approximately 5.6 months. The male: female ratio was 1:0.8. 86 patients had subsequent band removal at our institution *via* thoracotomy. Multiple complications were encountered following the surgical removal of the pulmonary artery band: post-operative infection, hemothorax, pneumothorax, pericardial effusions, atrioventricular block, choreoathetosis, cardiopulmonary arrest requiring resuscitation with pressors and intubation, re-intubation, and ischemic strokes.

Percutaneous removal of the pulmonary artery band was attempted in four patients during the same period. **Table 1** represents the demographic characteristics of these patients. Three patients had successful PA band removal *via* balloon catheter, while it was not possible in the fourth case, and the band had to be removed surgically. The mean age at the time of balloon angioplasty was 36 ± 6.24 months, the mean time between band placement and removal was approximately 32.6 months, and the average weight at the time of the procedure was 12.37 ± 3.7 Kg. The systolic gradient across the band site decreased from 71.67 ± 12.58 before band removal to 23.67 ± 2.89 mm Hg after the debanding. None of the three patients experienced post-procedure complications or required additional intervention. They didn't require mechanical ventilation, or intensive care admission. After discharge, the patients were followed up at 2 weeks, at 1 month and then at every 3-month interval post-debanding. If the patients had reassuring follow-up results, they would be followed up annually thereafter. One patient was lost to follow-up after 3 years from the procedure, while the remaining two patients are still being followed up on, with the most recent visits 9 and 10 years after the band removal. **Table 2** entails the procedural characteristics of the three patients. Below is a discussion of the four cases.

Case I: The first case of balloon dilation is a female patient who was diagnosed at birth with a large smooth muscular VSD measuring 13.5 mm in diameter and 7 mm in length. She had a PAB placed at the age of 2 months due to pulmonary overflow. At the age of 33 months, she presented for device VSD closure. Successful closure using a 16 mm amplatzer device was performed under general anesthesia without complications. Following the procedure, the right ventricular (RV) systolic pressure was measured at 85 mmHg, left ventricular (LV) systolic pressure was 95 mmHg, and the pressure gradient across the PA band was 60 mmHg. Three days later, balloon-based removal of the PA band was successfully performed under sedation, using 14 mm balloon (**Figure 3**). Pressure measurement following the procedure revealed: RV systolic pressure of 48 mmHg, and PA systolic pressure of 26 mmHg with a residual gradient of 22 mmHg across the band site. The patient tolerated the procedure well without complications and was pain-free by the second day following the operation, according to the Face, Legs, Activity, Cry, Consolability (FLACC) scale. She was followed up annually and when needed at the pediatric cardiology outpatient department *via* clinical and echocardiographic evaluation for 3

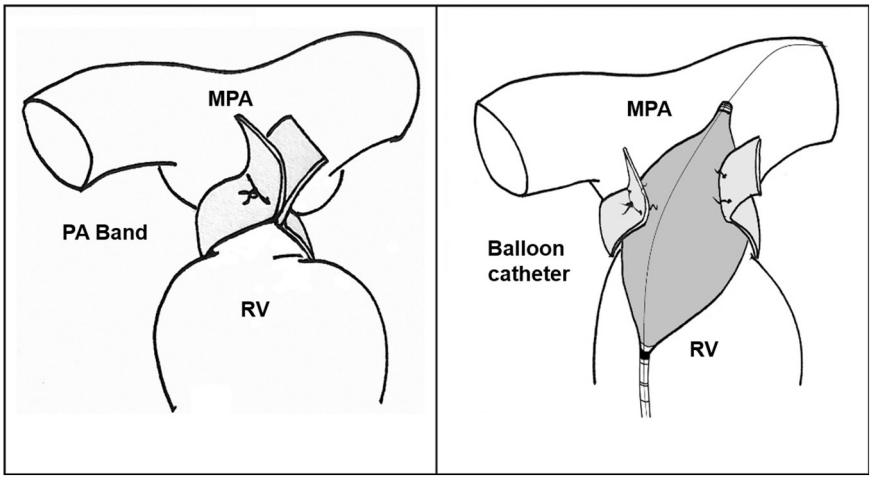

FIGURE 2
Pulmonary artery debanding *via* balloon catheter. RV, Right ventricle; MPA, Main pulmonary artery; PA, Pulmonary artery.

TABLE 1 Demographic characteristics of the patients.

Case	Sex	Age at banding (months)	Age at debanding (months)	Weight at debanding (Kg)	Underlying heart lesion
I	F	2	33	15	Large VSD
II	M	4	48	8.1	Multiple VSDs
III	F	4	27	14	Large VSD + hypoplasia of the transverse arch and descending aorta with a PDA supplying the descending aorta + coarctation of the aorta
IV	F	5	51	15.7	Large mid muscular VSD

F, female; M, Male; VSD, Ventricular septal defect; PDA, patent ductus arteriosus.

TABLE 2 Procedural details of the three patients who had undergone successful percutaneous PA band removal.

Case	I	II	III
Saturation before debanding (%)	100	98	100
Saturation after debanding (%)	100	100	100
RV systolic pressure pre-procedure (mmHg)	85	105	88
RV systolic pressure post-procedure (mmHg)	48	38	33
Pressure gradient across PA band pre-procedure (mmHg)	60	85	70
Pressure gradient across PA band site post-procedure (mmHg)	22	8	22
Vmax across main pulmonary artery pre-procedure (m/sec)	5.2	5.1	4.2
Vmax post-procedure (m/sec)	2.4	1.7	2.1
Follow up period	3 years	9 years	10 years
Most recent echo findings	VSD device in place, good LV and RV systolic function, RV systolic pressure of 40 mmHg, and mean gradient across the PA band site of 14 mmHg	Normal LV systolic function, multiple small apical muscular VSDs with left to right shunt, PA as well as its branches are of good size.	Vmax across MPA is 2 m/sec, RV systolic pressure of 35 mmHg, mean gradient of 8 across the PA band site. Pulmonary artery and branches are normal in size. Mild coarctation of the aorta with maximum velocity of 2.1 m/s

years following the percutaneous band removal; thereafter she was lost to follow up. At the last clinic visit, the patient was gaining weight adequately (weight = 20 Kg) and her systemic oxygen saturation was 100%. Her last echocardiographic imaging, at 3 years post-debanding, showed normal LV size and function, normal size of the main pulmonary artery, and

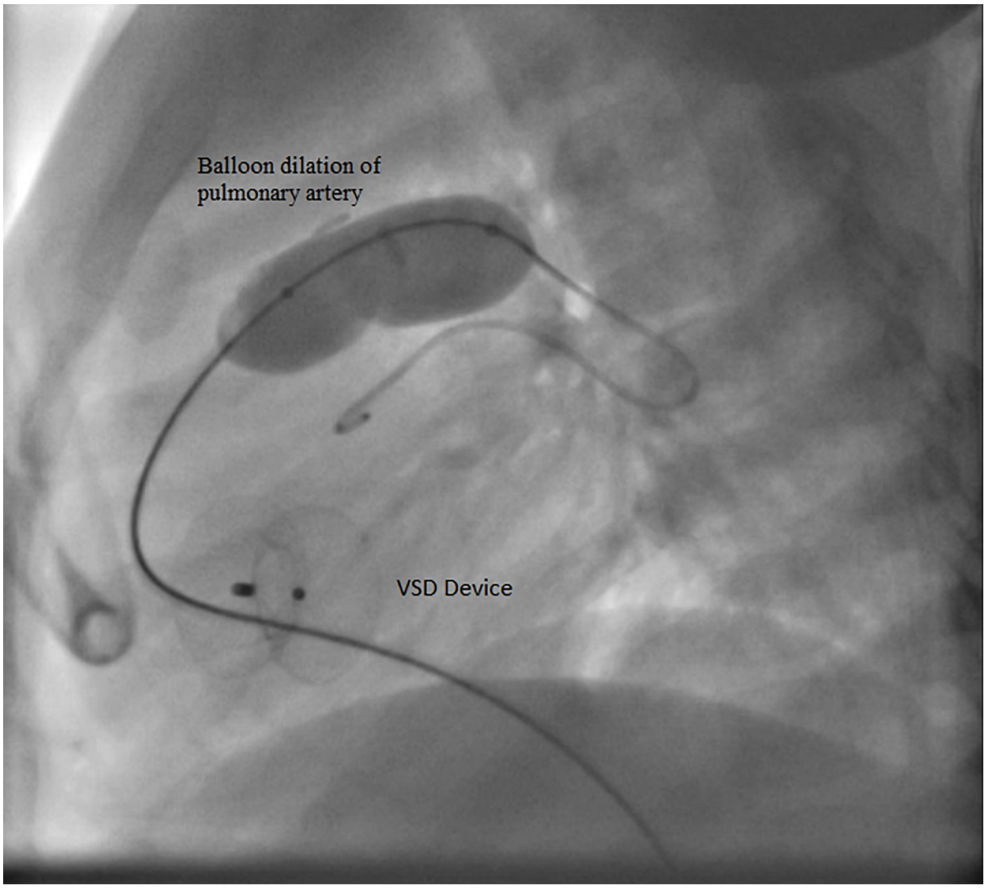

FIGURE 3
Balloon dilation of the pulmonary artery of Case I.

an estimated RV systolic pressure of around 36 mm Hg. The patient was not maintained on any cardiac medications. Figure 4 shows the echocardiographic findings of the patient before the debanding procedure and at 3-year follow-up post debanding.

Case II: A male patient was diagnosed at the age of 2 months with multiple apical muscular VSDs that are moderate to large. He had successful PA band placement at 4 months of age due to pulmonary overflow. He presented at the age of 4 years for catheter-based removal of his PA band. Before the procedure, echocardiography revealed severe narrowing of the PA with a systolic gradient of 85 mmHg across the band, an RV systolic pressure of 105 mmHg, and a PA systolic pressure of 20 mmHg. Following sedation, successful balloon dilation of the PA band was performed using a 15 mm balloon, which resulted in a reduced RV pressure of 38 mmHg, a residual gradient of 8 mmHg across the PA band, and a PA systolic pressure of 30 mmHg. On the same day post-debanding, the patient was free of pain according to the FLACC scale. No complications were encountered during or after the procedure, and he didn't require further intervention. The angiographic findings of the patient before and after the angioplasty are shown in Figure 5.

Case III: A female patient was admitted to the AUBMC pediatric intensive care unit (PICU) at the age of 4 months with a picture of acute respiratory distress syndrome and was found to have a large apical muscular VSD measuring 16 mm with a left-to-right shunt, complicated by pulmonary overflow, a small patent foramen ovale, hypoplastic transverse arch, a PDA supplying the descending aorta, and coarctation of the aorta. She underwent coarctation repair and PA banding during the same admission. At 27 months of age, she was admitted for catheter-based PA debanding. Before the debanding, the PA pressure was found to be 64 mmHg. The procedure was performed under sedation. No complications occurred during or after the procedure, and she was discharged 1 day post-debanding.

The second and third cases are still followed-up annually at the pediatric cardiology outpatient clinic. At the last annual clinic check-up for case II, at 9 years post-debanding, the patient had a normal pulmonary arterial pressure of 35 mmHg. He was also gaining weight properly. Similarly, during the last follow-up visit for case III, 10 years after debanding, the patient was doing

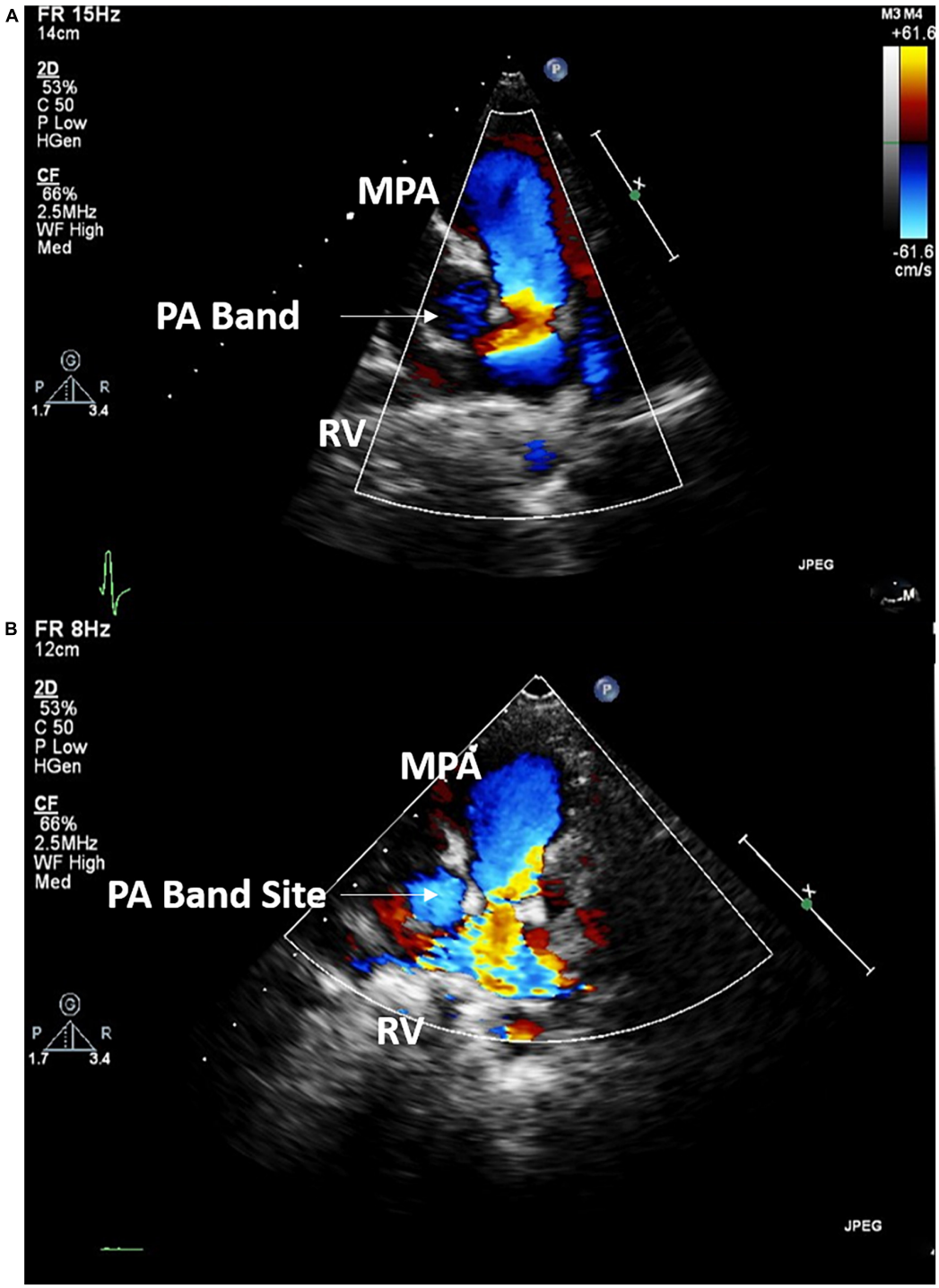

FIGURE 4
Echocardiographic imaging of Case I before **(A)** the debanding procedure and at 3-year follow up following the catheter-based debanding **(B)**. RV, right ventricle; MPA, Main pulmonary artery; PA, Pulmonary artery.

well with a good systolic function, a right ventricular systolic pressure of 35 mmHg, and a Vmax across the main pulmonary artery of 2.1 m/s. The systolic gradient across the PA band site was 17 mm Hg and the mean gradient was 10 mmHg.

Notably, these patients didn't require intubation, were able to tolerate oral intake and mobilize within the same day of the procedure, and they only required paracetamol for pain control. The hospital stays for the three patients ranged from 3

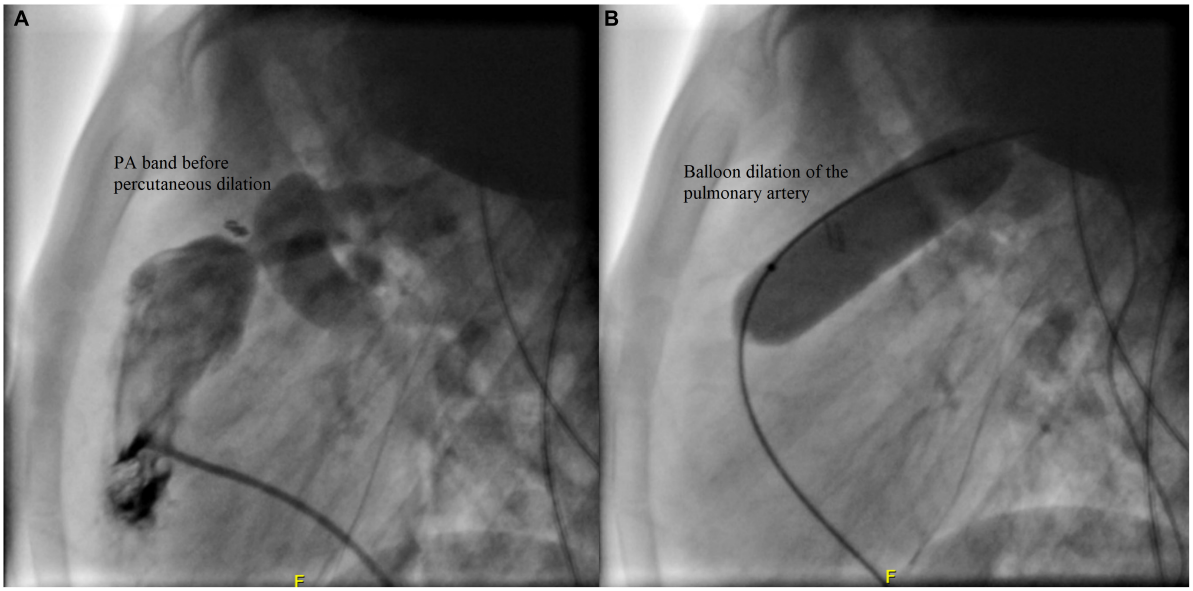

FIGURE 5
Angiographic findings of Case II before **(A)** and after **(B)** the debanding procedure.

to 7 days. The first case required 7 days of admission as balloon angioplasty was performed 3 days following the VSD device placement. Finally, the cost of balloon-dilation was around 8,000–10,000 U.S.D, which is around 17,000–20,000 U.S.D lower than the surgical removal.

Case IV: A female patient presented at 3 months of age with failure to thrive, recurrent infections, and fatigability upon feeding. She was found to have multiple apical VSDs and a large mid-VSD without any muscular or tissue covering. She later had a pulmonary artery band placed at 5 months of age due to pulmonary overflow. At the age of 5 years, she was admitted for diagnostic catheterization and possible balloon-debanding of the pulmonary artery, coupled with VSD closure. The patient underwent catheterization and debanding was attempted. The balloon was inflated without resolution of the band waist. The band could not be removed as multiple clips were used and placed in close proximity. The case was then converted to open heart surgery. The patient required intubation for 3 days and was discharged on day 5 post-debanding.

4 Discussion

A few studies have explored the use of pulmonary artery catheter-based debanding. All the studies were performed in developed countries. To our knowledge, this is the first study to report the use of this procedure at a tertiary center in a developing country like Lebanon.

To evaluate the efficacy and hospital course of the balloon-associated pulmonary artery debanding, our study retrospectively analyzed four cases who had attempted percutaneous pulmonary artery band removal. Three patients had successful percutaneous band removal, and all exhibited favorable outcomes. A decrease in the gradient across the PA band site was noted following the procedure in all patients. No complications during or after the catheter-based debanding were noted, and none required further interventions.

Variation in surgical practice, nevertheless, would impact the achievement of the procedure. The banding technique depicted in this manuscript is the usually implemented technique at our institution and is followed by many centers worldwide. Case IV had comparable demographic and baseline cardiac characteristics to the other patients who underwent catheter debanding; however, the debanding procedure couldn't be done percutaneously as multiple clips were used to maintain the band. All three other successful cases had only one clip placed at the pulmonary artery band, which facilitated the percutaneous debanding. A tighter band maintained by a high number of clips may not be easily reversed with a balloon catheter. Therefore, upon band placement, the surgeon should consider the possibility of future percutaneous debanding.

Catheter associated debanding saves the patient from open-heart surgery and its associated morbidity and mortality, especially in patients with spontaneously closing lesions who are not scheduled for additional surgeries. The debanding procedure can also be coupled with VSD device closure to save the patient additional procedures. In case I, VSD closure and the debanding procedure were performed 3 days apart as this was the first percutaneous band removal at our institution; however, the two procedures can be performed

simultaneously. Besides, in patients who require future surgical intervention, this approach can be used to delay the surgery. Furthermore, this newly adopted technique imparts smaller scars and reduces post-operative pain. In this case, paracetamol was the only medication used for pain control, compared to the need for multiple analgesics in the surgical debanding. In addition, none of the three patients required intensive care admission. The average hospital stay was 3 days, compared to the average stay of 9 days when the band is removed surgically at our institution. Likewise, our three patients were followed up for a relatively long period of time and the attained outcomes were encouraging. Two patients were followed up for 9 and 10 years, respectively. No significant stenosis was noted at the band site. They didn't require any additional interventions.

In developing countries, management of CHDs through surgery is usually hindered by the shortage of medical equipment, specialized centers, personnel, and expertise. Indeed, a specialized CHD surgical team is not always available in low-income countries, and the schedule of congenital cardiac anomaly correction operations strongly depends on visiting teams, which negatively affects the prognosis (16). On the contrary, our approach relies on widely accessible balloon catheters; and can be easily employed in low-income countries.

The catheter-based procedure saved around 17,000–22,000 USD when it was compared to surgical removal of the band. In most developing countries, a proper national healthcare system is almost non-existent. Due to financial restrictions, treating common and communicable diseases, like infectious diseases, takes priority over congenital heart surgery. In Lebanon, for example, philanthropic organizations pay about 30% of the cost of CHD surgeries, with the rest usually covered by patients and the hospital (17). Therefore, replacing the surgical approach with percutaneous intervention solves a major financial challenge for these patients.

Theoretically, this procedure is not risk-free. Complications such as rupture of the pulmonary artery, dissection or aneurysm exist. In this study, we didn't encounter any complications related to the procedure. Nevertheless, our data is extrapolated from a few patients. Hence, we argue that this technique should be studied in a larger population to assess its potential immediate and delayed complications.

The use of balloon catheters in band dilation or removal was described in previous studies as early as 1990. The first successful cases of pulmonary artery debanding *via* balloon catheter were described by Bjørnstad et al., in two patients (11). Brown et al., used dilatable bands to secure the ability to fully or partially expand the main pulmonary artery through balloon angioplasty in eight patients (13). No complications were noted during or after the procedure. They were able to record a significant decline in the gradient. Holmström et al. also performed successful catheter-based debanding on 17 patients (12). They suggested the use of a modified suture technique for the PA band that allows catheter-based debanding in the future. However, multiple complications were encountered during the procedure, including rupture of the pulmonary artery, temporary heart block requiring a pacemaker, contrast extravasation, and compromised coronary blood flow. *Morgan et al* also described two cases of balloon catheter debanding (18). A third case failed to dilate the balloon and was converted to open surgery; however, the patient had significant sub-valvular pulmonary stenosis. In another study, 12 successful percutaneous pulmonary artery debanding procedures were performed, two of which were for total debanding (19).

Many authors have discussed the use of dilatable bands or resorbable materials to avoid additional surgical intervention to remove the band. Unfortunately, such inventions didn't gain wide clinical attention. To start with, some studies proposed the use of an adjustable pulmonary artery band, which would allow prompt adjustment of PAB according to the patient's requirements. This would avoid surgical re-intervention for purposes of band adjustment. This approach relies on the use of a telemetric adjustable FloWatch-PAB pneumatic device to adjust the size of the PAB. By using this device, the authors reported a shorter intensive care stay and a smooth hospital stay. Nevertheless, the cost of the device remained a significant barrier (20, 21). Also, concerns have been raised regarding the need for additional surgical intervention when the removal of the device is necessary. Other possible reported complications such as pulmonary arterial aneurysm and dissection are also raised. All of this has restricted the clinical application of this technique.

Another suggested alternative practice relies on the use of absorbable PA band (22, 23). Bonnet et al., used polydioxanone bands to tighten the pulmonary artery (23). This technique spares patients the need for additional surgery for subsequent band removal. It is especially helpful in spontaneously closing lesions such as VSD. Unfortunately, the mean time for complete absorption of the band was 5.7–7.2 months following the operation, which may not be sufficient for complete resolution of the congenital lesions (22, 23). This limits the applicability of this technique in the dynamic cardiovascular system.

Finally, this study describes percutaneous pulmonary artery debanding along with the follow-up results. This procedure is feasible, inexpensive, and effective in securing the proper pressure goal. We propose that this technique might safely replace surgery-based band removal when performed by a well-trained pediatric cardiology team. It may also be coupled with other corrective procedures such as VSD closure. This approach requires readily accessible medical resources and thus can be performed in specialized centers in developing and developed countries. Further studies are needed to adequately evaluate the use of balloon catheters for pulmonary artery dilation.

This study has several limitations and concerns. The main limitation is inherent to the study design: retrospective chart review. The study is further constrained by the sparse patient

population. Additionally, many hospitals and institutes might not apply the banding approach described in this study. Additionally, the usefulness and effectiveness of this strategy may be constrained by the need for several sutures or clips to tighten the band. Besides, the fact that it was used to remove rather than to dilate the bands may limit its usefulness in patients who require band readjustment. We attest that a higher-quality study involving a larger number of patients followed-up for a longer duration is required to evaluate adequately the safety and efficacy of this procedure and determine the need for technique modification.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The Institutional Review Board at the American University of Beirut approved the study on August, 2020 under the ID: BIO-2020-0325. Written informed consent from the participants or their legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

MA developed the idea of the manuscript. RZ, SH, and NY collected and analyzed the data. RZ, SH, NY, and TT wrote the first draft of the manuscript. MA, IR, and FB did the final editing. All authors contributed to corrections and adjustment of subsequent iterations of the manuscript and approved and agreed with the content.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Outcomes of treatment for right atrial isomerism with functional single ventricle and extracardiac total anomalous pulmonary venous connection beyond neonatal period: Delayed surgical treatment, improving outcomes

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Objective: Total anomalous pulmonary venous connection (TAPVC) is frequently associated with right atrial isomerism (RAI), which is commonly complicated with an unbalanced atrioventricular canal with contralateral hypoplasia, complex systemic and pulmonary venous anatomy, and conotruncal abnormalities, resulting in increased risk of mortality. This study aimed to review the outcomes of delayed surgical treatment for patients with RAI complicated with functional single ventricle (FSV) and TAPVC at a single center.

Methods: In this retrospective study, we reviewed the medical records of 24 consecutive patients with RAI complicated with FSV and TAPVC who underwent initial surgical palliation after 5-month old between September 2008 and June 2019. Demographic data, concomitant anomalies, age at initial palliation, and surgical interventions were extracted and analyzed using the Cox proportional hazard model to assess risk factors for mortality and the Kaplan-Meier method to assess survival.

Results: The in-hospital mortality was 12.5% (three out of 24). The causes of death were pulmonary arterial hypertension and low cardiac output syndrome. Average follow-up was 65.2 ± 40.3 months (7–137 months). Another 4 patients died during the follow-up due to low cardiac output syndrome, protein-losing enteropathy and pulmonary arterial hypertension, respectively. Kaplan-Meier estimated survival at 1 and 5 years were 83.1 and 69.4%, respectively. Fontan completion was 45.8% (11/24). The mortality for patients with pulmonary venous obstruction (PVO) was 66.7% (4/6). Cox multivariate regression analysis indicated that preoperative PVO was the only risk factor for mortality ($p = 0.032$; hazard ratio, 10.000; CI 1.222–81.811).

Conclusion: Outcomes of delayed surgical treatment for patients with RAI complicated with FSV and TAPVC have improved significantly. The survival and Fontan completion were higher. However, preoperative PVO was still the risk factor for mortality.

KEYWORDS

right atrial isomerism, total anomalous pulmonary venous connection, heterotaxy syndrome, sutureless technique, single ventricle

Introduction

During the past 30 years, children with single ventricle lesions have demonstrated improved survival with the advent of early postnatal identification, innovative therapies, and staged surgical procedures culminating in the Fontan circulation (1–3). However, total anomalous pulmonary venous connection (TAPVC) is frequently associated with heterotaxy syndrome, especially right atrial isomerism (RAI), which commonly includes an unbalanced atrioventricular canal with contralateral hypoplasia, complex systemic and pulmonary venous anatomy, and conotruncal abnormalities, resulting in increased risk of mortality (4, 5).

RAI associated with TAPVC carries one of the worst outcomes in current surgical practice. Neonatal palliative surgery carries a high operative risk of early mortality. The report from the Society of Thoracic Surgeons Congenital Heart Surgery Database about patients with heterotaxy syndrome who underwent TAPVC repair at age of 90 days or younger confirmed the high mortality risk, particularly in patients with functionally univentricular physiology (4). Furthermore, surgical repair of RAI complicated with obstructed TAPVC during neonatal period is associated with frequent recurrence of pulmonary venous obstruction. Delayed surgical treatment may improve the outcomes. Delayed surgical treatment not only consists of inserting a stent to relief obstruction of TAPVC for selected critical neonates and perform the second stage operation after several months, but also means that surgical treatment occurs beyond the neonatal period for patients who are relatively stable. Even in developed countries, patients with TAPVC associated with a functional single ventricle exhibit high morbidity and mortality (6–11). The purpose of this study was to describe outcomes of delayed surgical treatment for patients with RAI complicated by TAPVC.

Methods

The study protocol was reviewed and approved by the Institutional Review Board at Guangzhou Women and Children's Medical Center, and individual consent for the study was waived owing to its retrospective medical record review design. The databases of the Department of Cardiac Surgery were searched for patients with RAI and TAPVC who had undergone operative treatment. Medical records, operative notes, and all available electrocardiograms, echocardiography reports, and cardiac catheterization reports were reviewed. From September 2008 to June 2019, 24 consecutive patients with RAI, functional single ventricle and extracardiac TAPVC underwent initial surgical palliation after 5-month old at our center. Twenty-two patients (91.6%) were male and 2 (8.4%) were female. The median age at the time of the initial operation was 522 days (range 165–3,718 days), and median body weight was 8.45 kg (range 6–19.2 kg).

The type of TAPVC was supracardiac in 23 patients and infracardiac in one patient. Pulmonary venous obstruction (PVO) was found to coexist in six (6/24, 25%) patients. In 20 patients, there was a complete atrioventricular canal (CAVC), and in most cases, there was an unbalanced opening into the morphologic right ventricle. Atrioventricular valve regurgitation $\geq$ moderate was demonstrated by echocardiography in four patients. Sixteen patients had bilateral superior vena cava, usually without a connecting innominate vein. A typical double outlet right ventricle, with a muscular outlet conus under each great vessel associated with pulmonary atresia, was present in 4 patients. Patient characteristics are shown in Table 1.

Surgical technique

TAPVC repair was performed in most patients during the initial palliation. Following median sternotomy, hypothermic cardiopulmonary bypass was performed. The ascending aorta was cannulated, and up to four venous cannulas were inserted into the superior vena cava, inferior vena cava (IVC), and hepatic veins when these did not drain into the IVC. Aortic cross clamping and cardioplegic arrest were performed. Repair of TAPVC was performed with the common pulmonary venous chamber and atrium anastomosis under mild hypothermia. A sutureless technique was used for most of the patients (including six patients with PVO). In patients who underwent a bidirectional Glenn procedure (BDG), the pulmonary artery was dissected and the anatomy of the systemic and pulmonary connections was inspected. Pulmonary arterioplasty

TABLE 1 Characteristics of patients with right atrial isomerism and TAPVC.

Age, median [day, median (range)]	522 (165–3,718)
Male, *n*	22 (91.6%)
Weight [kg, median (range)]	8.45 (6–19.2)
TAPVC type, *n*	
Supracardiac	23
Infracardiac	1
CAVC	20
AVVR ≥ moderate	4
Pulmonary atresia	4
Pulmonary stenosis	17
PVO	6
Bilateral superior vena cava	16
Apicocaval juxtaposition	8

AVVR, atrioventricular valve regurgitation; CAVC, complete atrioventricular canal; PVO, pulmonary venous obstruction; TAPVC, total anomalous pulmonary venous connection.

TABLE 2 Procedure for patients with RAI and TAPVC.

Procedure	Number
First stage	
TAPVC repair + BT shunt	1
BDG	4
BDG + TAPVC repair	15[#]
BDG + TAPVC repair + AVR	3[§]
Modified Fontan	1
Second stage	
AV replacement	1
PVO repair + AVR	1
Modified Fontan	11*
Third stage	
Modified Fontan	1

AV, atrioventricular valve; AVR, atrioventricular valve repair; BDG, bidirectional Glenn; BT, Blalock-Taussig; PVO, pulmonary venous obstruction; TAPVC, total anomalous pulmonary venous connection.
[#]One patient suffered low cardiac output syndrome and hypoxemia, and underwent bidirectional Glenn takedown and underwent central shunt for low cardiac output syndrome and hypoxemia 1 week after initial palliation.
[§]One patient suffered low cardiac output syndrome and hypoxemia, and underwent bidirectional Glenn takedown.
*One was taken down after 2 days.

was performed when necessary. The atrial septum was then opened in all patients. Modified Fontan (extracardiac Fontan) was likewise performed through a median sternotomy, with mild hypothermia and cardiopulmonary bypass. If there was no planned concomitant intracardiac procedure, the heart remained beating for the duration of the procedure. A total extracardiac Fontan was constructed using an 18–22 mm Gore-Tex tube graft anastomosed to the IVC and the ipsilateral pulmonary artery or the contralateral pulmonary artery. The route of Fontan connection was chosen according to our preference to obtain unobstructed flow of IVC and hepatic vein blood to the pulmonary artery without compromising pulmonary venous blood flow, or to obtain unobstructed flow of both vessels. A 3–4 mm fenestration was placed for all patients.

Data are presented as mean ± standard deviation or median and range, as appropriate. Cox proportional hazard models were used to analyze risk factors for survival. Estimated survival was determined by the Kaplan-Meier method based on the product-limit estimator, and 95% confidence intervals were constructed around curves using Greenwood's formula. Differences were considered statistically significant if the *P*-value was < 0.05.

Results

One out of 24 patients underwent TAPVC repair and Blalock-Taussig (BT) shunt prior to BDG. Eighteen patients underwent TAPVC repair at the same time as BDG. Concomitant atrioventricular valvuloplasty was performed in three patients. However, two out of 18 suffered low cardiac output syndrome and hypoxemia, and underwent BDG takedown. TAPVC persisted in five patients who underwent BDG ($n = 4$) and one-stage modified Fontan ($n = 1$; Table 2).

The mean cardiopulmonary bypass time was 154 ± 80 min; the mean aortic cross-clamping time ($n = 20$) was 54 ± 23 min.

The hospital mortality rate was 12.5% (three out of 24). They all underwent bidirectional Glenn+ TAPVC repair at the first stage. One underwent atrioventricular valve repair simultaneously, and one (70.2-month old) underwent Glenn takedown because central venous pressure went up to 25 mmHg due to pulmonary arterial hypertension. The causes of death were pulmonary arterial hypertension and low cardiac output syndrome. In five patients, TAPVC wasn't repair for the sites of pulmonary veins returned near the atrium and seemed confluent. The mean follow-up period was 65.2 ± 40.3 months (7–137 months) and follow-up was complete in all surviving patients. Four patients died during the follow-up. One died of protein-losing enteropathy 11 months after initial operation. One patient underwent cutback of a stenotic orifice and atrioventricular valve replacement for recurrent PVO and severe atrioventricular valve regurgitation 11 months after initial palliation, and died of low cardiac output syndrome 4 months after the second operation. One (22.8-month old) underwent TAPVC repair and BDG takedown due to central venous pressure up to 25 mmHg, and underwent modified BT shunt 1 week later, but died of a nervous system complication after 15 months. Another one underwent modified Fontan but the Fontan conduit was taken down after 2 days, and died of low cardiac output syndrome due to intraoperative coronary artery injury. Of the 17 survivors, one underwent atrioventricular valve replacement for severe atrioventricular valve regurgitation 14

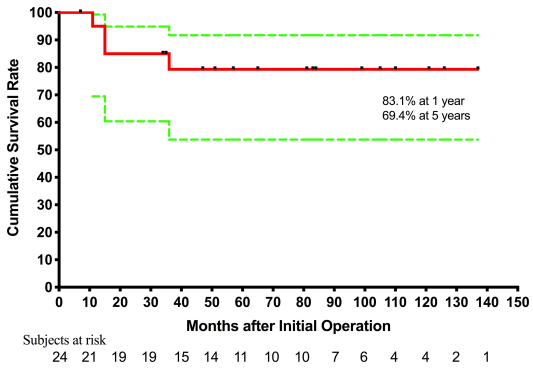

FIGURE 1
Cumulative incidence curve for estimated survival after initial palliation. Green lines denote 95% confidence intervals.

TABLE 3 Analysis of risk factors for survival.

Variable	Univariable	Cox multivariable analysis		
	P-value	Hazard ratio	*P*-value	95% CI
Age	0.310			
Weight	0.320			
PA	0.160			
AJ	0.204			
PVO	0.020	10.000	0.032	1.222–81.811
CAVC	0.160			
AVVR	0.315			

AJ, apicocaval Juxtaposition; AVVR, atrioventricular valve regurgitation; CAVC, complete atrioventricular canal defect; PA, pulmonary atresia; PVO, pulmonary venous obstruction.

months after initial operation. Totally, 13 patients underwent modified Fontan operation and 11 survived. The age at modified Fontan operation was 55.7 ± 28.2 months (range from 33.6 to 137.4 months). Fontan completion was 45.8% (11/24), while two are awaiting Fontan procedure, and two with higher PVR and PAH diagnosed by catheterization are accepting targeted therapy for PAH. Kaplan-Meier estimated survival after initial palliation was 83.1 and 69.4% at 1 and 5 years, respectively (Figure 1).

Univariate analysis and multivariate analysis both indicated that PVO was a significant risk factor for mortality ($p = 0.032$; hazard ratio, 10.000; CI 1.222–81.811). Age, weight, CAVC, pulmonary atresia, apicocaval juxtaposition, and atrioventricular valve regurgitation were not significantly associated with mortality (Table 3).

Discussion

Despite improvements in outcomes of isolated TAPVC treatment (12–14), previous reports on the overall outcomes for children with a single ventricle and TAPVC have generally shown a poor prognosis (6–11). Mortality following surgical treatment of these patients has been reported to range from 20 to 52% (6–11, 15–17), although an improvement has been noted over time. Staged surgical palliation has become standard therapy in most centers. Previously identified risk factors for mortality have included mixed TAPVC, younger age at first operation, TAPVC repair before BDG, low birth weight, extracardiac anomalies or genetic syndromes, and extracorporeal membrane oxygenation or ventricular assist device support, among others (6–11). According to our recent experience with 24 patients with RAI with functional single ventricle and extracardiac TAPVC, in-hospital mortality following the initial palliation was only 12.5%, and survival after initial palliation was 83.1 and 69.4% at 1 and 5 years, respectively, over a mean follow-up of 65.2 months. The risk factor for death identified by multivariate analysis was PVO.

Of the many associated malformations found in patients with a single ventricle and TAPVC, those requiring the repair of extracardiac TAPVC at a younger age are considered important risk factors for mortality (7). This indicates coexisting obstruction of pulmonary venous drainage pathways. In this study, PVO was indicated to be a risk factor for mortality. To address this problem, a sutureless technique was used for most of the patients. Application of a sutureless technique for relief of postoperative PVO was expected to improve the outcomes (18). However, four of six patients with PVO died in this study, and recurrent PVO developed in another one patient. It is reported that stent implantation has been used for patients with preoperative pulmonary venous obstruction, and might be an alternative approach to avoid early TAPVC repair. However, there are fewer documented experiences related to this treatment approach and it has not been shown to improve overall outcomes (11). We also realize that whether the pulmonary veins are obstructive or not, some neonates or small infants suffer severe hypoxemia and metabolic acidosis, emergency TAPVC repair is enforced and the morbidity and mortality are higher.

As with other reports, most patients in this study (88%) exhibited right atrial isomerism (4, 5, 9). Right atrial isomerism has been recognized as one of the worst forms of congenital heart disease (CHD), with overall 5-year survival ranging from 30 to 74% (19–21). Even though this was not found to be the case in this study ($p = 0.958$), patients with right atrial isomerism are well-known to have a lifelong risk of overwhelming infection, common atrioventricular valve regurgitation, and arrhythmia, which can increase the mortality and morbidity of surgical treatment.

In the past three decades, great socio-economic development has taken place since the adoption of the reform and opening policy in China, and tremendous progress has been made in the field of medicine. However, shortages of basic equipment, facilities, and quality medical service at a grassroots level have led to misdiagnosis of CHD. Furthermore, poor awareness of

public health issues results in delayed treatment, and most people from remote border districts are unable to afford the cost of treatment. As such, many patients undergo initial palliation at an older age. The median age at initial palliation in this study was 13.3 months, which is higher than other reports (median age from 4 to 69 days) (6–11). In most of the patients in our study, there was no severe PVO identified during the neonatal and early infant period, because coexisting obstruction of the pulmonary venous drainage pathways always requires early repair of extracardiac TAPVC. This likely reflects the stable nature of the patients who do not require earlier procedures. However, postoperative pulmonary arterial hypertension and increased pulmonary vascular resistance after initial palliation at an older age could increase mortality and lower the probability of Fontan completion. Only 11 (45.8%) patients achieved Fontan completion. In these patients, cyanosis disappeared and their general condition improved. The Fontan completion was only 26.3–46% for patients with functional single ventricle and extracardiac TAPVC who underwent initial operation at an early age (9–11, 22). For patients who did not complete the Fontan procedure, additionally close follow-up may be needed.

Given the dismal survival previously reported for patients with a functional single ventricle with TAPVC, some centers began to consider these patients for primary heart transplantation (HT) (23). Even though post-HT survival has improved for patients who failed to achieve Fontan completion, it is obviously limited by a shortage of donor organs and involves lifelong immunosuppressive therapy with its attendant risks and expenses (24, 25). The feasibility of transplantation for children is still uncertain in China.

Limitations

Two major limitations of the present study are its retrospective nature and that the relatively small number of patients included in the study makes it difficult to identify risk factors for mortality since the statistical power to discern differences is relatively low. Although all patients had clear documentation of the preoperative and postoperative variables, other interesting variables such as pulmonary vascular resistance and pulmonary arterial pressure were less well-documented and could not be examined in relation to the outcomes. Furthermore, there wasn't a comparative group with patients who underwent repair as neonates or before 5 months of age.

Conclusion

Surgical treatment can now be performed in patients with RAI with functional single ventricle associated and extracardiac TAPVC, with improving results. Initial palliation at an older age can be expected to lead to higher survival and higher probability of Fontan completion. Prompt and aggressive treatment may improve the outcomes for patients who underwent initial palliation at an older age.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Guangzhou Women and Children's Medical Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Risk factors of postoperative low cardiac output syndrome in children with congenital heart disease: A systematic review and meta-analysis

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Background: Low cardiac output syndrome (LCOS) is the most common complication after cardiac surgery, which is associated with the extension of postoperative hospital stay and postoperative death in children with congenital heart disease (CHD). Although there are some studies on the risk factors of LCOS in children with CHD, an unified conclusion is lack at present.
Purposes: To synthesize the risk factors of LCOS after CHD in children, and to provide evidence-based insights into the early identification and early intervention of LCOS.
Methods: The databases of the China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), PubMed, Cochrane Library, Embase and Web of Science were searched for relevant articles that were published between the establishing time of each database and January 2022. Based on retrospective records or cohort studies, the influencing factors of postoperative low cardiac output in children with congenital heart disease were included in Meta analysis.This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The risk of bias was evaluated according to the Newcastle-Ottawa Scale (NOS). RevMan 5.4 software was used to conduct the meta-analysis.
Results: A total of 1,886 records were screened, of which 18 were included in the final review. In total, 37 risk factors were identified in the systematic review. Meta- analysis showed that age, type of CHD, cardiac reoperation, biventricular shunt before operation, CPB duration, ACC duration, postoperative residual shunt, cTn-1 level 2 h after CPB > 14 ng/ml and postoperative 24 h MR-ProADM level > 1.5 nmol/l were independent risk factors of LCOS. Additionally, the level of blood oxygen saturation before the operation was found to have no statistically significant relationship with LOCS.

Conclusion: The risk factors of postoperative LCOS in children with CHD are related to disease condition, intraoperative time and postoperative related indexes, so early prevention should be aimed at high-risk children.
Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier: CRD42022323043.

KEYWORDS
children, congenital heart disease, low cardiac output syndrome, risk factors, meta-analysis, systematic review

Introduction

Congenital heart disease (CHD) is a congenital malformation caused by abnormal development of the heart and large vessels during the fetal period. At present, CHD ranks the first among birth defects in China and has become a major public health problem affecting children's physical and mental health and the quality of life (1). The report shows that there are more than 130,000 new children with CHD in China every year (2).

Low cardiac output syndrome (LCOS) is a clinical syndrome in which cardiac oxygen supply is reduced due to myocardial dysfunction and cardiovascular dysfunction, thus, insufficient oxygen can be provided to tissues and terminal organs to meet the body's metabolic needs (3). LCOS is the most common complication after cardiac surgery, which is associated with high morbidity and mortality (4).The incidence of postoperative LCOS in children with CHD is 25%∼60%, which usually occurs 6∼18 h after the operation (5–7), and the mortality rate can exceed 20% (8). The occurrence of LCOS may lead to poor prognosis, the extended hospitalization time, and the increased risk of adverse complications and high medical expenses, which brings a heavy burden on the child, family, and society (9). Therefore, reducing the incidence of postoperative LCOS in children with CHD is important to reduce the perioperative morbidity and mortality of children with CHD.

So far, there are some studies on the associated factors for the postoperative, intraoperative risk factors and postoperative risk factors. The preoperative risk factors included age, type of CHD, blood oxygen saturation, body weight, cardiac function grade and so on. The intraoperative risk factors include the duration of cardiopulmonary bypass (CPB), the type of cardioplegia, circulatory temperature and so on. The postoperative risk factors included residual shunt, 2 h cTn-1 level after CPB, 12 h ScvO2 level after CPB and so on.However, the results of studies on risk factors of LCOS in children with CHD in China and abroad are not consistence. One study (9) found that preoperative blood oxygen saturation was statistically significant with the incidence of LCOS in CHD children, which was not significant in another study (10). Mao (11) found that the preoperative left ventricular end-diastolic diameter was a protective factor for postoperative LCOS, but no other studies confirmed this conclusion.There are many similar results, and the same factor has not been uniformly confirmed in different studies.Therefore, we conducted a systematic review of the existing domestic and international publications; in addition, we applied meta-analysis to evaluate the impacts of certain risk factors on the incidence of LCOS. Efforts can be made on the modifiable factors when developing early interventions to reduce the incidence of LCOS, and eventually to improve the quality of life of children and their caregivers.

Methods

Search strategy

Both the systematic review and the meta-analysis were drafted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study was registered in PROSPERO, number CRD42022323043. We searched the databases of the China National Knowledge Infrastructure (CNKI), Wanfang Database and China Science and Technology Journal Database (VIP), PubMed, Cochrane Library, Embase, and Web of Science, and the references included were searched retrospectively. The search time limit is from the establishment of the database to January 8, 2022. The following MeSH terms and free words were combined to construct systemic searches: "congenital heart disease/Heart Defects, Congenital", "low cardiac output syndrome/Cardiac Output, Low/low cardiac output" and "risk factor*/relevant factor*/predictor/associate factors/influence*/root case analysis".

The diagnosis of LCOS

The diagnosis of LCOS was made if patients met more than two of following diagnostic criteria: ① Heart index < 2 $L.min^{-1}.m^{-2}$; ② Left ventricular ejection fraction < 40%; ③ Systolic blood pressure < 90 mmHg or systolic blood pressure decreased by more than 20% compared with preoperative

blood pressure; ④ Central venous pressure > 15 cm H2O, or prolonged capillary refill > 3s or Central venous oxygen saturation < 50%; ⑤ Postoperative dopamine dosage > 10ug/(kg.min) can maintain systolic blood pressure and cardiac output, and the duration of administration is longer than that of 30 min; ⑥ Lactic acid > 3.5 mmol/L, or metabolic acidosis (PH < 7.4, Lactic acid > 3.0 mmol/L, base excess < −2 mmol/L); ⑦ Urine volume < 0.5 ml/(kg.h) for more than 2 h; ⑧ The difference between the central temperature and the peripheral temperature > 5°C, and the limbs were cold.

Types of populations

The subjects were postoperative children with CHD (age<18 years old).

Types of interventions and comparators

According to whether LCOS occurred after operation, the patients were divided into LCOS group and no LCOS group.

Types of outcome measures

The risk factors of postoperative LCOS in children with CHD were obtained by multivariate regression analysis.

Types of studies

The type of study was prospective study or retrospective, and the published language was English or Chinese. The data of odd ratio (OR), 95% confidence interval (CI), and standard error (SE) or the values of the mean (x) and standard deviation (s) were provided or converted into the results of the study.

Exclusion criteria

Incomplete or contradictory data, publications without peer review and repeated publication or without full text are excluded from review.

Data extraction

The data extraction was carried out independently by two researchers (WPY and CLB) according to the criteria of literature inclusion and exclusion. If there was any disagreement, it would be solved by discussing it with each other or consulting the third researcher. The contents of the data extraction included author, country, study period, participants, type of study, sample size, age, and findings.

Quality assessment

The quality was evaluated independently by two researchers (WPY and CLB) using the Newcastle-Ottawa scale (NOS), and the evaluation results were checked. If they disagreed, they were resolved by discussing with each other or consulting a third researcher. NOS included the selection of subjects (4 items, 1 point each), comparability between groups (1 item, 2 points), and exposure or outcome evaluation (3 items, 1 point each), with a total score of 9. The score ≥ 7indicates a good quality, while < 7 indicates a poor quality.

Meta-analysis

RevMan 5.4 software was used for statistical analysis. The statistical effects of counting data were expressed by OR and 95%CI, while those of continuous data were expressed by mean difference (MD) and 95%CI. If $p < 0.1$ and $I^2 \geq 50\%$, it suggests that a heterogeneity exists between studies. Sensitivity analysis was used to explore the source of heterogeneity, and the comprehensive effect was calculated after excluding heterogeneity. A fixed-effect was selected for meta-analysis.

Results

Study selection

A total of 1,886 articles were searched and selected, including 913 in Chinese and 973 in English. After the repetitive literature was excluded, there were 1,752 reading titles and abstracts, and 1,719 reading titles and abstracts were deleted. The remaining 33 read the full text, 15 were excluded after reading the full text, and finally included 18,9 in Chinese and 9 in English. The literature screening process and results are shown in **Figure 1**.

Characteristics of included studies

Table 1 presents the general characteristics and main findings of the included studies. Among the 18 articles, there were 11 prospective studies and 7 retrospective studies,. The total sample size was 12,048, and the LCOS case group size was 1,681. The incidence of LCOS was 13.95%. The publication time of the study is from 2007 to 2021.

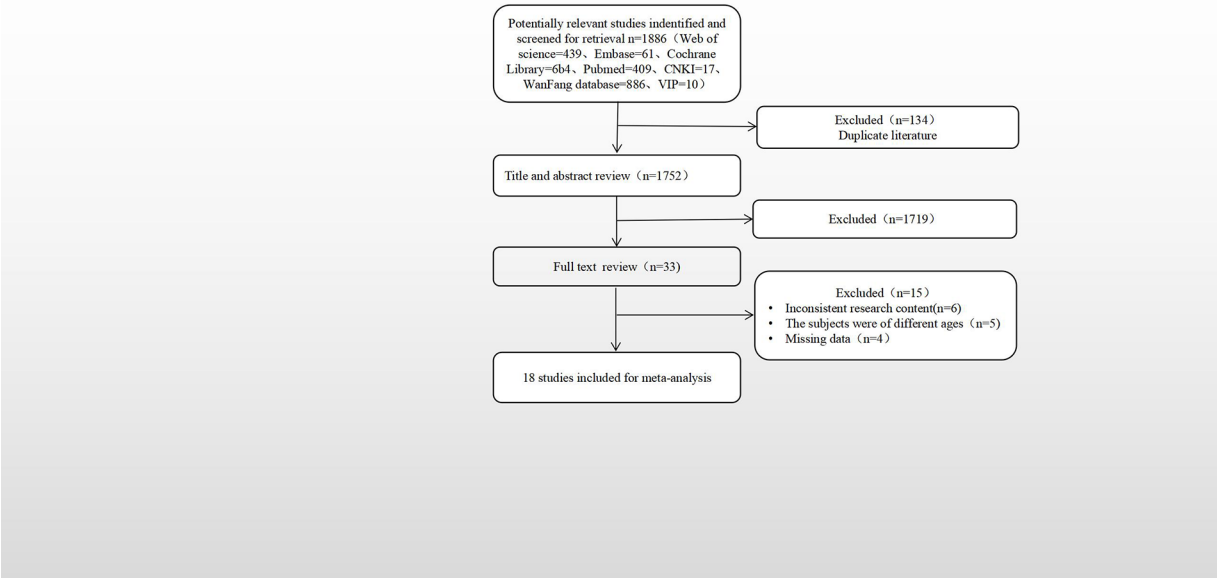

FIGURE 1
Flow diagram for the selection of included articles.

Quality assessment

Table 2 shows the results of the methodological quality evaluation. The scores of quality evaluation of 18 studies were all above 7 points.

Meta- analyses

Nine studies reported that the age of children was related to postoperative LCOS in children with CHD, among them, seven studies had the same data type, and meta analysis showed that there was heterogeneity between the results (I^2: 93%, $P <$ 0.0001). Sensitivity analysis, 3 articles causing heterogeneity were excluded, and the remaining 4 articles did not have heterogeneity (OR = 1.88, 95% CI: 1.63,2.16; $P < 0.001$, Figure 2); Three studies reported the effect of the type of CHD on the incidence of LCOS, and there was no heterogeneity between the results (OR = 3.47, 95% CI:2.16,5.58; $P < 0.001$; Figure 3); Two studies reported that re-cardiac surgery was associated with postoperative LCOS of CHD (OR = 2.18, 95% CI:1.32,3.60; $P = 0.002$, Figure 4); Two studies reported that preoperative blood oxygen saturation was associated with postoperative LCOS of CHD, and there was no heterogeneity between the results. However, the level of blood oxygen saturation before the operation were not significant (OR = −1.28, 95% CI:-2.64,0.08; $P = 0.06$, Figure 5); Two studies reported that the presence of biventricular shunt before operation was associated with postoperative LCOS of CHD (OR = 2.43, 95% CI:1.48,4.01; $P = 0.0005$, Figure 6); Ten studies reported that CPB duration was related to postoperative LCOS in children with CHD. Among them, six studies had the same data type and meta analysis showed that there was heterogeneity between the results (I^2: 83%, $P <$ 0.0001). Sensitivity analysis, 2 articles causing heterogeneity were excluded, and the remaining 4 articles did not have heterogeneity. Fixed effect model was used for analysis. It was concluded that CPB duration was the influencing factor of postoperative LCOS in children with CHD (MD = 27.99, 95% CI:19.49,36.50; $P = 0.00001$, Figure 7). The results of the other two studies reported the relationship between the duration of CPB > 120 min and postoperative LCOS in children with CHD, using fixed effect model for combined analysis, it was concluded that the duration of CPB > 120 min was the influencing factor of postoperative LCOS in children with CHD (OR = 2.82, 95% CI:1.53,5,22; $P = 0.0009$, Figure 8); Three studies reported the effect of ACC duration on the occurrence of LCOS, and there was no heterogeneity between the results (MD = 13.95, 95% CI:9.12,18.78; $P < 0.00001$, Figure 9); Three studies reported the effect of postoperative residual shunt on the occurrence of LCOS, and there was no heterogeneity among the results. Using fixed effect model for combined analysis, it was concluded that postoperative residual shunt was a risk factor for postoperative LCOS of CHD (OR = 1.89, 95% CI:1.24,2.89; $P < 0.001$, Figure 10); Two studies reported the correlation between the level of 2 h cTn-1 > 14 ng/ml after CPB and the occurrence of LCOS after CHD (OR = 4.69 95% CI:2.07,10.63; $P < 0.001$, Figure 11); Two studies reported that postoperative 24 h MR-ProADM >

TABLE 1 Characteristics of the included studies.

	Authors	Year	Country	Study period	Participants	Type of the study design	Sample size (number of LCOS cases)	Age ($\bar{x} \pm s$) (Days OR Years OR Month)		Main findings
								LCOS	No LCOS	
1	Song et al. (9)	2021	China	2019.01-2020.10	Children (<14) with CHD.	Retrospective	283 (35)	3.1 ± 2.6 (Y)	6.9 ± 5.2 (Y)	Age ≤ 4y, preoperative oxygen saturation ≤93%, biventricular shunt before operation, duration of CPB ≥ 60 min,the postoperative residual shunt was the independent risk factor of LCOS in patients with CHD.
2	Drennan et al. (12)	2021	USA	2017.06-2018.12	Children with CHD born ≥36 weeks gestational age, with a birth weight greater than 2.5 kg, and less than 6 months old.	Prospective	26 (11)	20.2 ± 22.5 (D)	21.4 ± 34.0 (D)	The duration of aortic cross clam (ACC) and, the level of postoperative IL-8 were independent risk factors of LCOS in patients with CHD.
3	Iliopoulos et al. (10)	2020	USA	2015.07	Children with CHD (<17 were admitted to ICU after cardiac surgery.	Prospective	47 (6)	NA	NA	In children after congenital heart surgery, their preoperative neutrophil-lymphocyte ratio was associated with a higher chance of low cardiac output in the postoperative period.
4	Du et al. (11)	2020	China	2014.01-2017.12	Children with CHD (<18 y) after cardiac surgery.	Retrospective	8,660 (864)	272.5 ± 307.1 (D)	501.4 ± 569.8 (D)	Age, tricuspid regurgitation, Risk Adjustment in Congenital Heart Surgery-1 risk grade, aortic shunt, atrial shunt, ventricular level shunt, postoperative residual shunt, left ventricular outflow tract obstruction, right ventricular outflow tract obstruction, circulating temperature, duration of CPB, myocardial preservation using histidine-tryptophan-ketoglutarate, and mitral insufficiency were independent risk predictors of LCOS in patients with CHD.
5	Xiang et al. (13)	2020	China	2012.01-2018.12	Children with CHD (≤14y)who underwent correction of intracardiac malformation under CPB.	Retrospective	476 (45)	3.1 ± 4.3 (Y)	6.9 ± 6.2 (Y)	Age, biventricular shunt before operation and cardiac reoperation, ACC duration, and postoperative residual shunt were independent risk factors for LCOS after CHD in children.

(*continued*)

TABLE 1 Continued

	Authors	Year	Country	Study period	Participants	Type of the study design	Sample size (number of LCOS cases)	Age ($\bar{x} \pm s$) (Days OR Years OR Month)		Main findings
								LCOS	No LCOS	
6	Mao et al. (14)	2020	China	2014.01-2018.01	Children with CHD (<18 y) need total anomalous pulmonary venous connection.	Retrospective	153 (50)	3.00 ± 3.1 (M)	6.41 ± 7.5 (M)	The preoperative left ventricular end-diastolic diameter and preoperative oxygen saturation were protective factors for LCOS after TAPVC, while the CPB duration was an independent risk predictor of LCOS.
7	Dai et al. (15)	2020	China	2017.04-2018.03	Children with CHD (<18 y) were admitted to PICU after CPB.	Prospective	70 (22)	52.56 ± 26.9 (M)	79.78 ± 39.7 (M)	The level of cTn-1 at 2 h after CPB and the oxygen saturation at 12 h after CPB were independent risk factors of LCOS.
8	Murni et al. (16)	2019	Canada	2014.04-2015.03	Children with CHD (<18 y) were admitted to CICU after CPB.	Prospective	257 (51)	NA	NA	Predictors of LCOS were cyanotic CHD, longer duration of CPB, high inotropes, and an increase in lactate >0.75 mmol/l/h or more in the first 24 h.
9	Perez-Naveroet al. (17)	2019	Spain	NA	Children with CHD (<18 y) were admitted to PICU after CPB.	Prospective	115 (33)	NA	NA	Age, duration of CPB, VIS score, The level of cTn-1 at 2 h after CPB, and the level of MR-ProADM at 24 h after CPB were independent risk predictors of LCOS.
10	Sobieraj et al. (18)	2018	Poland	2006-2012	Children with CHD (<18 y) after CPB.	Retrospective	1,129 (399)	NA	NA	Age, duration of CPB, presence of specific CHDs, cardiac reoperation, the urgency of operation, operation time, and crystalloid cardioplegia were independent risk predictors of LCOS.
11	Pérez-Navarro et al. (19)	2017	Spain	NA	Children with CHD (<18 y) were admitted to PICU after CPB.	Prospective	117 (33)	NA	NA	The level of cTn-1 at 2 h after CPB and the level of MR-ProADM at 24 h after CPB were independent risk predictors of LCOS.
12	Wang et al. (20)	2014	China	2011.01-2014.07	Children (<18 y) with CCHD.	Prospective	60 (15)	5.6 ± 2.1 (M)	7.5 ± 2.3 (M)	Age, duration of CPB, BNP before the operation, and BNP 6 h after the operation are independent predictors of LCOS.

(*continued*)

TABLE 1 Continued

	Authors	Year	Country	Study period	Participants	Type of the study design	Sample size (number of LCOS cases)	Age ($\bar{x} \pm s$) (Days OR Years OR Month)		Main findings
								LCOS	No LCOS	
13	Zhou et al. (21)	2011	China	2001.01-2010.12	Children with (<18 y) Tetralogy of Fallot.	Prospective	191 (20)	6.75 ± 1.3 (M)	14.35 ± 4.6 (M)	Age ≤ 6 months, Nakata index < 140mm^2/m^2, perioperative accident, and the duration of CPB > 150 min were the risk factors of LCOS after radical resection of TOF in children.
14	Yang (22)	2009	China	2008.05-2008.07	Children with CHD (<18 y) after CPB.	Prospective	22 (5)	NA	NA	The level of NT-proBNP before CPB was an independent risk predictor of LCOS.
15	Wang et al. (23)	2008	China	2004.01-2007.12	Children with CHD (<18 y) after CPB.	Retrospective	310 (21)	NA	NA	Age, the duration of CPB, type of CHD, and cardiac function before CPB were independent factors of LCOS.
16	Song et al. (24)	2008	China	NA	Children with complex CHD (<18 y) undergoing radical surgery	Prospective	64 (30)	9.8 ± 11.3 (M)	18.3 ± 21.5 (M)	Age, body weight, preoperative pulmonary hypertension, risk Adjustment for Congenital Heart Surgery, ACC duration, CPB duration, and high systemic and pulmonary vascular resistance after operation were the risk of LCOS.
17	Carmona et al. (25)	2008	USA	2017.06-2018.11	Infants younger than 6 months with CHD.	Prospective	46 (29)	7.23 ± 14.0 (M)	8.78 ± 12.9 (M)	The level of NT-proBNP before CPB and the level of postoperative IL-8 were independent risk predictors of LCOS.
18	Zhu et al. (26)	2007	China	2000.01-2005.12	Low birth weight children with CHD.	Retrospective	22 (12)	NA	NA	NA

1.5 nmol/L was associated with postoperative LCOS in CHD (OR = 10.14, 95% CI:4.41,23.32; $P < 0.001$, **Figure 12**).

Discussion

This review collected 18 studies that reported the risk factors of LCOS after cardiac surgery and identified nine risk factors including age, type of CHD, cardiac reoperation, biventricular shunt before operation, CPB duration, ACC duration, postoperative residual shunt, cTn-1 level 2 h after CPB > 14 ng/ml and postoperative 24 h MR-ProADM level > 1.5 nmol/L.

A total of nine studies reported that age was related to postoperative LCOS in children with CHD. Four articles reported that age was related to postoperative LCOS in children with CHD without heterogeneity were analyzed by fixed effect model, and it was concluded that age was the influencing factor of postoperative LCOS in children with CHD. The results of the included articles all showed that younger children with CHD had a higher risk of developing LCOS. However, according to the results of the study, we are unable to determine the specific age of the child is more useful for clinical early warning. Moreover, few studies have stratified the age of the children, and the age nodes of the stratification are different, some are four years old (9), some

TABLE 2 Included study quality evaluation.

Study	Quality evaluation (points)			NOS total score
	Selection	Selection of the non-exposed cohort	Exposure or outcome	
Song (2021)	4	2	2	8
Drennan (2021)	4	1	3	8
Iliopoulos (2020)	3	2	2	7
Du (2020)	4	2	2	8
Xiang (2020)	4	2	2	8
Mao (2020)	4	2	2	8
Dai (2020)	4	2	3	9
Murni (2019)	4	1	2	7
Perez-Navero (2019)	4	2	3	9
Sobieraj (2018)	4	1	2	7
Pérez-Navero (2017)	4	2	3	9
Wang (2014)	4	1	2	7
Zhou (2011)	4	2	1	7
Yang (2009)	4	2	3	9
Wang (2008)	3	1	3	7
Song (2008)	4	1	3	8
Carmona (2008)	4	2	3	9
Zhu (2007)	3	1	2	7

are six months (21). More studies are needed to explore the relationship between different age stratification and postoperative LCOS in children with congenital heart disease.

Re-cardiac surgery mainly occurs in complex intracardiac malformations that need to be corrected by stages and residual or secondary lesions need to be further corrected. Jacobs (27) according to the data of the Society of Thoracic Surgeons Congenital Heart Database (STSCHD database), the operation situation of CHD children in North America from 2007 to 2011 was about 1/3 for re-operation, and the incidence of LCOS is significantly increased after re-operation.

We found that the longer the CPB duration, the higher the risk of postoperative LCOS in children with CHD, but which node the CPB duration exceeds has more early warning effect on the clinic. This study can not draw a conclusion. four of the included studies divided CPB duration nodes, two studies (16) were divided by CPB duration > 120 min, and one study (9) was divided by CPB duration > 60 min. Another item (23) divides the CPB duration into < 50 min, 50~100 min, 100~150 min, and > 150 min. More research is needed to find the duration of CPB that can be used as an early warning for clinical practice.

During aortic occlusion, the heart is in a state of inhibition, ischemia, and hypoxia (28). After the opening of the aorta, myocardial reperfusion induces systemic inflammation and endothelial cell activation, resulting in intracellular oxygen free radicals and calcium overload, resulting in cardiomyocyte injury and affecting the systolic and diastolic function of the heart (29). Drennan (12) found that children with ACC duration > 45 min have a higher risk of developing LCOS after operation, but the sample size of this study is smaller, and larger sample size studies are needed to prove this point.

The postoperative residual shunt is a common postoperative complication in children with CHD, with an incidence of 5~25% (30, 31). Postoperative residual shunt mainly occurred in children with intracardiac malformations with severe pulmonary hypertension (17), most of these children were in a serious condition and had a poor basic cardiac function (32). Hemodynamic abnormalities caused by residual shunts can also aggravate the myocardial injury and eventually lead to LCOS.

The level of cTn-I increases rapidly after cardiac injury, which could be used as a predictor of cardiac biomarkers in patients with coronary heart disease after cardiac surgery (33).

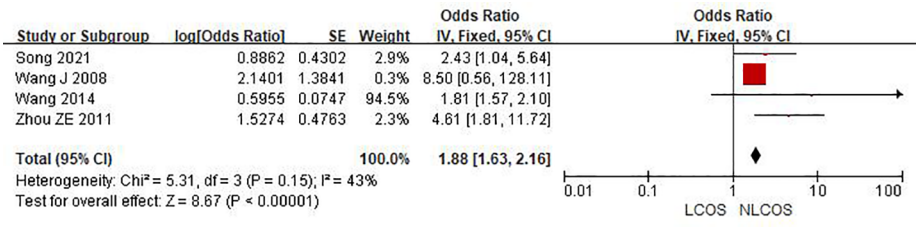

FIGURE 2
Age of children in forest plot.

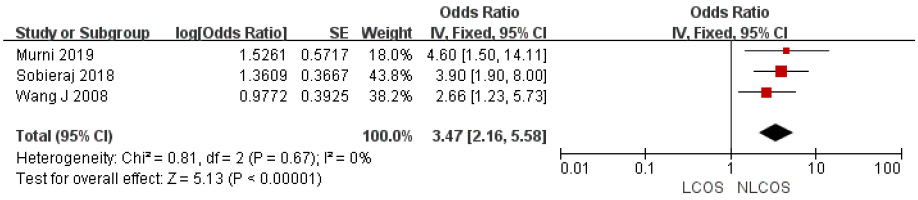

FIGURE 3
Types of congenital heart disease forest plot.

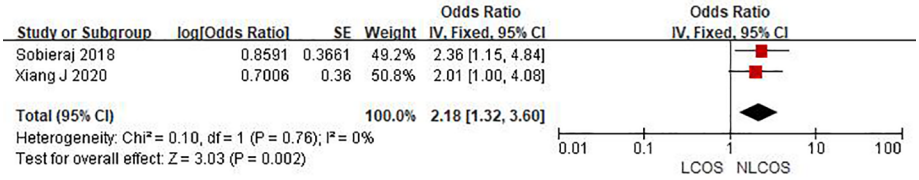

FIGURE 4
History of a cardiac surgery forest plot.

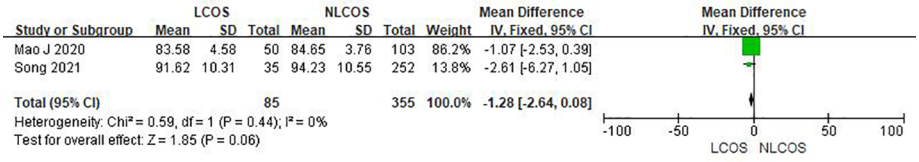

FIGURE 5
Preoperative oxygen saturation forest plot.

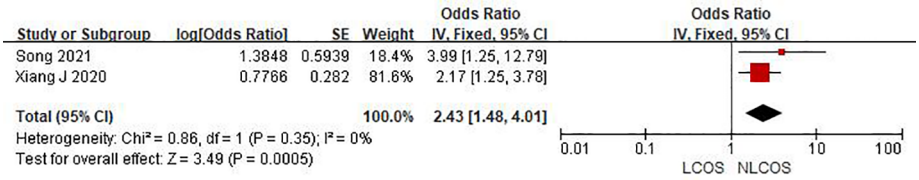

FIGURE 6
Biventricular shunt before operation forest plot.

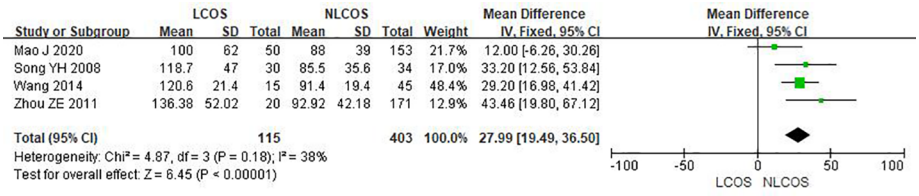

FIGURE 7
Duration of CPB forest plot.

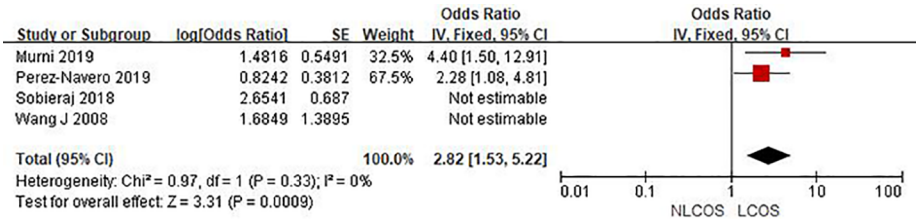

FIGURE 8
CPB duration forest plot.

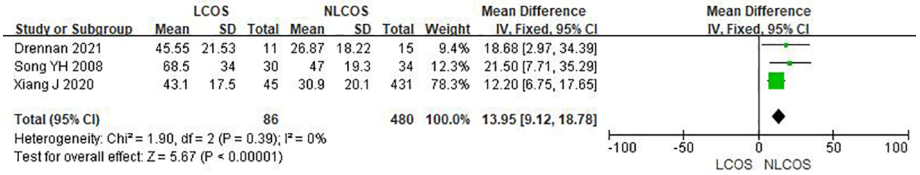

FIGURE 9
ACC duration forest plot.

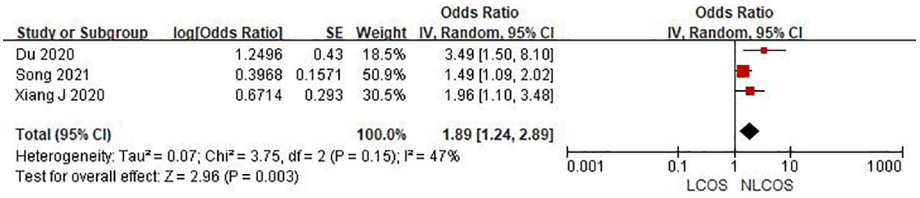

FIGURE 10
Postoperative residual shunt forest plot.

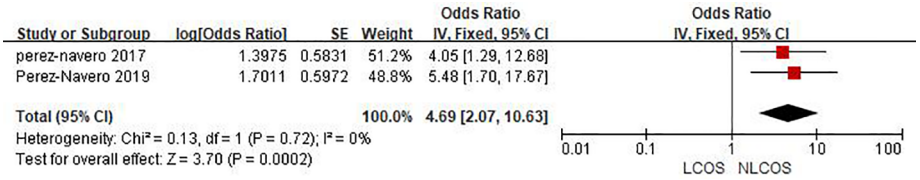

FIGURE 11
CTn-1 level 2 hours after CPB forest plot.

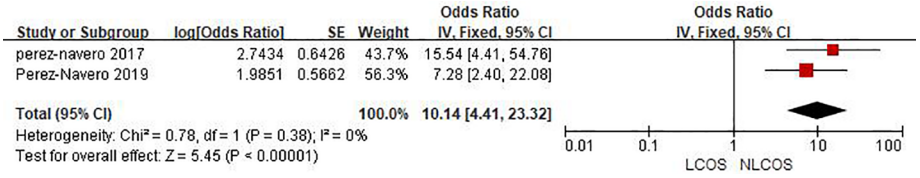

FIGURE 12
Postoperative 24h MR-ProADM level forest plot.

Bojan (34) describe that early increases in cTn-I levels may help predict the course of disease in newborns and infants after heart surgery. Many studies have shown that MR-proADM alone or in combination with other indicators can predict LCOS in children with CPB (35, 36).

At present, it has been agreed that LCOS is a risk factor for poor prognosis after cardiac surgery (37). Through strict monitoring of cardiac output indicators, early diagnosis of LCOS and early identification the causes can help to reduce mortality, and improve the prognosis. Therefore, the timing of the operation should be strictly grasped according to the disease and age of the children. When physicians communicate with family members whose children are at high risk of LCOS, the risk factors should be emphasized to help family members adjust their expectations on the operation and prognosis, which may avoid the miscommunication between professionals and patients as well as their caregivers. Operation should be carefully conducted to reduce the residual shunt and avoide a second operation. Physicians should constantly improve their surgical techniques to shorten the aortic cross-clamping time as much as possible, and to improve the perioperative management and identification of LCOS.

Strengthes and limitations

This systematic review includes not only articles published in English, but also articles published in Chinese as many as possible. To our best knowledge, it has covered all the relevent studies on the risk factors of postoperative LCOS of CHD that we could found in both domestic and international databases. In addition, the meta-analysis of this study used sensitivity analysis to explore the sources of heterogeneity on the basis of heterogeneity test, and calculated the comprehensive effects after excluding the heterogeneity study, which increased the reliability of results.

However, there are still several limitations warranting for attention. First, there are great differences in the sample size and age distribution of patients in each study, which may lead to the dispersion and heterogeneity of the included survey results. Second, there are many scattered influencing factors included in the literature report, On the other hand, there are few articles on some influencing factors, so it is suggested that a large sample multicenter study should be carried out in the future to further explore the incidence and risk factors of postoperative LCOS in patients with congenital heart disease.

Conclusion

A total of 1,886 records were screened, of which 18 were included in the final review. We have identified 9 risk factors were found in the systematic review. Meta-analysis demonstrated that age, type of CHD, reoperation, biventricular shunt before the operation, CPB time, ACC time, postoperative residual shunt, cTn-1 level 2 h after CPB > 14 ng/ml and postoperative 24 h MR-ProADM level > 1.5 nmol/l were independent risk factors of LCOS. Efforts can be made on the modifiable factors when developing early interventions to reduce the incidence of LCOS, and eventually to improve the quality of life of children and their caregivers.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Author contributions

WPY and FCC proposed the idea and designed the whole research plan. WPY and CLB conducted the database search and extracted the data. WPY, FCC, CLB, TXM, JCD, JHC and BGN performed the data analysis and prepared the figures and the tables. WPY and FCC wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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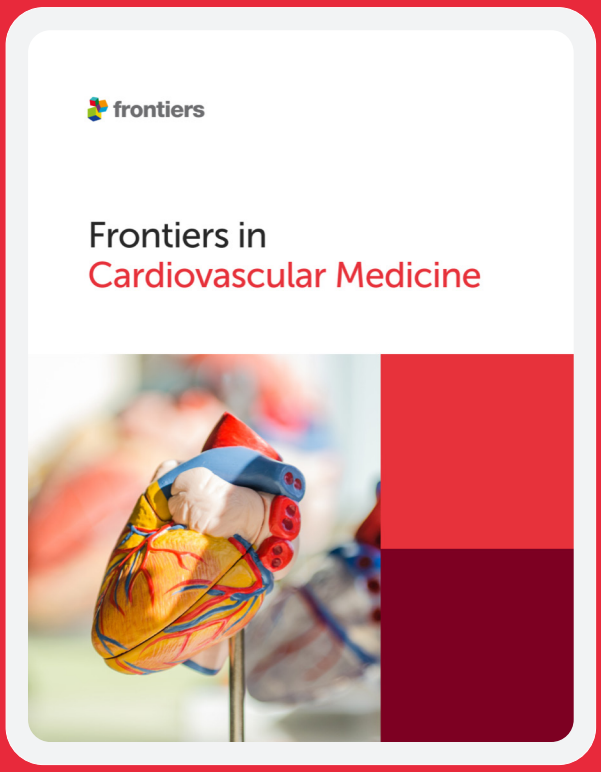

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