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Women in pediatric cardiology 2021

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Women in pediatric cardiology 2021

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Table of contents

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Editorial: Women in pediatric cardiology 2021

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Editorial on the Research Topic
Women in pediatric cardiology 2021

Throughout the history of pediatric cardiology, multiple outstanding contributions have led to where this subspeciality stands today. In this editorial, we aim to review some of the extraordinary work of exceptional women in the field of congenital heart diseases and to collect current works led or performed by women in different fields of pediatric cardiology. In the early 30s, *Helen Taussig*- often referred as the mother of pediatric cardiology- established one of the first clinics for children with congenital heart defects and one of the first training programs for residents in pediatric cardiology in the United States (1). Her study on the "blue babies" and her idea on how to reconstruct a duct to relieve cyanosis in children with pulmonary valve atresia or critical stenosis led to the Blalock- Thomas-Taussig shunt, which, though modified, is still in use today. Two early fellows of Helen Taussig, *Mary Allen Engle* and *Ruth Whittemore*, also left an outstanding contribution by further establishing training programs in pediatric cardiology at Cornell and Yale Universities and being instrumental in the establishment of Pediatric Cardiology as a subspecialty at the America Academy of pediatrics (2). Dr. Whittemore was the recipient of the American Academy of Pediatrics Founders Award in 1995 for her study on the heritability in congenital heart diseases. In the early thirties, *Maude Abbott*, a Canadian pathologist, also published her "Atlas of Congenital Heart Disease" (3). Abbott's seminal work became crucial during the advent and progression of cardiac surgery.

With the development of new diagnostic techniques and new therapeutic options, survival of children with complex heart diseases increased tremendously; it became clear that congenital heart diseases required continuous follow-up into adulthood and that it was no longer a specialty dedicated to children. In 1975, *Jane Sommerville* established in London one of the first clinics for adults with congenital heart diseases worldwide. This initiative led to the birth of the Adult Congenital Heart Disease (ACHD) subspecialty (2), which is currently a recognized subgroup of the European Society of Cardiology (ESC). In addition to these great women, women like *Carolyn McCun*, *Jaqueline Noonan*, *Lynn Mahony*, or *Jane Newburger* have, in more recent years, made a great contribution to the field of pediatric cardiology. Writing about all of them would require a dedicated editorial.

With the increasing numbers of women in medical school and pediatric (cardiology) residency, the contribution to the field by women is rapidly increasing. Despite these high numbers of female students, the percentage tapers rapidly when looking at positions of higher responsibility. Women are still underrepresented in research and on editorial boards. As an example, a recent publication in JACC showed that only 19% of editorial board members among pediatric cardiology journals were

women and all editors-in-chief were men (4). The causes of this discrepancy are multiple and fall beyond the scope of this editorial. This issue deserves a topic in itself.

In this special edition of Frontiers in Pediatric Cardiology, we collect current works led or performed by women in different fields of pediatric cardiology. It represents a glimpse of the latest not-yet-published work led by women in this field, although cannot reflect the vast amount of worldwide work performed by female researchers in pediatric cardiology.

Heart failure and myocardial disease

Al Wakeel-Marquard et al show that an increased extracellular volume might be a non-invasive tissue marker of heart failure in patients with (congenitally corrected) transposition of the great arteries and systemic right ventricle. Although this study is limited by the amount of included patients ($N = 13$ and mild reduction of ventricular function- LVEF $51 \pm 2\%$), it can trigger further study which can lead to the development of specific therapies to prevent heart failure in these patients.

Seidel et al. show in their manuscript that children with biopsy-proven myocarditis and lower levels of anti-β2-adrenergic receptor antibody, in comparison to the median, had a worse cardiovascular prognosis and less-event free survival. This finding requires further research but might help identify a group of children who might benefit from immunoglobulin therapy.

In their manuscript, *Thom et al.* identified that 72% of children with SARS-CoV2-associated multisystemic inflammatory syndrome present myocarditis with a good response to treatment with immunoglobulins and steroids.

Brunet-García et al, described for the first time that almost 90% of patients with congenital myotonic dystrophy type I present ECG anomalies, of which the most common are conduction disorders. Almost 2% of the patients in their cohort needed a pacemaker due to syncope in the context of progressive conduction disease and 7% of their patients died without a clear cause of death. This study highlights the importance of appropriate follow-up of arrhythmia and merits further study.

Exercise physiology

Two of the studies included in this series focused on physical activity in Fontan patients and in patients affected by primary hypertension.

Callegari et al. show that only 18% of patients with Fontan circulation achieve the recommended 60 min/day moderate to vigorous physical activity. Physical activity, however, is positively correlated with physical well-being and mental health. Furthermore, it seemed to have a positive effect on sleep and behavior in this group of patients.

Zhang et al. describe impaired exercise capacity in children with primary arterial hypertension. Factors associated with decreased exercise capacity were female sex, younger age, greater BMI, and higher 24 h average diastolic blood pressure.

These studies suggest that appropriate training programs for adolescents with Fontan circulation or primary arterial hypertension might improve their physical performance and quality of life.

Neurodevelopmental

The manuscripts of *Girch et al.* and Pfitzer et al. explore psychosocial and neurodevelopmental aspects of congenital heart diseases. Early hospitalization and interventions in children with congenital heart diseases are a source of stress which might influence their neurodevelopment. Family-centered care (FCC) has shown to reduce stress and improve healthy development in premature infants. The German EMPHATIC-30 questionnaire was previously used to evaluate FCC at neonatology and intensive care units. In Girch et al. the authors evaluate, for the first time, the psychometric properties of this questionnaire in children with congenital heart diseases.

Pfitzer et al. show that head circumference more than body weight and length might predict neurologic development and psychiatric problems in children with congenital heart diseases. Routine follow-up neurologic examination should be offered to all those children with congenital heart disease and especially to those at higher risk.

Maternal and fetal outcome

In the manuscript of *Erba et al.* the authors describe maternal and fetal outcome in a large cohort ($N = 307$) of women with mechanical valves during pregnancy in Sudan. Due to the high cost of low Molecular weight heparin and the difficulty of regular measurement of anti-Xa levels, women with mechanical valves in Sudan are kept under an oral anticoagulant, warfarin, during pregnancy. Out of 307 pregnancies, only 47.6% had good maternal and neonatal outcomes. As a comparison, data from the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC) showed that 58% of the pregnancies included in the registry were uncomplicated (5).

Seidl-Mlczoch et al. focus on the outcome of fetuses with heterotaxy. Both left and right heterotaxia are associated with complex congenital heart defects and extracardiac problems. Termination of pregnancy rates are approximately 25% for both right and left isomerism. Postnatal survival is lower in those children presenting with right in comparison to left heterotaxy (46% vs. 67% at 5 years). This study confirms previous knowledge and helps prenatal counselling of fetuses with heterotaxy.

This special edition of Frontiers in pediatric cardiology collects a snapshot of the work led by female researchers in pediatric cardiology around the world. It shows the wide range of scientific fields, from myocardial and exercise physiology to neurodevelopmental and maternal and fetal outcome, which are covered by female scientists.

Author contributions

LM-M has made a substantial contribution to the concept and design of the editorial and has approved the final version.

SN has made a substantial contribution to the concept and design of the editorial and has approved the final 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.

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References

1. Neubauer K, Murphy AM. Helen brooke taussig: pediatric cardiology leader and innovator. *Adv Pediatr*. (2013) 60:1–9. doi: 10.1016/j.yapd.2013.04.003

2. Noonan JA. A history of pediatric specialties: the development of pediatric cardiology. *Pediatr Res*. (2004) 56:298–306. doi: 10.1203/01.PDR.0000132662.73362.96

3. Abbots M. Dr. Maude abbott's Atlas of congenital cardiac disease. *Can Med Assoc J*. (1936) 34(2):194–5. PMID: 20320168; PMCID: PMC1561408

4. Dunne E, Zuhlke L, Krishna Kumar R, Casey FA, Penny DJ, McMahon CJ. Editorial board composition among pediatric cardiology journals. *JACC Adv*. (2022) 1:1–8. doi: 10.1016/j.jacadv.2022.100137

5. van Hagen IM, Roos-Hesselink JW, Ruys TPE, Merz WM, Goland S, et al.. Pregnancy in women with a mechanical heart valve: data of the european society of cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation*. (2015) 132(2): 132–42. doi: 10.1161/CIRCULATIONAHA.115.015242

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ORIGINAL RESEARCH
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Compensatory Upregulation of Anti-Beta-Adrenergic Receptor Antibody Levels Might Prevent Heart Failure Presentation in Pediatric Myocarditis

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Background: Myocarditis can be associated with severe heart failure and is caused by different inflammatory and autoimmune responses. The aim of this study was to describe the immunological response in children with myocarditis by analyzing anti-beta-adrenergic receptor antibodies (anti-β-AR Abs).

Methods: Sera of children who were hospitalized with biopsy-proven myocarditis were prospectively collected between April 2017 and March 2019. Anti-β1-AR Ab, anti-β2-AR Ab, and anti-β3-AR Ab were quantified by a CE-certified ELISA kit. According to normal values for immunoglobulin G (IgG), three age groups, <1, 1–5, and >5–17 years, were defined. Children without inflammatory cardiac pathology and no heart failure signs were served as a control group.

Results: We compared 22 patients with biopsy-proven myocarditis and 28 controls. The median age (interquartile range) of the myocarditis group (MYC) was 12.1 (2.7–16.4) years, 13 men, left ventricular ejection fraction (LVEF) 51% and for control group, the median age was 5.0 (3.0–6.8) years, nine men, LVEF 64%. Myocarditis patients in the age group >5–17 years showed significantly higher anti-β3-AR Ab levels as compared to controls ($p = 0.014$). Lower anti-β2-AR Ab and anti-β3-AR Ab levels were significantly correlated with higher left ventricular diameters in myocarditis patients. The event-free survival using a combined endpoint (mechanical circulatory support [MCS], transplantation, and/or death) was significantly lower in myocarditis patients with antibody levels below the median as compared to myocarditis patients with antibody levels ≥ the median.

Conclusion: Anti-β-AR Ab levels are increased in children with myocarditis and >5 years of age. These antibodies might be upregulated compensatory to prevent further cardiac deterioration. A worse event-free survival in patients with lower anti-β-AR Ab levels might be a therapeutic target for immunoglobulin substitution.

Keywords: anti-beta-adrenergic receptor antibodies, myocarditis, autoimmune, pediatric, endomyocardial biopsy

INTRODUCTION

Myocarditis is an inflammatory disease of the myocardium that is caused by various different triggers (1). In children, it is one major cause of the development of acute or chronic heart failure (2). One of the most striking findings in pediatric patients with myocarditis is the high prevalence of heart failure with severely reduced systolic function in patients under 1 year of age (3, 4). This specific cohort often experiences adverse events, such as the need for mechanical circulatory support (MCS) or heart transplantation (HTx) and death, whereas adolescents mostly present with preserved or mild impaired left ventricular ejection fraction (LVEF) and angina pectoris (4, 5). At the same time, studies on the therapeutic use of immunoglobulins have failed to show any positive effects in adults and adolescents but showed encouraging effects in young children (6). Both findings might be related to the fact that the immunological activities, such as immunoglobulin production, only reach a mature state at the age of >5 years (7). Focusing on anti-beta-adrenergic receptor antibodies (anti-β-AR Ab), levels have been described as increased in patients with myocarditis and dilated cardiomyopathy (DCM) and are associated with heart failure and arrhythmogenic events (8–10). In children with DCM and poor clinical outcomes, high anti-β1-AR Ab levels were described (11). However, a multicenter study in children with myocarditis could not verify this for anti-β1- and anti-β2-AR Ab (12). In adults with an ST-elevation myocardial infarct (STEMI), lowered anti-β1-AR Ab levels led to higher rates of re-infarction and cardiovascular death pointing toward a possible protective effect of these antibodies (13). Referring to these divergent results, the impact of anti-β-AR Ab remains not fully understood, especially in children.

The aim of this study was to analyze anti-β-AR Ab levels in pediatric patients with biopsy-proven myocarditis and pediatric controls to gain knowledge on their distribution in the different age groups and their impact on the outcome.

Abbreviations: Anti-β-AR Ab, anti-beta-adrenergic receptor antibodies; ASD, atrial septal defect; CRP, C-reactive protein; CTRL, control group; DCM, dilated cardiomyopathy; DNA, Deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; EMB, endomyocardial biopsy; HTx, heart transplantation; IgG, immunoglobulin G; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diastolic diameter; MCS, mechanical circulatory support; MYC, myocarditis group; NT-proBNP, N-terminal-pro brain natriuretic peptide; PDA, persistent ductus arteriosus; STEMI, ST-elevation myocardial infarct; RNA, Ribonucleic acid; (RT)-PCR, (real-time)-polymerase chain reaction.

MATERIALS AND METHODS

Patient Data and Follow-Up

Sera from patients under 18 years of age with suspected myocarditis and enrollment within the MYKKE registry between April 2017 and March 2019 were collected at the Pediatric Cardiology Departments of the German Heart Center Berlin and the Charité - Universitätsmedizin Berlin, Berlin, Germany. The study was approved by the institutional ethics committee (Charité - Universitätsmedizin Berlin, EA2/131/10, EA2/074/13). All parents or guardians of patients <18 years gave written informed consent.

Serum was collected at the time of admission, centrifuged at 20°C and 3,800 g for 10 min, and frozen at −80°C. Clinical parameters, diagnostic cardiac imaging, and endomyocardial biopsy (EMB) were assessed routinely. Initial clinical and follow-up data were entered into the online MYKKE study database (4). Patients without EMB or not proven myocarditis in EMB were excluded from further analyses.

Patients with proof of myocarditis in EMB were called the myocarditis group (MYC). Patients under 18 years of age, administered for elective cardiac catheterization, and without inflammatory cardiac pathology served were as a control group (CTRL). See the study flow chart for further details (**Figure 1**).

Regarding outcomes, the occurrence of adverse events, such as MCS, HTx, and/or all-cause death, was defined as a combined endpoint.

Detection of Anti-β-Adrenergic Antibodies

Anti-β1-AR Ab, anti-β2-AR Ab, and anti-β3-AR Ab were measured with commercially available enzyme-linked immunosorbent assays (ELISA; CellTrend GmbH, Luckenwalde, Germany) according to the instructions of the manufacturer (14). All these assays provided native receptors presented in their physiological membrane environment as immunogenic targets of immunoglobulin G (IgG) binding.

Analysis of Endomyocardial Biopsies

All EMB specimens were analyzed histopathologically and immunohistologically and by polymerase chain reaction [(RT-)PCR] for myocardial detection of viral RNA/DNA by one specialized center for Cardiopathology (Institute for Pathology and Neuropathology, University Hospital Tübingen, Tübingen, Germany) as previously described (15).

The diagnosis of myocarditis was confirmed according to the established criteria and grouped in accordance with the WHO definition in (16, 17):

(a) Acute myocarditis: Infiltrate of ≥14 leucocytes/mm² and presence of myocyte damage.

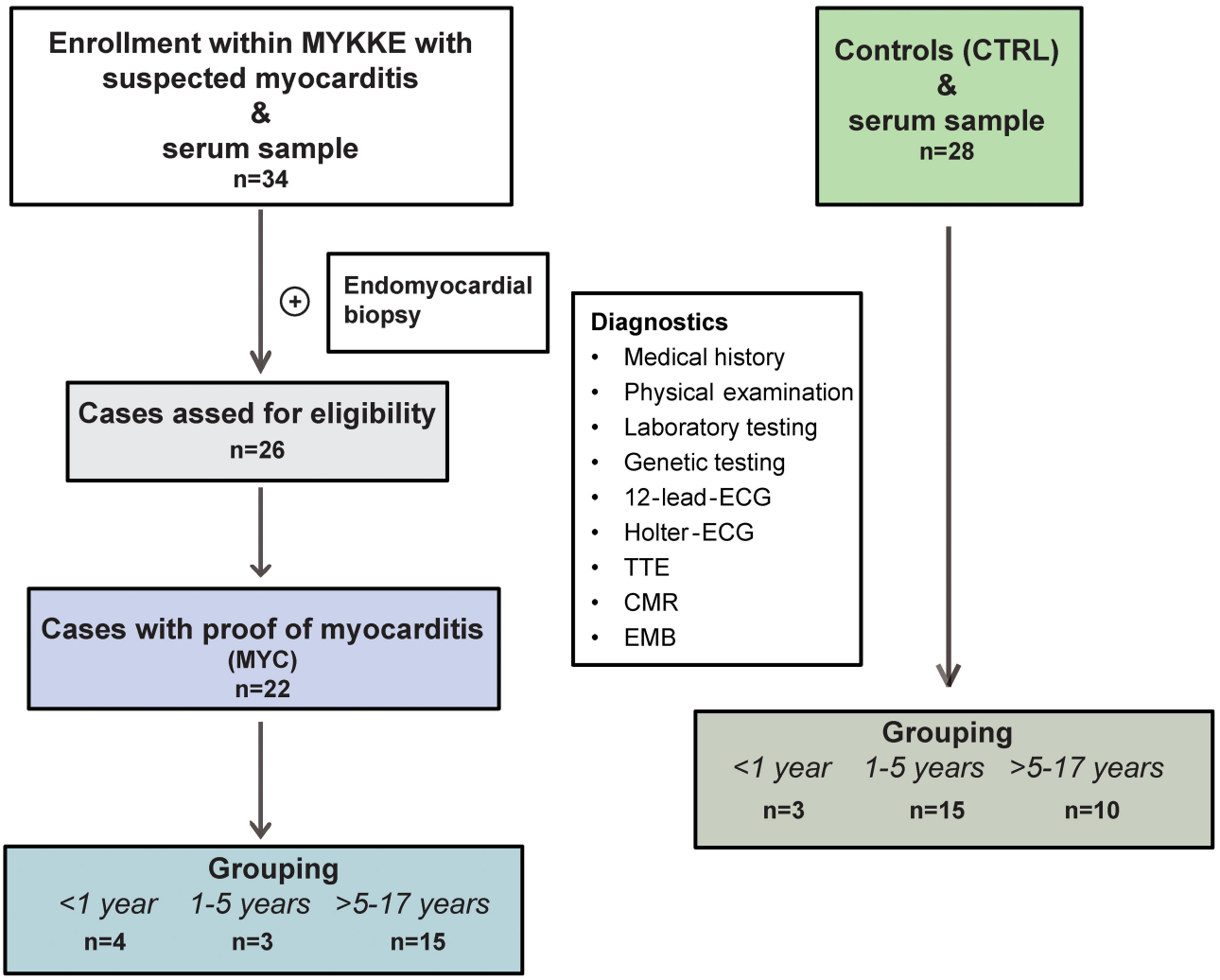

FIGURE 1 | Study flow chart. Selection of enrolled patients within the MYKKE registry depends on sera withdrawal and the proof of myocarditis in the endomyocardial biopsy. Four cases diagnosed with dilated cardiomyopathy in EMB could not be included in the final analysis. Grouping was conducted according to normal values for immunoglobulin G into three age groups. CMR, cardiac magnetic resonance; ECG, electrocardiogram; EMB, endomyocardial biopsy; TTE, transthoracic echocardiography.

(b) Healing/chronic myocarditis: Infiltrate of ≥14 leucocytes/mm² and absence of myocyte damage but the presence of fibrosis.

(c) Healed myocarditis: Multifocal fibrosis or scarring without inflammation (0–3 leucocytes/mm²).

Statistical Analysis

Categorical variables were summarized by frequencies and percentages. For continuous measures, data were presented as median values with interquartile range (IQR). Pearson's chi-square test and Fisher's exact test were used to compare dichotomous variables. For comparison of independent groups, the Mann-Whitney U and Kruskal-Wallis test were applied. For correlation of antibody levels and laboratory and clinical parameters, Spearman's rho test was used. Kaplan-Meier curves and log-rank tests were employed for survival analysis. Therefore, the groups < median and ≥ median were built according to the median anti-β-AR Ab levels of the MYC. A probability value of <0.05 was considered statistically significant. Data were analyzed using IBM Corp. SPSS Version 24.0 (Armonk, NY, USA).

RESULTS

Basic Characteristics

We enrolled 22 patients with biopsy-proven myocarditis and median age (IQR) of 12.1 (2.7–16.4) years, 13 were men (MYC). Twenty-eight patients served as controls with a median age of 5.0 (3.0–6.8) years, 9 were men (CTRL).

The control group was administered due to the following diagnoses: atrial septal defect (ASD; $n = 19$), persistent ductus arteriosus (PDA; $n = 6$), a combination of ASD and PDA ($n = 1$), aortic isthmus stenosis ($n = 1$), and mild pulmonary

TABLE 1 | Basic characteristics of the myocarditis (MYC) and control group (CTRL).

	MYC group $n = 22$	CTRL group $n = 28$	p-Value
Gender, male	13 (59)	9 (32)	0.086
Age (years)	12.1 (2.7–16.4)	5.0 (3.0–6.8)	**0.042**
BSA (kg/m²)	1.6 (0.6–1.8)	0.8 (0.6–1.2)	0.063
Echocardiography			
Z-score LVIDd (mm)	1.9 (0.1–5.3)	−0.8 (−1.6–0.4)	**<0.001**
LVEF (%)	51.0 (28.0–60.0)	63.5 (57.8–72.3)	**<0.001**
Antibody levels			
Anti-β1-AR Ab (U/ml)	7.7 (3.8–24.3)	5.0 (3.7–8.2)	0.125
Anti-β2-AR Ab (U/ml)	6.0 (2.4–19.9)	3.6 (2.6–4.7)	0.077
Anti-β3-AR Ab (U/ml)	6.4 (2.9–18.8)	3.5 (3.0–6.8)	**0.035**

Values are given as n (%) or median (interquartile range).
Anti-β-AR Ab, anti-beta-adrenergic antibodies; BSA, body surface area; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diastolic diameter. Bold values represents significant values.

valve stenosis ($n = 1$). The MYC had significantly lower LVEF in echocardiography and higher Z-scores of the left ventricular internal diastolic diameter (LVIDd; $p < 0.001$, respectively). Detailed basic characteristics are given **Table 1**.

Basic Characteristics of MYC Patients and Controls Within Age Groups

According to known values for overall IgG and its age-depending distribution in childhood, three age subgroups (<1 year, 1–5 years, and >5–17 years) were defined for both groups (MYC and CTRL, see **Table 2**) (7).

Four patients with myocarditis and three in the control group belonged to the age group < 1 year. The MYC group was presented with a severely reduced LVEF and dilated left ventricles. They were presented with signs of heart failure and a median (IQR) value of N-terminal-pro brain natriuretic peptide (NT-proBNP) of 133,389 (103,375–177,557) ng/l. Troponin Ths was increased with 1,425 ng/l. No pathologies in the blood count or C-reactive protein (CRP) increment were detected. Two had the diagnosis of healing/chronic myocarditis and one of acute myocarditis in EMB. The control group ($n = 3$) was presented with normal LVEF and had no dilated ventricles.

The age group of 1–5 years consisted of 3 MYC patients and 15 controls. Again, patients with MYC showed signs of heart failure with severely reduced LVEF and left ventricular dilatation. The median NT-proBNP was 35,000 ng/l, Troponin Ths was 85 ng/l. Leucocytes, thrombocytes, and hemoglobin were in a normal range. The CRP was slightly increased at 17.0 mg/dl. Two patients with MYC were diagnosed with acute myocarditis in EMB, one with a chronic/healing myocarditis. The controls in the age groups 1–5 years had a normal LVIDd and LVEF.

Fifteen patients with myocarditis and a median age of 15.6 (11.9–16.9) years belonged to the age group >5–17 years, 12 were men. All had biopsy-proven lymphocytic myocarditis: 12 reported chronic/healing myocarditis, 2 with acute, and 1 with healed myocarditis (see **Table 2**). They presented with a median Z-score of the LVIDd of 0.5 (−0.4 to 2.4) and an LVEF of 57.0 (50.0–61.0)% (18). NT-proBNP was increased at 577.0 (175.8–1885.8) ng/l and Troponin Ths with 672.0 (523.5–1427.0) ng/l. Leucocytes, thrombocytes, and hemoglobin were in a normal range, whereas CRP was increased with 37.6 (1.4–137.0) mg/l. Ten patients served as a control group with a median age of 10.5 (6.0–17.0) years, 5 were men.

The myocarditis patients in the age group >5−7 years did not differ significantly in LVEF and Z-scores of the LVIDd as compared to controls (see **Table 2**; $p = 0.071$, respectively).

Further, MYC patients with Anti-β3-AR Ab level ≥10 U/ml had a significantly lower Z-Score of LVIDd than MYC patients with Anti-β3-AR Ab <10 U/ml [−0.1 (−1.4 to 0.5) vs. 2.3 (0.2–3.5); $p = 0.036$]. There was no significant difference in age, body surface area, sex, LVEF, NT-proBNP, the combined endpoint, or the diagnosis in the EMB.

Antibody Levels Within Age Groups

The comparison of anti-β-AR Ab levels between myocarditis patients and controls within the first two age groups (<1 year and 1–5 years) did not differ significantly. Patients >5 years of age showed significantly higher anti-β3-AR Ab levels as compared to controls ($p = 0.014$; see **Table 2**). The distribution of the different anti-β-AR Ab levels over age are shown in **Figure 2**.

Correlations of Antibody Levels and Clinical Parameters

Lower anti-β2-AR Ab and anti-β3-AR Ab levels were significantly correlated with increased Z-score of the LVIDd in patients with MYC across all ages (β2: $p = 0.029$; β3: $p = 0.045$, see **Figure 3**). An inverse correlation was detected between anti-β2-AR Ab levels and NT-proBNP ($p = 0.034$, see **Figure 3**). No significant correlations between anti-β-AR Ab levels and other inflammatory laboratory parameters were found in the myocarditis patients.

Impact of Antibody Levels on the Combined Endpoint

Seven out of 22 myocarditis patients reached the combined endpoint of MCS, HTx, or death. All seven patients needed MCS, three were transplanted. No patient had died. Four patients were belonged to the age group <1 year, two to the age group 1–5 years, and one was in the age group >5–17 years.

Five out of 11 patients with anti-β-AR Ab levels under the median reached the combined endpoint. Patients with antibody levels ≥ median experienced less adverse events, only 2 out of 11 patients ($p = 0.361$). The event-free survival using the combined endpoint of MCS, HTx, or death was significantly lower in MYC patients with anti-β-AR Ab levels below the median as compared to myocarditis patients with anti-β-AR Ab levels ≥ median (anti-β1/2/3-AR Ab: $p = 0.049$; **Figure 4**).

DISCUSSION

In this study, we investigated the anti-β-AR Ab levels in pediatric patients with biopsy-proven myocarditis according to different age groups and related outcomes.

TABLE 2 | Anti-beta-adrenergic antibody levels and echocardiographic parameters of controls (CTRL) and myocarditis (MYC) patients in different age groups.

	Age group <1 year			Age group 1–5 years			Age group >5–17 years		
	MYC group $n = 4$	CTRL group $n = 3$	*p*-value	MYC group $n = 3$	CTRL group $n = 15$	*p*-value	MYC group $n = 15$	CTRL group $n = 10$	*p*-value
Gender, male	0 (0)	1 (33)	0.429	3 (100)	5 (33)	0.069	12 (71)	5 (28)	0.111
Age (years)	0.4 (0.2–0.7)	0.0*	0.057	3.2*	4.0 (3.0–5.0)	0.426	15.6 (11.9–16.9)	10.5 (6.0–17.0)	**0.015**
Echocardiography									
Z-score LVIDd (mm)	6.0 (1.5–7.9)	−1.0*	0.057	6.2*	−0.7 (−1.6-0.3)	**0.005**	0.5 (−0.4–2.4)	−1.1 (-3.1–0.9)	0.071
LVEF (%)	25.5 (14.3–36.8)	72.0*	0.057	22.0*	65.0 (57.5–73.0)	**0.004**	57.0 (50.0–61.0)	59.5 (57.0–68.5)	0.071
Antibody levels									
Anti-β1-AR Ab (U/ml)	3.6 (1.0–13.2)	1.9*	0.857	8.3*	5.5 (4.3–10.8)	0.498	8.2 (4.5–29.8)	4.5 (3.8–6.3)	0.071
Anti-β2-AR Ab (U/ml)	1.7 (0.7–6.1)	2.7*	0.629	6.6*	3.6 (2.6–5.5)	0.130	6.2 (2.9–22.7)	3.8 (2.6–4.5)	0.080
Anti-β3-AR Ab (U/ml)	1.2 (1.0–5.8)	4.5*	0.400	7.2*	3.5 (3.0–5.3)	0.076	6.6 (3.4–19.4)	3.3 (2.4–4.5)	**0.014**
EMB									
Acute myocarditis	1 (25)	n.a.		2 (67)	n.a.		2 (13)	n.a.	
Chronic/healing myocarditis	3 (75)	n.a.		1 (33)	n.a.		12 (80)	n.a.	
Healed myocarditis	0 (0)	n.a.		0 (0)	n.a.		1 (7)	n.a.	

*EMB, endomyocardial biopsy; MYC, patients with biopsy proven inflammatory myocardial disease; CTRL, patients without inflammatory myocardial disease. Values are given as n (%) or median (interquartile range). *Only median. Anti-β-AR Ab, anti-beta-adrenergic antibodies; BSA, body surface area; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diastolic diameter. Bold values represents significant values. n.a.; not applicable.*

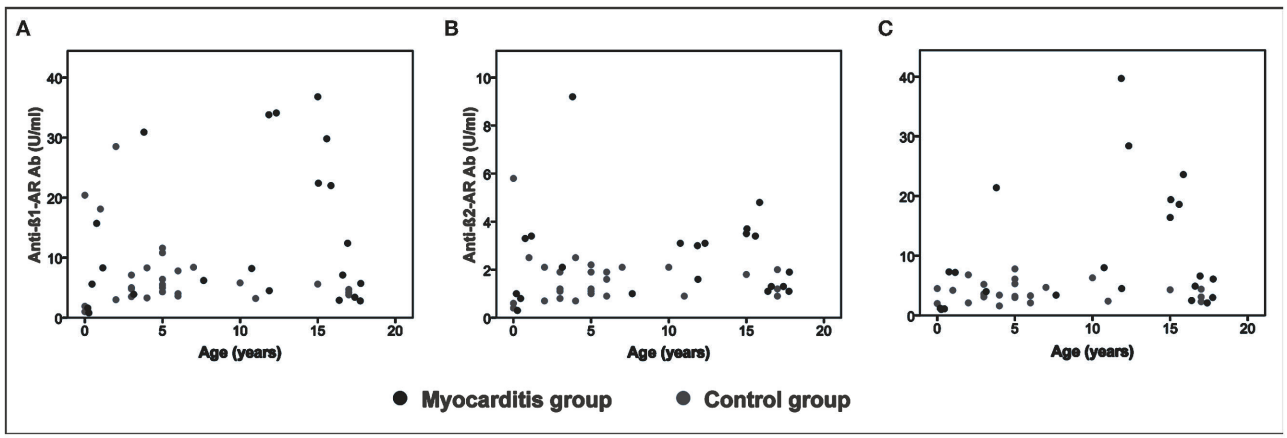

FIGURE 2 | Antibodies over age. Distribution of anti-β-adrenergic antibodies (anti-β-AR Ab) over age for the myocarditis group (dark gray dots) and controls (light gray dots). **(A)** anti-β1-AR Ab. **(B)** anti-β2-AR Ab. **(C)** anti-β3-AR Ab.

We could detect anti-β-AR Ab in all pediatric myocarditis patients and controls, which underlines their pre-existence also in healthy or in patients without heart failure (19, 20). In the age group >5 years, anti-β3-AR Ab levels were significantly increased in patients with MYC as compared to CTRL. Throughout all age groups, anti-ß-AR Ab levels were consistently higher in patients with MYC as compared to CTRL, supporting the thesis of antibody increment in heart failure (21). However, the comparisons did not reach statistical significance in most age groups, this may be due to the small sample sizes. These results are in conflict with the ones of Simpson et al., where they did not find increased anti-β-AR Ab levels in children with myocarditis. An explanation could be that they did not group their cohort according to age, which might have been resulted in a non-significant difference in the whole cohort as compared to controls (12).

A possible mechanism in older myocarditis patients with higher anti-ß-AR Ab levels might be an innate Ab upregulation with an agonistic effect on the beta-adrenergic receptors in order to overcome cardiac dysfunction triggered by the myocardial inflammation. The initial upregulation might represent a normal immunological response rather than an autoimmunity process resulting in lower receptor expression and receptor desensitization and finally chronic heart failure (22–24). This could be supported by the fact that after ventricular assist implantation, anti-β1-AR Abs were undetectable in patients with DCM and increased anti-β1-AR Ab before implantation (25).

Our data cannot absolutely support the thesis of a protective effect of these antibodies described in other studies, but we found higher levels in the myocarditis age group of >5–17 years, which presented with less severe adverse events and better LVEF as compared to the other MYC age groups (19, 26). On the other

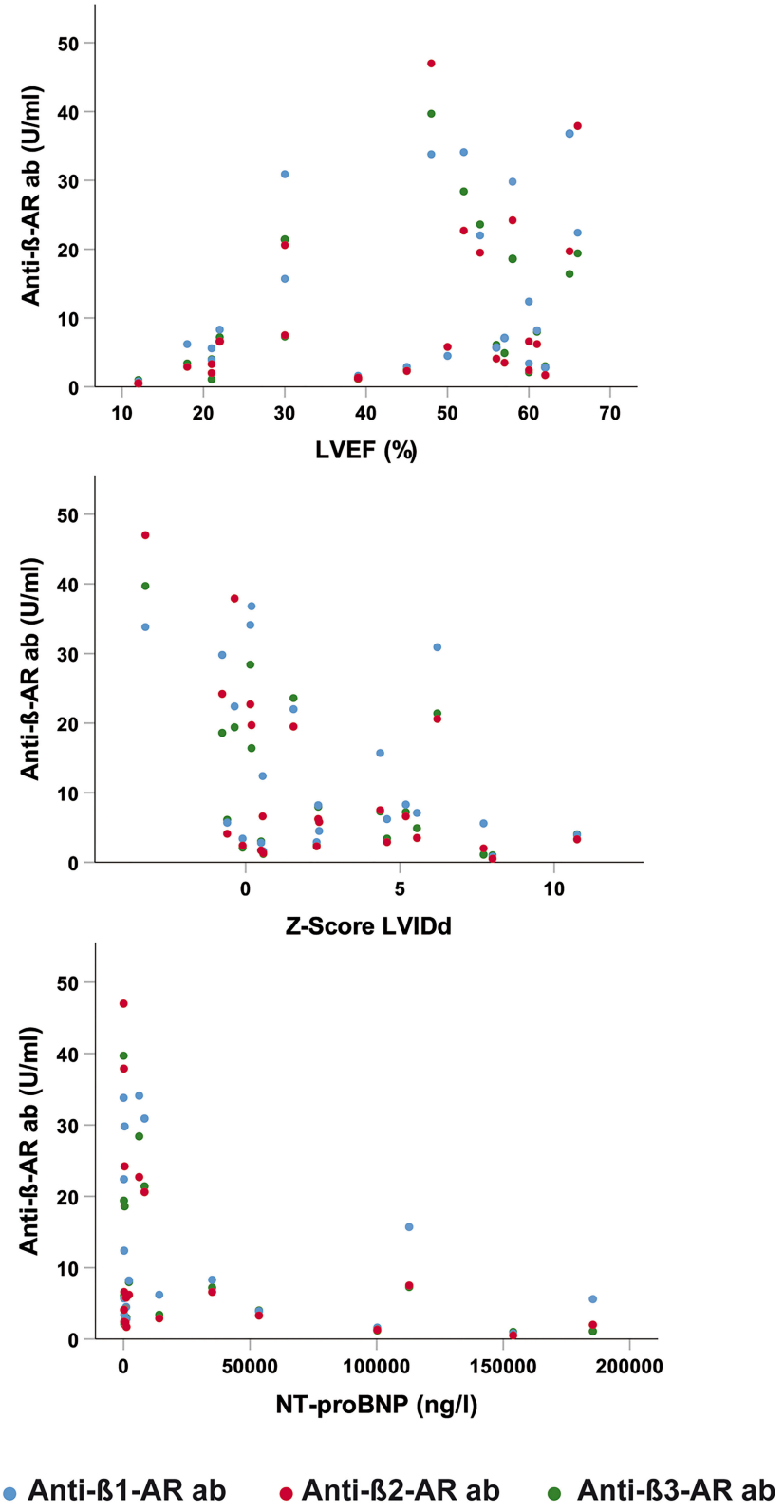

FIGURE 3 | Correlation of anti-β-AR ab levels and clinical parameters. (Upper) Correlation of anti-β-AR ab levels and left ventricular ejection fraction (LVEF). (Middle) Correlation of anti-β-AR ab levels and Z-score of the left ventricular internal diastolic diameter (LVIDd). (Lower) Correlation of anti-β-AR ab levels and N-terminal-pro brain natriuretic peptide (NT-proBNP). Blue dots: anti-β1-AR ab. Red dots: anti-β2-AR ab. Green dots: anti-β3-AR ab.

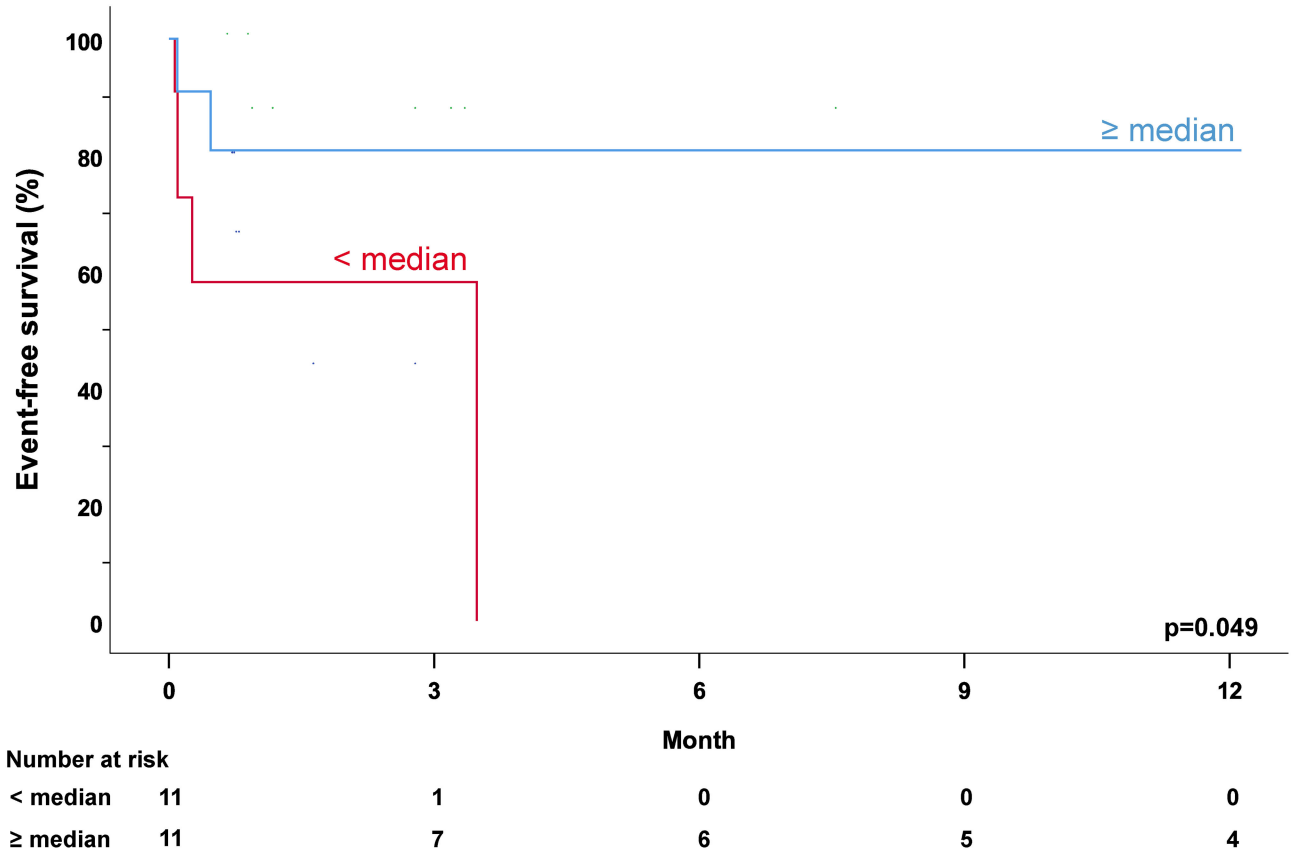

FIGURE 4 | Anti-β1-adrenergic antibody levels and outcome across all age groups. Combined endpoint of mechanical circulatory support, heart transplantation, and/or death of myocarditis patients with regard to the median of anti-β1-adrenergic antibody (anti-β1-AR Ab) levels following hospital admission. Patients with anti-β1-AR Ab levels below the median (red) showed a lower event-free survival compared to patients with anti-β1-AR Ab levels ≥ median (blue; $p = 0.049$).

end, the lowest antibody levels and worst disease courses with severely reduced left ventricular function were seen in patients <1 year of age. In this age group, the absence of a specific anti-β-AR Ab upregulation might be explained by inherently low overall IgG levels at this age. Therapeutic substitution of immunoglobulins might help to promote an immune response that resembles that of subjects with mature immune systems when applied early in this age group (2).

CONCLUSION

There are age-dependent different anti-β-AR Ab levels in children with biopsy-proven myocarditis and controls. In myocarditis patients >5 years of age, anti-β3-AR Ab levels are significantly increased as compared to controls which might rather be compensatory to trigger a receptor agonistic effect than primarily upregulated as they do not present with severe heart failure. Especially children <5 years with lower anti-β-AR Ab levels experience more often adverse events, which might be a missing compensatory effect due to lower innate IgG levels and a potential therapeutic target for immunoglobulin substitution.

Limitations

We analyzed, especially in the young age groups, a small number of patients and controls group. The size of these groups does not allow for drawing conclusions on the effects of anti-β-AR Ab on their outcome. Moreover, the children with myocarditis in the age group >5–17 years were older than the controls in this group. Additionally, even there was no myocardial inflammation or sign of heart failure, all controls had a simple isolated congenital heart defect, which could also have an influence on anti-β-AR Ab levels.

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 Ethics Committee Charité - Universitätsmedizin Berlin (EA2/131/10, EA2/074/13). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FS, DM, and SS put down the concept and designed the study. FS analyzed the datasets, did the statistical analysis, wrote the initial draft, and finalized the article. CS helped design the study, analyze the datasets, and reviewed the manuscript draft. HH helped design the study, performed the measurements, analyze the dataset, and reviewed the manuscript draft. BO-R enrolled patients and reviewed the manuscript draft. TP was responsible for the ethics approval and biobanking. KK analyzed the biopsies. KK, FB, DM, and SS have reviewed, critically revised the initial, and final drafts of the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. (2013) 34:2636–48, 48a—48d. doi: 10.1093/eurheartj/eht210
2. Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A, et al. Update on myocarditis. *J Am Coll Cardiol.* (2012) 59:779–92. doi: 10.1016/j.jacc.2011.09.074
3. Butts RJ, Boyle GJ, Deshpande SR, Gambetta K, Knecht KR, Prada-Ruiz CA, et al. Characteristics of clinically diagnosed pediatric myocarditis in a contemporary multi-center cohort. *Pediatr Cardiol.* (2017) 38:1175–82. doi: 10.1007/s00246-017-1638-1
4. Messroghli DR, Pickardt T, Fischer M, Opgen-Rhein B, Papakostas K, Bocker D, et al. Toward evidence-based diagnosis of myocarditis in children and adolescents: Rationale, design, and first baseline data of MYKKE, a multicenter registry and study platform. *Am Heart J.* (2017) 187:133–44. doi: 10.1016/j.ahj.2017.02.027
5. Schubert S, Opgen-Rhein B, Boehne M, Weigelt A, Wagner R, Muller G, et al. Severe heart failure and the need for mechanical circulatory support and heart transplantation in pediatric patients with myocarditis: results from the prospective multicenter registry "MYKKE". *Pediatr Transplant.* (2019) 23:e13548. doi: 10.1111/petr.13548
6. Huang X, Sun Y, Su G, Li Y, Shuai X. Intravenous immunoglobulin therapy for acute myocarditis in children and adults. *Int Heart J.* (2019) 60:359–65. doi: 10.1536/ihj.18-299
7. Schur PH, Rosen F, Norman ME. Immunoglobulin subclasses in normal children. *Pediatr Res.* (1979) 13:181–3. doi: 10.1203/00006450-197903000-00010
8. Bornholz B, Roggenbuck D, Jahns R, Boege F. Diagnostic and therapeutic aspects of beta1-adrenergic receptor autoantibodies in human heart disease. *Autoimmun Rev.* (2014) 13:954–62. doi: 10.1016/j.autrev.2014.08.021
9. Dorner A, Kallwellis-Opara A, Pauschinger M, Kuhl U, Schultheiss HP. Cardiac autoantibodies in viral myocarditis. *Heart Fail Clin.* (2005) 1:333–43. doi: 10.1016/j.hfc.2005.06.010
10. Nussinovitch U, Shoenfeld Y. The clinical significance of anti-beta-1 adrenergic receptor autoantibodies in cardiac disease. *Clin Rev Allergy Immunol.* (2013) 44:75–83. doi: 10.1007/s12016-010-8228-9
11. Camino M, Morales MD. Beta1-adrenergic receptor antibodies in children with dilated cardiomyopathy. *Front Biosci (Elite Ed).* (2019) 11:102–8. doi: 10.2741/e849
12. Simpson KE, Cunningham MW, Lee CK, Ward K, Tong A, Danon S, et al. Autoimmunity against the heart and cardiac myosin in children with myocarditis. *J Card Fail.* (2016) 22:520–8. doi: 10.1016/j.cardfail.2016.02.009
13. Ernst D, Westerbergh J, Sogkas G, Jablonka A, Ahrenstorf G, Schmidt RE, et al. Lowered anti-beta1 adrenergic receptor antibody concentrations may have prognostic significance in acute coronary syndrome. *Sci Rep.* (2019) 9:14552. doi: 10.1038/s41598-019-51125-9
14. Scherbaum I, Heidecke H, Bunte K, Peters U, Beikler T, Boege F. Autoantibodies against M5-muscarinic and beta1-adrenergic receptors in periodontitis patients. *Aging (Albany NY).* (2020) 12:16609–20. doi: 10.18632/aging.103864
15. Degener F, Salameh A, Manuylova T, Pickardt T, Kostelka M, Daehnert I, et al. First paediatric cohort for the evaluation of inflammation in endomyocardial biopsies derived from congenital heart surgery. *Int J Cardiol.* (2020) 303:36–40. doi: 10.1016/j.ijcard.2019.10.006
16. Maisch B, Portig I, Ristic A, Hufnagel G, Pankuweit S. Definition of inflammatory cardiomyopathy (myocarditis): on the way to consensus. A status report. *Herz.* (2000) 25:200–9. doi: 10.1007/s000590050007
17. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. *Circulation.* (1996) 93:841–2. doi: 10.1161/01.CIR.93.5.841
18. Kampmann C, Wiethoff CM, Wenzel A, Stolz G, Betancor M, Wippermann CF, et al. Normal values of M mode echocardiographic measurements of more than 2000 healthy infants and children in central Europe. *Heart.* (2000) 83:667–72. doi: 10.1136/heart.83.6.667
19. Cabral-Marques O, Marques A, Giil LM, De Vito R, Rademacher J, Gunther J, et al. GPCR-specific autoantibody signatures are associated with physiological and pathological immune homeostasis. *Nat Commun.* (2018) 9:5224. doi: 10.1038/s41467-018-07598-9
20. Liu HR, Zhao RR, Zhi JM, Wu BW, Fu ML. Screening of serum autoantibodies to cardiac beta1-adrenoceptors and M2-muscarinic acetylcholine receptors in 408 healthy subjects of varying ages. *Autoimmunity.* (1999) 29:43–51. doi: 10.3109/08916939908995971
21. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation.* (2006) 113:1807–16. doi: 10.1161/CIRCULATIONAHA.106.174287

22. Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WS, Lurie K, et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. *N Engl J Med.* (1982) 307:205–11. doi: 10.1056/NEJM198207223070401
23. Lohse MJ. Molecular mechanisms of membrane receptor desensitization. *Biochim Biophys Acta.* (1993) 1179:171–88. doi: 10.1016/0167-4889(93)90139-G
24. Magnusson Y, Wallukat G, Waagstein F, Hjalmarson A, Hoebeke J. Autoimmunity in idiopathic dilated cardiomyopathy. Characterization of antibodies against the beta 1-adrenoceptor with positive chronotropic effect. *Circulation.* (1994) 89:2760–7. doi: 10.1161/01.CIR.89.6.2760
25. Dandel M, Weng Y, Siniawski H, Potapov E, Drews T, Lehmkuhl HB, et al. Prediction of cardiac stability after weaning from left ventricular assist devices in patients with idiopathic dilated cardiomyopathy. *Circulation.* (2008) 118(14 Suppl):S94–105. doi: 10.1161/CIRCULATIONAHA.107.755983
26. Nagatomo Y, Li D, Kirsop J, Borowski A, Thakur A, Tang WH. Autoantibodies specifically against beta1 adrenergic receptors and adverse clinical outcome in patients with chronic systolic heart failure in the beta-blocker era: the importance of immunoglobulin G3 subclass. *J Card Fail.* (2016) 22:417–22. doi: 10.1016/j.cardfail.2016.03.005

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Factors Affecting the Exercise Capacity in Pediatric Primary Hypertension

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Purpose: Exercise training is crucial to the early intervention of pediatric primary hypertension (PHT). However, much less is known about exercise capacity in this disease. This work investigated the exercise capacity in pediatric PHT and analyzed the factors affecting exercise capacity.

Methods: The study enrolled children with PHT at the Children's Hospital Capital Institute of Pediatrics between July 2017 and July 2020. The Bruce protocol of the treadmill exercise test (TET) was used to assess exercise capacity. Multivariate ordinal logistic regression and generalized linear models were used to analyze factors affecting exercise capacity.

Results: Of 190 patients, 146 (76.8%) were male, and the median age was 13 (11, 14). Most children accomplished TET and achieved the submaximal heart rates (189 [99.5%]). Children with lower resting diastolic blood pressure (DBP) and 24 h average diastolic blood pressure (ADBP) could achieve a TET stage of 6 or more, whereas children with higher DBP and ADBP could only achieve a TET stage of 3 (P all < 0.05). Children with lower DBP and 24 h ADBP were also associated with greater metabolic equivalents (METs; $r = -0.237$, $r = -0.179$, P all < 0.05). The completion of TET stages was negatively associated with female (OR = 0.163), younger age (OR = 1.198), greater body mass index (BMI, OR = 0.921), and higher 24 h ADBP (OR = 0.952, P all<0.05). In addition, METs were negatively associated with female ($\beta = -1.909$), younger age ($\beta = 0.282$), greater BMI ($\beta = -0.134$), and higher 24 h ADBP ($\beta = -0.063$, P all < 0.05).

Conclusions: Exercise capacity was impaired among pediatric PHT patients. Female gender, younger age, greater BMI, and higher 24 h ADBP are independently associated with the exercise capacity in pediatric PHT. These findings may help developing scientific exercise prescriptions for pediatric PHT.

Keywords: primary hypertension, children, treadmill exercise test, exercise capacity, cardiology, pediatrics

1. INTRODUCTION

Hypertension, as a major risk factor for cardiac events and kidney diseases, is surprisingly common in pediatric population. A recent study established that the overall prevalence of hypertension in children and adolescents aged 0–18 years is 3–5% (1). Historically, the most prevalent form of hypertension in childhood used to be secondary hypertension. This situation has changed within the last two decades. PHT is now the dominant cause of hypertension in children above 6, especially in adolescents (2). Although the exact prevalence of pediatric PHT remains unknown, some studies showed that PHT accounted for 43% of pediatric hypertension in the US and 21.2–78% of cases in China (2–4). Childhood hypertension is likely to pose long-term damage, increasing the prevalence and severity of hypertension in adulthood (5). Therefore, active control of childhood PHT is far-reaching. Exercise intervention is a primary treatment for pediatric PHT (6, 7). So far, no validated exercise prescription is available in children with PHT, so this is a high unmet need. However, the development of exercise prescriptions is hampered by limited knowledge of exercise capacity in pediatric PHT.

Treadmill exercise test (TET) is a non-invasive test frequently used to measure exercise capacity by regulating the exercise load of participants with the alteration of treadmill movements (8). The indicators reflecting cardiac function, such as blood pressure (BP), heart rate, exercise stage achieved, and metabolic equivalents (METs), are monitored throughout the test and could be related to patients' exercise capacity.

In this study, we evaluated the exercise capacity in pediatric PHT by TET and identified the factors affecting the exercise capacity in this disease.

2. METHODS

2.1. Patient Population

We conducted a retrospective study of children with PHT at the Children's Hospital Capital Institute of Pediatrics between July 2017 and July 2020. The diagnosis of pediatric PHT was based on the Current Clinical Practice Guideline on Pediatric hypertension in Children and Adolescents Pediatrics (9) and the Chinese Guidelines for the Prevention and Treatment of Hypertension (6). In brief, systolic blood pressure (SBP) and diastolic blood pressure (DBP) should be $\geqslant$ 95th percentile in children with the same age, sex, and height for 3 consecutive records, and 2 weeks' interval is required between each recording. Meanwhile, patients with secondary hypertension were excluded. Hypertension was categorized: for children <13 years of age, stage 1 hypertension was defined as $\geq$95th percentile to < 95th percentile + 12 mmHg (on the basis of age, sex, and height percentiles), or 130/80 to 139/89 mmHg (whichever is lower), and stage 2 hypertension was defined as $\geq$ 95th percentile + 12 mmHg, or $\geq$ 140/90 mmHg (whichever is lower); for children $\geq$ 13 years of age, stage 1 hypertension was defined as 130/80 to 139/89 mmHg, and stage 2 hypertension was defined as $\geq$ 140/90 mmHg (9). Exclusion criteria included patients with severe hypertension (SBP > 200 mm Hg and/or DBP > 120 mm Hg); patients with a lower-extremity injury who could not perform TET; and patients who had used any medication before TET. This study was approved by the Ethics Committee of the Capital Institute of Pediatrics (No. SHERLL2019003). Informed consent was signed by the parents and guardians of all subjects.

2.2. Treadmill Exercise Test

Before testing, the subjects would rest for 15–20 min, during which bodyweight, height, 12-lead ECG, and resting BP were measured. Exercise capacity was then assessed by a graded exercise test on the treadmill (Guangzhou Dimao Information Technology Co. TM-18). The speed and slope of the treadmill sequentially increased to adjust the exercise load volume. The endpoint of the TET was reaching the target heart rate [submaximal target heart rate = (220 - age) × 85%]. To prevent accidents, the test would be terminated immediately if any of the indications for termination happened. Participants were continuously being monitored during the 8-min rest after TET.

Our method followed the Bruce protocol (8, 10) with two minor modifications: the time of each exercise stage was shortened to 1–2 min, and the overall duration of exercise was controlled at 8–11 min. Accordingly, exercise in TET was graded 1–7 (**Table 1**). Higher stages of exercise signify better exercise capacity.

2.3. Assessment of Metabolic Equivalents

Metabolic equivalents were used to describe the exercise stress at the endpoint of TET. One MET is the amount of oxygen consumed by the body while sitting at rest, which is approximately 3.5 mL O^2/kg/min (11). Larger METs values indicate higher intensity of exercise and better exercise capacity (12). The METs was calculated as following:

$$METs = [(\frac{speed}{6.0} + speed \times slope \times \frac{3.0}{1000.0}) \div 3.5 + 1 - last\ second\ METs] \times \frac{j}{120.0} + last\ second\ METs$$

j: total time per stage, time in seconds.

2.4. Assessment of the Cardiac Involvement

Echocardiograms were measured using a Phillips iE33 (Phillips, The Netherlands). Left ventricular end-diastolic diameter, interventricular septal end-diastolic thickness, and left

TABLE 1 | Revised Bruce protocol.

Stages	Speed (km/h)	Slope (%)	Time (min)
1	2.8	10	1–2
2	4.0	12	1–2
3	5.5	14	1–2
4	6.7	16	1–2
5	8.0	18	1–2
6	8.8	20	1–2
7	9.6	22	1–2

TABLE 2 | Comparison of exercise capacity between different hypertension stages.

		Stage 1 PHT ($n = 90$)	Stage 2 PHT ($n = 99$)	*P*	*P'*
Clinical characteristics					
Age (years)		13 (11,14)	13 (11,14)	0.17	-
Sex (male [%])		61 (67.8%)	85 (85.9%)	0.003	-
BMI Mean ± SD(kg/m^2)		25.6 ± 4.5	28.1 ± 4.6	<0.001	-
Exercise capacity					
METs		10.2 (8.3, 11.3)	9.3 (8.2, 11.3)	0.317	0.109
TET stages	3 n (%)	6 (37.5%)	10 (62.5%)	0.419	0.25
	4 n (%)	41 (50.6%)	40 (49.4%)		
	5 n (%)	32 (43.2%)	42 (56.8%)		
	≥ 6 n (%)	11 (61.1%)	7 (38.9%)		

P', P-value after corrected with age, gender, and BMI; PHT, primary hypertension; BMI, body mass index; METs, metabolic equivalents; TET, treadmill exercise test.
Data are presented as median[P_{25},P_{75}], except where otherwise indicated.

TABLE 3 | Comparison of blood pressure value between different TET stages.

		Resting SBP (mmHg)	Resting DBP (mmHg)	ASBP (mmHg)	ADBP (mmHg)
TET stages	3 ($n = 16$)	124 (120, 129)	70 (62, 74)	124 (119, 133)	74 (69, 80)
	4 ($n = 81$)	123 (118, 129)	67 (61, 72)	122 (117, 131)	70 (67, 74)
	5 ($n = 74$)	123 (117, 127)	63 (57, 68)	127 (119, 133)	71 (66, 75)
	≥6 ($n = 18$)	125 (118, 133)	60 (56, 67)#	128 (116, 133)	70 (63, 72)*
P		0.810	0.003	0.342	0.034
P'		0.121	0.012	0.905	0.026

P', P-value after corrected with age, gender, and BMI; SBP, systolic blood pressure; DBP, diastolic blood pressure; ASBP, average systolic blood pressure; ADBP, average diastolic blood pressure.
#The lower resting DBP of patients achieved stage ⩾6 TET compared with that of patients achieved stage 3TET.
**The lower ADBP of patients achieved stage ⩾6 TET compared with that of patients achieved stage 3 TET.*
Data are presented as median[P_{25},P_{75}], except where otherwise indicated.

ventricular posterior wall thickness were measured from the parasternal long-axis view. Left ventricular mass (LVM) was calculated according to the formula recommended by Devereux et al. (13). Left ventricular hypertrophy (LVH) was defined as LVMI ≥ 45g/m$^{2.7}$ in boys, and LVMI ≥ 40 g/m$^{2.7}$ in girls (14).

2.5. Statistical Methods

For the normal continuous variables, the *t*-tests were done to compare two groups; the one-way ANOVA were done to compare multiple groups; and the least significant difference tests were done to compare variables within one group. For the non-normal continuous variables, Wilcoxon rank-sum tests were done to compare two groups; Kruskal–Wallis *H*-tests were used to compare multiple groups; Spearman correlation coefficients analysis was done to analyze the connection between two groups; and partial correlation analysis was done to analyze the connection between two groups when corrected with cofounders. Variables were described as mean ± SD (or median [P_{25}, P_{75}] for non-normal data). If needed, baseline data were compared between different groups to assess for imbalance. Any data that was unbalanced at baseline and associated with the results were included in the partial correlation model and logistic regression model as cofounders.

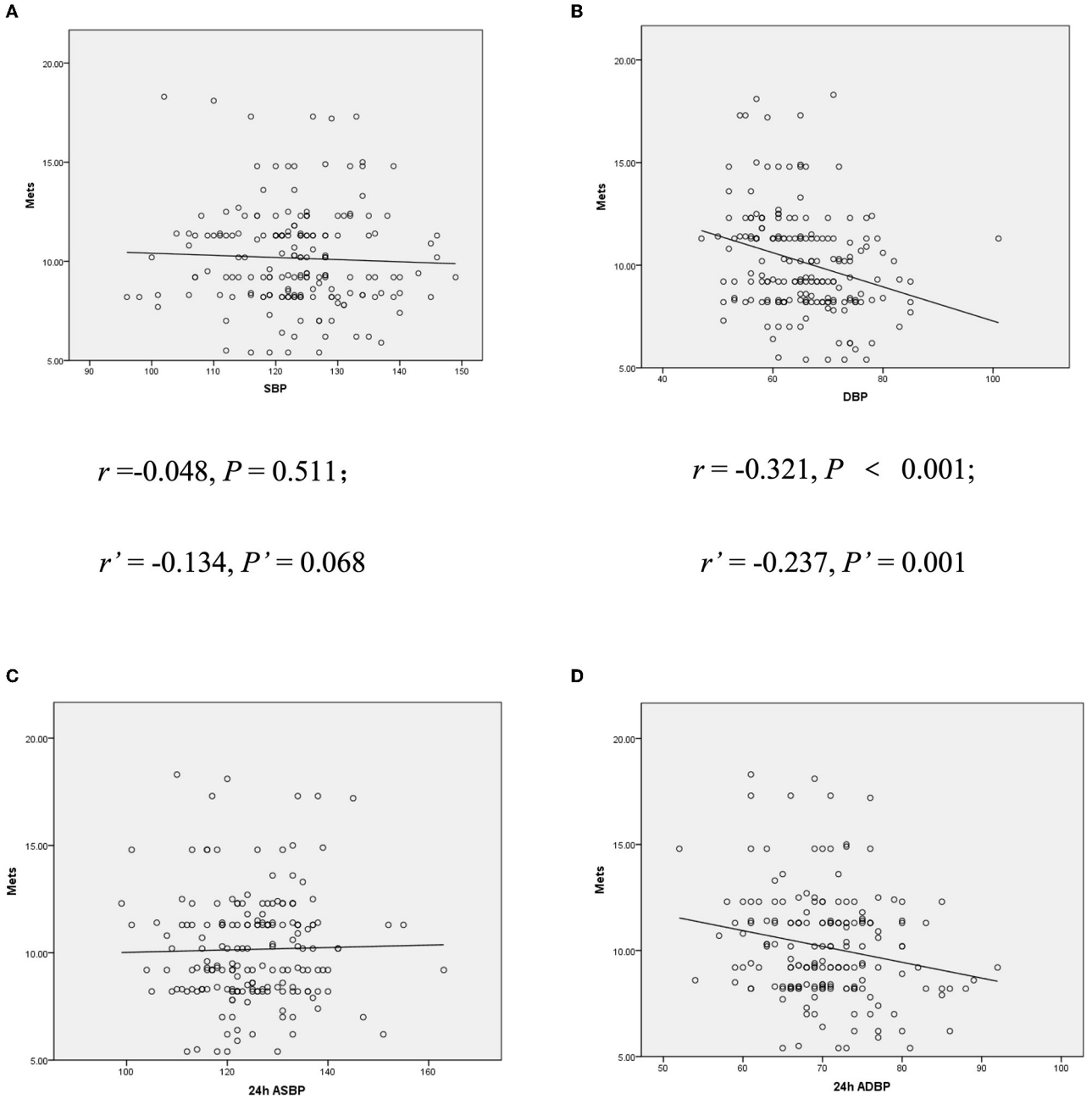
To analyze factors associated with exercise capacity, the multivariate ordinal logistic regression was used to identify the factors affecting patients' completion of TET stages, and the generalized linear model was used to identify the factors affecting METs. The dependent variables of the models were TET stages and METs, respectively; age, sex, BMI, LVH, and ADBP were included as influencing factors. P-values <0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS 22.0.

3. RESULTS

3.1. Characteristics of Patient Population

A total of 190 children with PHT were included in this study. There was a male dominance (76.8%), the median age was 13 years (11 years,14 years), and 189 patients (99.5%) achieved the target heart rate and completed the TET. Only 1 child (0.5%) terminated the TET prematurely at minute 4 due to dizziness and unsteadiness. The patient was a 14-year-old girl with stage 2 PHT and LVH and had no anomaly in her echocardiogram or resting ECG.

Of 189 patients completed the TET, 90 (47.6%) had stage 1 PHT (61 [67.8%] were boys), 99 (52.4%) had stage 2 PHT (85



r =-0.048, P = 0.511;

r' = -0.134, P' = 0.068

r = -0.321, P < 0.001;

r' = -0.237, P' = 0.001

r = 0.05, P = 0.493;

r' = -0.005, P' = 0.949

r = -0.162, P = 0,025;

r' = -0.179, P' = 0.014

FIGURE 1 | (A) Correlation between resting SBP and METs. **(B)** Correlation between resting DBP and METs. **(C)** Correlation between 24 h ASBP and METs. **(D)** Correlation between 24 h ADBP and METs. r, Spearman rank correlation coefficient; r', bias correlation coefficient corrected with gender and BMI; P', *P*-value when corrected with age, gender, and BMI; DBP, diastolic blood pressure; METs, metabolic equivalents; ASBP, average systolic blood pressure.

TABLE 4 | Comparison of exercise capacity between patients with and without left ventricular hypertrophy.

		Without LVH ($n = 184$)	With LVH ($n = 5$)	*P*	*P'*
Clinical characteristics					
Age (years)		13 (11, 14)	14 (13, 14)	0.248	-
Sex (male; %)		144 (78.3%)	2 (40%)	0.079	-
BMI (kg/m^2)		26.5 (23.0, 29.7)	34.5 (29.3, 39.3)	0.008	-
Exercise capacity					
METs		9.6 (8.3, 11.4)	9.2 (6.9, 11.3)	0.474	0.609
TET	3 n (%)	15 (93.8%)	1 (6.2%)		
	4 n (%)	79 (97.5%)	2 (2.5%)	0.456	0.610
	5 n (%)	72 (97.3%)	2 (2.7%)		
Stages	≥6 n (%)	18 (100%)	0 (0%)		

P', P-value corrected with age, gender, and BMI; BMI, body mass index; LVH, left ventricular hypertrophy; TET, treadmill exercise test; METs, metabolic equivalents. Data are presented as median[P_{25},P_{75}], except where otherwise indicated.

TABLE 5 | Multivariate analysis regarding TET stages in children with PHT.

Indicators	**TET stages**				**Multivariate***		
	3 ($n = 16$)	**4 ($n = 81$)**	**5 ($n = 74$)**	**≥6 ($n = 18$)**	**OR**	**95%CI (OR)**	***P-value***
Age (years)	13 (12, 14)	12 (11, 14)	13 (11, 14)	13 (12, 14)	1.198	1.052, 1.364	0.007
Sex							
Girls (%)	7 (43.7)	28 (34.6)	8 (10.8)	0 (0.0)	0.163	0.079, 0.333	<0.001
Boys (%)	9 (56.3)	53 (65.4)	66 (89.2)	18 (100.0)	Ref	Ref	
BMI (kg/m^2)	29.93 (25.90, 32.89)	26.56 (23.08, 30.27)	26.51 (23.08, 30.27)	25.67 (23.08, 30.27)	0.921	0.863, 0.981	0.01
Without LVH (%)	15 (93.8%)	79 (97.5%)	72 (97.3%)	18 (100%)	0.586	0.095, 3.613	0.563
With LVH (%)	1 (6.2%)	2 (2.5%)	2 (2.7%)	0 (0%)	Ref	Ref	
ADBP (mmHg)	74 (69,80)	70 (67,74)	71 (66,75)	70 (63,72)	0.952	0.912, 0.993	0.025

OR, odds ratio; 95%CI, 95% confidence interval; Ref, reference value; BMI, body mass index; LVH, left ventricular hypertrophy; ADBP, average diastolic blood pressure. Data are presented as median[P_{25},P_{75}], except where otherwise indicated.

**The multivariate ordinal logistic regression analysis model included TET stages as dependent variable and age, sex, BMI, LVH, and ADBP as independent variables.*

[85.9%] were boys), 184(97.4%) did not have LVH (144 [78.3%] were boys), and 5(2.6%) had LVH (2 [40.0%] were boys).

3.2. Blood Pressure and Exercise Capacity

A comparison of the baseline data showed significant differences in gender and body mass index (BMI; $p < 0.05$) between children with stage 1 and stage 2 hypertension.

An analysis of correlation between hypertension stages and exercise capacity was done. The result showed that the TET stage patients achieved ($p = 0.250$) and the METs ($p = 0.109$) did not differ between children with stage 1 and stage 2 hypertension when adjusted for age, gender and BMI (**Table 2**), suggesting that there was no significant difference in exercise capacity between children with various hypertension stages.

Further analysis of correlation between BP value and exercise capacity showed that children with lower resting DBP and 24 h average blood pressure (ADBP) could achieve a TET stage of 6 or greater, but those with higher DBP and 24 h ADBP could only achieve a TET stage of 3 ($p < 0.05$). The results were consistent when corrected for age, gender and BMI ($p < 0.05$, seen in **Table 3**). In addition, METs was negatively correlated with resting DBP ($r = -0.321$; $p < 0.001$) and 24 h ADBP ($r = -0.162$; $p < 0.05$). After adjustment for age, gender and BMI, the correlation between METs and resting DBP ($r' = -0.237$; $p < 0.05$) and 24 h ADBP ($r' = -0.179$; $p < 0.05$) hardly changed (**Figure 1**). Meanwhile, there was no significant difference in SBP between children with different exercise capacity.

3.3. LVH and Exercise Capacity

Analyses were performed to explore the difference in exercise capacity between the children with ($n = 5$) and without LVH ($n = 184$). There was no significant difference in the METs nor TET stages ($p > 0.05$). Factors associated with exercise capacity in this study (including age, sex, and BMI) were adjusted in the comparison, after which no significant differences in the TET stages ($p = 0.610$) nor METs ($p = 0.609$) were detected (**Table 4**).

3.4. Factors Affecting Exercise Capacity

In the multivariate ordinal logistic regression, there was collinearity between resting DBP and 24 h ADBP, thus 24 h ADBP was included in the model. The results showed that the completion of TET stages was positively associated with age (OR = 1.198, 95% CI 1.052 to 1.364, $p < 0.05$) and negatively

TABLE 6 | Multivariate analysis regarding METs in children with PHT.

Indicators	Univariate			Multivariate*		
	β	95%CI	*P-value*	*β*	95%CI	*P-value*
Age	0.168	0.006,0.329	0.041	0.282	0.134, 0.429	<0.001
Sex						
Girls	−1.755	−2.576, −0.943	<0.001	−1.909	−2.672, −1.146	<0.001
Boys	Ref	Ref		Ref	Ref	
BMI(kg/m^2)	−0.13	−0.203, −0.057	<0.001	−0.134	−0.205, −0.063	<0.001
Without LVH	1.089	−1.126, 3.304	0.335	−0.663	−2.714, 1.388	0.526
With LVH	Ref	Ref		Ref	Ref	
ADBP (mmHg)	−0.075	−0.127, −0.022	0.005	−0.063	−0.112, −0.014	0.011

β, regression coefficient; 95%CI, 95% confidence interval; Ref, reference value; BMI, body mass index; LVH, left ventricular hypertrophy; ADBP, average diastolic blood pressure.
**The generalized linear model analysis model included METs as dependent variable and age, sex, BMI, LVH, and ADBP as independent variables.*

associated with female gender (OR = 0.163, 95% CI 0.079 to 0.333, $p < 0.05$), BMI (OR = 0.921, 95% CI 0.863 to 0.981, $p < 0.05$), and 24 h ADBP (OR = 0.952, 95% CI 0.912 to 0.993, $p < 0.05$; **Table 5**).

The analyses of generalized linear model showed that METs, similar to TET stages, were positively associated with age ($\beta = 0.282$, 95%CI 0.134 to 0.429, $p < 0.05$) and negatively associated with female gender ($\beta = -1.909$, 95% CI −2.672 to −1.146, $p < 0.05$), BMI ($\beta = -0.134$, 95% CI −0.205 to −0.063, $p < 0.05$), and 24 h ADBP (β: −0.063, 95%CI: [−0.112, −0.014], $p < 0.05$; **Table 6**).

4. DISCUSSION

This study evaluated exercise capacity in pediatric PHT through TETs. In the study, 99.5% of children with PHT completed TETs and achieved the submaximal heart rate, indicating that exercise interventions could be applied to most pediatric PHT patients. Among children who completed TETs, exercise capacity was negatively correlated with DBP and 24 h ADBP. Furthermore, lower exercise capacity was associated with female gender, younger age, greater BMI, and higher 24 h ADBP.

Exercise training was recommended as a primary non-pharmacological intervention which should be implemented in all hypertensive patients (4). A meta-analysis reported that aerobic exercise training could effectively reduce mean SBP and DBP (15). However, the "optimal" dose of exercise training for BP control, which is critical to maximize intervention efficiency (16), has not been defined. Hansen et al. (17) suggested that higher exercise intensity was associated with greater effectiveness of aerobic exercise training, while another research showed that moderate-intensity resistance training may lead to similar BP reductions (18). Moreover, according to Aslani et al. (19), very strenuous prolonged exercise could raise the possibility of cardiac fatigue. To find the most suitable exercise intensity for children with PHT, we raised an investigation on the exercise capacity of these children.

In our study, we noticed that children with higher BP had worse exercise capacity. At one level, children with lower DBP and 24 h ADBP could achieve higher TET stages. On another scale, METs were also negatively correlated with DBP and 24 h ADBP levels. Note that SBP did not differ between different groups, suggesting that DBP might be a better predictor of poor exercise capacity than SBP, especially in young populations. Interestingly, DBP has also been regarded as the strongest predictor of coronary heart disease in younger populations (< 50 years) (20). A possible explanation for this might be that young patients are less likely to suffer from the peripheral amplification of SBP caused by wave reflection, which is the main reason for the age-related BP changes in the hypertensive population (21). As both poor exercise capacity and coronary heart disease lead to negative outcomes, DBP is thereby a potential predictor for worse prognoses of pediatric PHT.

Despite the inconsistency in DBP and SBP, our finding of the link between BP and exercise capacity are in accord with the studies in adults (22, 23), which showed that the exercise capacity of the hypertensive group was significantly lower than that of the healthy control group. The studies also suggested that the deterioration of exercise capacity in hypertensive patients began long before the alteration of cardiac structure. The lower exercise capacity may prevent patients from high-intensity training. This relatively poor exercise capacity also intrigued us to the factors affecting exercise capacity in pediatric PHT, which were then explored by multifactor analyses.

An unexpected result of the analyses was the lack of association between LVH and METs. This result is contradictory to previous studies, which showed that exercise capacity was negatively related to LVH in hypertensive patients (22, 24). The relationship may be explained by the shortage of blood flow in coronary and non-coronary arteries and myocardial blood reserve in patients with hypertension with LVH. We presume that the inconsistency of the results may be attributed to the relatively small sample size of patients with LVH.

Furthermore, we found that girls had significantly lower exercise capacity than boys, which was consistent with healthy children (25). The results may be explained by the relatively lower oxygen uptake of females, which may impair their exercise capacity (26). This lower oxygen uptake is brought by their smaller muscle mass, hemoglobin and blood volume, and stroke volume (8).

Our data also suggest a positive association between exercise capacity and age, a finding similarly reported by Cumming et

al. (25) with healthy children and Ulrich et al. (27) when using the 6-min walk test (6MWT) to estimate the exercise capacity in healthy children and adolescents. The result is contradicted to the findings in adults (8). This discrepancy may be due to that the pediatric population is in a stage of growth and development, and hence their physical strength and exercise capacity develop with age.

It is generally believed that children's BMI is related to their exercise capacity. Previous studies show that obese children falter in several aspects of exercise capacity, including muscle explosive strength, muscle endurance, and running speed (28, 29). Obesity also poisons hemodynamic parameters, according to a study by Fornitano et al. (30). Our study found that BMI was related to exercise capacity in children with PHT. The METs of the patients and the TET stage they could achieve dropped with the increase of BMI. One possible reason for this anticorrelation is that the overweight populations have a hypoadrenergic state during exercise (31). Moreover, obesity could impair exercise-related physiological functions, such as lung function (32, 33), oxygen saturation (34), cardiovascular function (35), and the biological function of skeletal muscle(36).

Twenty-four hours ADBP was negatively associated with exercise capacity in our study, indicating that exercise capacity declines with the increase of BP. A similar result was shown in adults: 43.9% of hypertensive patients failed to achieve the predictive distance of 6WMT (37). An animal model also suggested that hypertensive subjects had lower exercise capacity than healthy ones (38). A possible explanation for this might be that higher BP results in higher peripheral resistance, causing a greater cardiac output during exercise, resulting in the decline in exercise capacity.

Our study had several limitations. One was the small sample size in single center, especially of the LVH group, which is due to the rather mild condition of our patients. The study was also limited by the lack of a healthy control group, given the difficulty in recruiting volunteers during the COVID pandemic. An additional problem is that pulmonary function was not evaluated in our study, which should be included in future studies to provide a comprehensive assessment of exercise capacity.

5. CONCLUSIONS

Our study showed that exercise capacity was impaired in pediatric PHT, due to the higher DBP and 24 h ADBP. We also found that female gender, younger age, greater BMI, and higher 24 h ADBP were both independently associated with lower exercise capacity in pediatric PHT. Future prospective studies with a larger sample size and healthy control may be of use.

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 the Ethics Committee of the Capital Institute of Pediatrics. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HZ collected the data, performed the data analyses, and drafted the paper. YC wrote the manuscript. TZ carried out the treadmill exercise test and performed the analyses. MZ contributed to data collection. XL designed the study and revised the manuscript. LS monitored data collection for the trial. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Song P, Zhang Y, Yu J, Zha M, Zhu Y, Rahimi K, et al. Global prevalence of hypertension in children: a systematic review and meta-analysis. *JAMA Pediatr*. (2019) 173:1154–63. doi: 10.1001/jamapediatrics.2019.3310
2. Gupta-Malhotra M, Banker A, Shete S, Hashmi SS, Tyson JE, Barratt MS, et al. Essential hypertension vs. secondary hypertension among children. *Am J Hypertens*. (2015) 28:73–80. doi: 10.1093/ajh/hpu083
3. Li T, Yue Y, Lu G, Qin W, Lang C. Clinical analysis of 165 children with hypertension. *Chin Pediatr Emerg Med*. (2021) 28:617–20. doi: 10.3760/cma.j.issn.1673-4912.2021.07.015
4. Dan L, Xiaohui L, Lin S, Aijie L, Mingming Z, Yang L. Etiology and clinical analysis of 232 hospitalized children with hypertension. *Chin J Appl Clin Pediatr*. (2019) 34:993–6. doi: 10.3760/cma.j.issn.2095-428X.2019.13.007
5. Bao W, Threefoot SA, Srinivasan SR, Berenson GS. Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: the Bogalusa Heart Study. *Am J Hypertens*. (1995) 8:657–65. doi: 10.1016/0895-7061(95)00116-7
6. Joint Committee for Guideline Revision. 2018 Chinese guidelines for the management of hypertension. *Chin J Cardiovasc Med*. (2019) 24:24–56. doi: 10.11909/j.issn.1671-5411.2019.03.014
7. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. *J Hypertens*. (2013). 31:1281–357. doi: 10.1097/01.hjh.0000431740.32696.cc
8. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training. *Circulation*. (2013) 128:873–934. doi: 10.1161/CIR.0b013e31829b5b44
9. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. (2017) 140:e20171904. doi: 10.1542/peds.2017-1904
10. Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, et al. Clinical stress testing in the pediatric age group. *Circulation*. (2006) 113:1905–20. doi: 10.1161/CIRCULATIONAHA.106.174375

11. Franklin BA, Brinks J, Berra K, Lavie CJ, Gordon NF, Sperling LS. Using metabolic equivalents in clinical practice. *Am J Cardiol*. (2018) 121:382–7. doi: 10.1016/j.amjcard.2017.10.033
12. Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. (1990) 13:555–65. doi: 10.1002/clc.4960130809
13. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. (1986) 57:450–8. doi: 10.1016/0002-9149(86)90771-X
14. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. *J Am Soc Echocardiogr*. (2009) 22:709–14. doi: 10.1016/j.echo.2009.03.003
15. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. (2002) 136:493–503. doi: 10.7326/0003-4819-136-7-200204020-00006
16. Amir NH, Dorobantu DM, Wadey CA, Caputo M, Stuart AG, Pieles GE, et al. Exercise training in paediatric congenital heart disease: fit for purpose? *Arch Dis Child*. (2021) 1–10. doi: 10.1136/archdischild-2020-321390. [Epub ahead of print].
17. Hansen D, Niebauer J, Cornelissen V, Barna O, Neunhauserer D, Stettler C, et al. Exercise prescription in patients with different combinations of cardiovascular disease risk factors: a consensus statement from the EXPERT working group. *Sports Med*. (2018) 48:1781–97. doi: 10.1007/s40279-018-0978-1
18. Cornelissen VA, Fagard RH. Effect of resistance training on resting blood pressure: a meta-analysis of randomized controlled trials. *J Hypertens*. (2005) 23:251–9. doi: 10.1097/00004872-200502000-00003
19. Aslani A, Babaee BMA, Moaref AR, Aslani A. Effect of extreme exercise on myocardial function as assessed by tissue Doppler imaging. *Echocardiography*. (2009) 26:1036–40. doi: 10.1111/j.1540-8175.2009.00919.x
20. Li Y, Wei FF, Wang S, Cheng YB, Wang JG. Cardiovascular risks associated with diastolic blood pressure and isolated diastolic hypertension. *Curr Hypertens Rep*. (2014) 16:1–6. doi: 10.1007/s11906-014-0489-x
21. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? *Circulation*. (2001) 103:1245–49. doi: 10.1161/01.CIR.103.9.1245
22. Nair VM, Tekin UN, Khan IA, Rahmatullah SI, Arora P, Mahankali BD, et al. Worsening of left ventricular diastolic dysfunction during exercise causes decreased exercise tolerance in hypertension. *Clin Cardiol*. (2000) 23:660–4. doi: 10.1002/clc.4960230906
23. Modesti PA, Olivo G, Carrabba N, Guarnaccia V, Pestelli F, Malfanti PL, et al. Early impairment of the cardiopulmonary exercise capacity of hypertensive patients. *Int J Cardiol*. (1994) 44:163–9. doi: 10.1016/0167-5273(94)90021-3
24. Akinboboye OO, Idris O, Goldsmith R, Berekashvili K, Chou RL, Bergman SR. Positron emission tomography, echo-doppler, and exercise studies of functional capacity in hypertensive heart disease. *Am J Hypertens*. (2002) 15(10 Pt 1):907–10. doi: 10.1016/S0895-7061(02)02985-0
25. Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. *Am J Cardiol*. (1978) 41:69–75. doi: 10.1016/0002-9149(78)90134-0
26. McArdle WD, Katch FI, Katch VL. *Exercise Physiology: Nutrition, Energy, and Human Performance*. Philadelphia, PA: Lippincott Williams & Wilkins (2010).
27. Ulrich S, Hildenbrand FF, Treder U, Fischler M, Keusch S, Speich R, et al. Reference values for the 6-minute walk test in healthy children and adolescents in Switzerland. *BMC Pulm Med*. (2013) 13:49. doi: 10.1186/1471-2466-13-49
28. Shang X, Liu A, Li Y, Hu X, Du L, Ma J, et al. The association of weight status with physical fitness among Chinese children. *Int J Pediatr*. (2010) 2010:515414. doi: 10.1155/2010/515414
29. Halme T, Parkkisenniemi S, Kujala UM, Nupponen H. Relationships between standing broad jump, shuttle run and Body Mass Index in children aged three to EI. *J Sports Med Phys Fitness*. (2009) 49:395–400.
30. Fornitano LD, Godoy MF. Exercise testing in individuals with morbid obesity. *Obes Surg*. (2010) 20:583–8. doi: 10.1007/s11695-008-9692-7
31. Gustafson AB, Farrell PA, Kalkhoff RK. Impaired plasma catecholamine response to submaximal treadmill exercise in obese women. *Metabolism*. (1990) 39:410–7. doi: 10.1016/0026-0495(90)90257-D
32. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest*. (2006) 130:827–33. doi: 10.1378/chest.130.3.827
33. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol*. (2010) 108:206–11. doi: 10.1152/japplphysiol.00694.2009
34. Garg S, Gupta S, Mobeen MS, Madhu SV. Effect of obesity and glycated hemoglobin on oxygen saturation in ambulatory type 2 diabetic individuals: a pilot study. *Diabetes Metab Syndr*. (2016) 10:157–60. doi: 10.1016/j.dsx.2016.01.012
35. Cote AT, Harris KC, Panagiotopoulos C, Sandor GG, Devlin AM. Childhood obesity and cardiovascular dysfunction. *J Am Coll Cardiol*. (2013) 62:1309–19. doi: 10.1016/j.jacc.2013.07.042
36. Guo A, Li K, Tian H, Fan Z, Chen Q, Yang Y, et al. FGF19 protects skeletal muscle against obesity-induced muscle atrophy, metabolic derangement and abnormal irisin levels via the AMPK/SIRT-1/PGC-pathway. *J Cell Mol Med*. (2021) 25:3585–600. doi: 10.1111/jcmm.16448
37. Kurpaska M, Krzesinski P, Gielerak G, Uzieblo-Zyczkowska B, Banak M, Piotrowicz K, et al. Multiparameter assessment of exercise capacity in patients with arterial hypertension. *Clin Exp Hypertens*. (2019) 41:599–606. doi: 10.1080/10641963.2018.1523917
38. Campos HO, Drummond LR, Rodrigues QT, Lima PM, Primola-Gomes TN, Coimbra CC. Exercise capacity in different stages of hypertension in spontaneously hypertensive rats. *J Sports Med Phys Fitness*. (2020) 60:800–5. doi: 10.23736/S0022-4707.20.10369-4

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BRIEF RESEARCH REPORT
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Cardiac Manifestations of Myotonic Dystrophy in a Pediatric Cohort

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Myotonic dystrophy type 1 (DM1) is the most prevalent inherited neuromuscular dystrophy in adults. It is a multisystem disease with cardiac manifestations. Whilst these are well-defined in adults, there are scarce published data in the pediatric population. This study aimed to investigate the yield and progression of cardiac disease in pediatric DM1 patients, focusing on congenital DM1 (cDM1).

Methods: A retrospective observational study of all pediatric DM1 patients referred to our center (December 2000-November 2020) was conducted. Patients were classified into DM1 forms according to age of symptom onset and disease severity. Patients underwent clinical and cardiac evaluation with 12-lead ECG, transthoracic echocardiography and 24-h ECG Holter monitoring.

Results: 67 DM1 pediatric patients were included: 56 (83.6%) cDM1 and 11 (16.4%) non-cDM1. Median follow-up time of cDM1 patients was 8.0 [3.25–11.0] years. 49 (87.5%) cDM1 patients had baseline 12-lead ECG and 44 (78.6%) had a follow-up 12-lead-ECG, with a median follow-up time from diagnosis to baseline ECG of 2.8 [1.0–8.5] years and to follow-up ECG of 10.9 [5.7–14.2] years. Overall, 43 (87.8%) presented ECG abnormalities, most commonly in the form of asymptomatic conduction disease (n = 23, 46.9%), of which 21 (42.9%) had first degree atrioventricular block (1st AVB). There was an increase of prevalence from baseline to follow-up ECG in low QRS voltage (16.7%), poor R wave progression (13.9%), abnormal repolarisation (11.9%) and 1st AVB (7.6%). one patient (1.8%) underwent pacemaker implantation for syncope in the context of progressive conduction disease. No patients developed left ventricular systolic dysfunction. 4 (7.1%) cDM1 patients died during follow up, including three who died suddenly with no clear cause of death.

Conclusions: This study is the first to analyse the prevalence and progression of ECG abnormalities in cDM1 pediatric patients. The high prevalence of abnormal findings, progressive changes and number of potentially associated events (1 pacemaker implantation and 3 unexplained sudden deaths) stresses the importance of systematic and continued cardiac evaluation of these patients.

Keywords: myotonic dystrophy (DM1), congenital myotonic dystrophy, pediatric population, neuromuscular disorder, cardiac conduction disease, electrocardiographic abnormalities

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INTRODUCTION

Myotonic dystrophy type 1 (DM1) is the most prevalent inherited neuromuscular disease in adults with 1:8000 incidence (1). It is caused by an autosomal-dominant expansion of a cytosine–thymine–guanine (CTG) trinucleotide repeat on chromosome 19q13.3 (2). Anticipation in consecutive generations associates with earlier onset and an increased severity of the disorder (3). This multisystem disease is primarily characterized by progressive muscle weakness and myotonia, but can include endocrine, respiratory, central nervous, gastrointestinal, ocular, urinary and cardiac manifestations. The risk of sudden death in DM1 patients has been reported to be 0.56% per year (4). Based on age of onset and the clinical severity, pediatric DM1 patients can be divided into congenital (cDM1), infantile (iDM1) and juvenile (jDM1) forms (4). cDM1 patients is the more severe form with the lowest life expectancy (5). The mortality rate is up to 40% in the neonatal period due to respiratory diseases and the mean life expectancy is 45 years (6).

cDM1 presents with hypotonia at birth, respiratory failure, difficulties with feeding and developmental delay. cDM1 is almost exclusively associated with maternal inheritance (7).

Cardiac manifestations in adults with DM1 include ventricular dysfunction, progressive conduction defects and ventricular arrhythmias which can lead to sudden cardiac death (SCD) (1). Nonetheless, data on progressive cardiac abnormalities in the pediatric population are scarce. This study, therefore, aimed to investigate the prevalence, progression and clinical impact of cardiac disease in pediatric DM1 patients, focusing on cDM1.

METHODS

Data Collection

A retrospective observational study was conducted of all consecutive pediatric individuals (aged ≤18 years) with a diagnosis of DM1 seen at Great Ormond Street Hospital between December 2000 and November 2020. The study was approved by the Research Board and consent waived in view of the retrospective data collection. Electronic patient records were systematically reviewed.

Clinical Evaluation

DM1 was clinically diagnosed and confirmed by genetic testing. The following clinical forms were defined owing to the age of onset of first clinical manifestation: cDM1 (birth-1 month), iDM1 (1 month—10 years) and jDM1 (11-20 years) (4).

We specifically developed a systemic severity score that consisted of the 8 more representative extra-cardiac features from our cDM1 cohort: learning difficulties, non-invasive ventilation, fecal incontinence, nasogastric or gastrostomy feeding, dysphagia, sleep disorder, urinary incontinence and full/partial wheelchair dependence. This score was evaluated in each patient at the end of the study period.

Patients underwent annual cardiac evaluation including medical and family history, physical examination, resting 12-lead ECG; transthoracic echocardiography; signal averaged ECG (SAECG); and ambulatory 24-h ECG Holter monitoring (AECG). Nevertheless, if cardiac symptoms and/or significant ECG abnormalities were observed, patients were more frequently evaluated.

Exercise testing (ETT) is recommended for young DM1 patients as physical exertion has been reported to be pro-arrhythmogenic (8, 9). However, we performed an ETT depending on the age range and physical capability of our patients. We used a treadmill test following a modified Bruce protocol. Electrophysiological study (EPS) was carried out when clinically indicated according to current guidelines to check for conduction abnormalities not apparent on surface ECG as per standard practice. Specifically, it was performed for establishment of atrioventricular block as the main cause of symptoms, and for identification of the anatomic site of block that may dictate the potential need of permanent pacing (8, 10, 11). Clinical data were collected at baseline and during follow-up until patients were transitioned to adult services around the age of 18, the end of the study period or until patient's death.

Electrocardiographic Analysis and Interpretation Criteria

12-lead ECG was recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV. When more than one tracing was available, baseline (ECG1) and latest available follow-up 12-lead ECG (ECG2) were analyzed independently and blindly by two investigators (LB and EC), and re-reviewed by the senior author (EC) when assessor opinion varied. Normal limits for ECG parameters were defined according to Rijnbeek et al. and current guidelines (12–14).

We defined sinus bradycardia as a heart rate $\leq 2^{nd}$ percentile (12, 13). Mean frontal plane electrical axis was considered normal between 0° and 120° (birth-1 month); between 0° to 90° (1 month-16 years) and between −30° and 90° (>16 years). We defined left-axis deviation when the mean frontal plane electrical axis was <0° (birth-16 years) or <-30° (>16 years); right-axis deviation from 120° to 180° (in the first month of life) and from 90° to 180° (adults); extreme-right axis deviation between −90° and 180°. The axis was considered as indeterminate when there were isodiphasic QRS complexes in the frontal plane, with no dominant QRS deflection (14). Poor R wave progression was established when R wave amplitude in lead V3 was ≤3 mm and R wave amplitude in lead V2 was ≤ to the R wave amplitude in V3 (15). Low QRS voltage was defined as QRS amplitude ≤5 mm (0.5 mV) in each peripheral lead and/or QRS amplitude ≤10 mm (1 mV) in each precordial lead (16). Non-specific intraventricular conduction delay was defined according to current guidelines (14). SAECG was recorded at 40 Hz high-pass filtering. The presence of late potentials was determined in patients with a QRS <110 ms considering 3 SAECG parameters: filtered QRS duration ≥114 ms, duration of terminal QRS <40 μV or a root-mean-square voltage of the last 40 ms of QRS <20 μV (17). We considered SAECG to be abnormal when ≥2 parameters were abnormal. Conduction defect was defined as the presence of first or higher degree atrioventricular block (AVB), left or right bundle branch block (RBBB) or left anterior fascicular block (LAFB) on

12-lead ECG (14). ECG was considered abnormal when any of the aforementioned alterations and/or abnormal repolarisation (considering T wave abnormalities and QTc duration) were present (18). AECG was considered to be abnormal when any of the previously described ECG abnormalities were found.

Cardiac Imaging

Echocardiogram data were collected during follow-up. Cardiac dimensions were assessed against normal values as per recent published datasets (19). Standard clinical parameters were used to define structural cardiac abnormalities. Normal left ventricular systolic function was defined as left ventricular ejection fraction >55% (20).

Statistics

Normally distributed data are presented as mean values [±standard deviation (SD)] and non-normally distributed variables as a median [interquartile range (IQR)]. Categorical variables are presented as number (n) and percentages (%).

We explored for normality by a Kolmogorov-Smirnov test. Chi-squared or Fisher's exact test were used for comparing of categorical variables and Student's *t*-test for continuous measurements. A $P < 0.05$ was considered to be statistically significant for all data. Significance was only analyzed where n≥3 in each group. The variant "learning difficulties" was not included in the statistical analysis as it was present in all cDM1 patients. Statistical analysis was performed using R Studio software version 1.2.1335.

RESULTS

The study cohort consisted of 67 DM1 pediatric patients: 56 (83.6%) cDM1, 8 (11.9%) iDM1 and 3 (4.5%) jDM1. **Table 1** shows baseline demographic characteristics of DM1 patients; **Supplementary Table 1** the non-cardiac clinical manifestations. Due to the small number of non-cDM1 patients and potential for a different prevalence of cardiovascular findings in the different subgroups, we divided the cohort into cDM1 and non-cDM1. Results are presented separately.

TABLE 1 | Baseline characteristics of patients with DM1.

Baseline information	cDM1 ($n = 56$)	iDM1 and jDM1 ($n = 11$)
Female, *n* (%)	33 (58.9)	7 (63.6)
Gestational age		
Pre-term, *n* (%)	27/50 (54.0)	1/10 (10.0)
Mean gestational age pre-term patients (±SD)	33.9 (±2.5)	36 (±0)
Polyhydramnios, *n* (%)	23/31 (74.2)	0/6 (0)
Mean age at first symptoms, months (±SD)	0.01 (±0.02)	100 (±66.5)
Mean age at genetic diagnosis, years (±SD)	1.4 (±2.9)	8.5 (±5.7)
Ethnicity		
Caucasian, *n* (%)	40 (71.4)	9 (81.8)
Asian, *n* (%)	7 (12.5)	0 (0)
Other/not known, *n* (%)	5 (8.9)	2 (18.2)
Maternally inherited, *n* (%)	54 (96.4)	3 (27.3)
Paternally inherited, *n* (%)	2 (3.6)	8 (72.7)
Median follow-up, years [IQR]	8.0 [3.3–11.0]	3.0 [1.0–11.0]
Symptoms (palpitations, syncope, chest pain or dizziness)		
Absent, *n* (%)	49 (87.5)	8 (81.8)
Palpitations, *n* (%)	2 (3.6)	0 (0)
Syncope, *n* (%)	2 (3.6)	1 (9.1)
Chest pain, *n* (%)	2 (3.6)	0 (0)
Dizziness, *n* (%)	1 (1.8)	0 (0)
Pacemaker, *n* (%)	1 (1.8)	0 (0)
Implantable cardioverter defibrillator, *n* (%)	0 (0)	0 (0)

Fractions give the absolute number of patients divided by the number of patients with available clinical information for each item. Values are n (%).
cDM1, Congenital Myotonic Dystrophy type 1; iDM1, Infantile Myotonic Dystrophy type 1; jDM1, Juvenile Myotonic Dystrophy type 1; IQR, Interquartile Range; SD, Standard Deviation.

Congenital Myotonic Dystrophy Type 1 Cohort

Clinical Events and Symptoms

During follow-up, 7 (12.5%) cDM1 patients experienced symptoms (**Table 1**). One patient presented at 8 years of age with 2 syncopal episodes with clonic movements and prolonged post-ictal period which were considered seizures. At the age of 11, he had recurrence of syncope and investigations documented progressive atrioventricular conduction defects on 12-lead ECG and AECG in the form of 1st AVB, second degree AVB Mobitz type I, Mobitz type II and 2:1 AVB. His AECG additionally showed a median heart rate of 84 bpm (minimum of 56 bpm and maximum of 141 bpm) with no significant sinus pauses nor arrhythmias. Due to his syncopal episode in the context of second degree AVB, according to international guidelines, he underwent an elective EPS which confirmed conduction disease (HV interval of 60 ms) with no inducible sustained ventricular tachycardia (8). Therefore, a transvenous pacemaker was implanted, according to current guidelines (Class I recommendation) (11). This patient is alive and symptom-free, with no ventricular arrhythmias documented through pacemaker downloads and has not required further interventions after 32 months of follow-up. No patients underwent implantable cardioverter defibrillator implantation.

Four (7.1%) patients died at a median age of 8.5 [6.25-16.75] years. One of them (1.8%) died due to progression of the disease and respiratory failure; he had right axis deviation, low QRS voltage and abnormal repolarisation at both ECG1 and ECG2. The remaining deaths ($n = 3$, 5.4%) were sudden and unexplained, with no available data on death circumstances and no post-mortem examination performed. The ECG was only available for two out of these three patients, showing right axis deviation and indeterminate axis, low QRS voltage

TABLE 2 | Electrocardiographic findings of congenital DM1 patients.

Baseline information	Baseline ECG ($n = 49$)	Follow-up ECG ($n = 44$)	*P*-value	Increased prevalence (%)
Median age at the ECG, years [IQR]	4.1 [1.7–10.5]	12.2 [6.9–16.1]		
Sinus bradycardia	1 (2.0)	1 (2.3)		0.3
1st degree AV block, *n* (%)	13 (26.5)	15 (34.1)	0.5465	7.6
Nonspecific intraventricular conduction delay	12 (24.5)	13 (29.6)	0.3711	5.1
Right BBB, *n* (%)	2 (4.1)	0 (0)		
Left BBB, *n* (%)	0 (0)	0 (0)		
Left Anterior Fascicular Block, *n* (%)	2 (4.1)	5 (11.4)		7.3
QRS axis				
Normal, *n* (%)	21 (42.9)	18 (40.9)	>0.999	
Left axis deviation, *n* (%)	7 (14.3)	10 (22.7)	0.1824	8.4
Right axis deviation, *n* (%)	12 (24.5)	9 (20.5)	0.505	
Superior axis deviation, *n* (%)	5 (10.2)	5 (11.4)	>0.999	1.2
Indeterminate axis, *n* (%)	6 (12.2)	4 (9.1)	0.6171	
Low QRS voltage, *n* (%)	13 (26.5)	19 (43.2)	0.023	16.7
Poor R-wave progression, *n* (%)	1 (2.0)	7 (15.9)		13.9
Abnormal repolarisation (Flat/inverted T waves)	12 (24.5)	16 (36.4)	0.4227	11.9
Inferiorly	4 (8.2)	4 (9.1)	>0.999	0.9
Inferolaterally	3 (6.1)	8 (18.2)	0.2278	12.1
Inferior and anterior leads	1 (2.0)	1 (2.3)		0.3
Generalized	4 (8.2)	3 (6.8)	>0.999	
QTc ≥450	1 (2.0)	1 (2.3)		0.3
Overall ECG abnormalities	43 (87.8)	43 (97.7)	0.1336	9.9

AV, Atrioventricular; BBB, Bundle Branch Block; DM1, Myotonic Dystrophy type 1.

and abnormal repolarisation. One developed 1st AVB and non-specific intraventricular conduction delay at follow-up. They were asymptomatic.

Supplementary Table 2 shows the comparison of ECG abnormalities in the deceased and alive patients with cDM1; **Supplementary Table 3** shows the association between mortality and the presence of systemic features of cDM1. Overall, there was a trend toward statistical significance between mortality and a higher systemic severity score ($P = 0.088$).

Supplementary Figure 1 depicts the number of systemic features in cDM1 patients as a surrogate for clinical severity. Median severity score was 7.5 [4.75–8.0] in deceased patients and 4.0 [3.0–6.0] in alive patients.

Cardiac Investigations

Diagnostic work-up is shown in **Supplementary Figure 2**.

12-Lead ECG and SAECG Findings

Forty-nine patients (87.5%) had an ECG1 and 44 (78.6%) at least one ECG2, with median interval of 7.5 [5.2–5.6] years between the two (**Table 2**). **Supplementary Figure 3** depicts QRS and PR interval distribution at ECG1 and ECG2 (12–14).

Overall, forty-three of the forty-nine patients (87.8%) that underwent at least one ECG had ECG abnormalities: abnormal repolarisation ($n = 21$, 42.9%), 1st AVB ($n = 21$, 42.9%), low QRS voltage ($n = 19$, 38.8%), non-specific intraventricular conduction delay ($n = 17$, 34.7%) and poor R wave progression ($n = 9$, 18.4%).

Twenty-six (44.8%) patients had a SAECG (**Supplementary Table 4**).

Ambulatory 24-h ECG Holter Monitoring and Exercise ECG Findings

Forty patients (71.4%) had an AECG. No patients had significant arrhythmias or sinus pauses (>3 s), 14 (35.0%) had occasional isolated supraventricular ectopics, 11 (27.5%) isolated ventricular ectopics and 3 (7.5%) junctional rhythm. **Table 3** includes conduction defects after 12-lead and AECG analysis.

Two of the three patients (5.4% of the total cohort) who underwent an ETT had 1st AVB at ECG1. There was no evidence of any higher degree block on exercise. All three patients had sinus rhythm with no arrhythmias on exertion and were asymptomatic throughout the test.

Association Between ECG Findings and Extracardiac Features

There was no statistical association between the presence of any conduction defect and systemic features of cDM1 (**Supplementary Table 5**) nor with the use of invasive ventilation in neonatal period ($P = 0.246$) or a significant difference with a higher median systemic severity score ($P = 0.587$). There was a statistically significant difference between abnormal SAECG and a greater systemic severity score ($P = 0.029$). There was no

TABLE 3 | Overall conduction defects in congenital DM1 patients with at least one 12-lead ECG including 12-lead ECG and ambulatory ECG monitoring data.

Conduction defects	Study population ($n = 49$)
Any conduction defect, *n* (%)	23 (46.9)
1st degree AV block, *n* (%)	21 (42.9)
Isolated 1st degree AV block, *n* (%)	13 (26.5)
And RBBB *n* (%)	1 (2.0)
And Left anterior fascicular block, *n* (%)	4 (8.2)
And RBBB and Left anterior fascicular block, *n* (%)	0 (0)
And Mobitz type I and II and 2:1 AV block, *n* (%)	1 (2.0)
Isolated left anterior fascicular block, *n* (%)	1 (2.0)
Isolated RBBB, *n* (%)	1 (2.0)

AV, atrioventricular; RBBB, Right Bundle Branch Block.

significant difference between median systemic severity score and an abnormal ECG (**Supplementary Table 6**).

There was a statistically significant association between low QRS voltage at ECG1 and low QRS voltage at either ECG1 or ECG2 and the need for non-invasive ventilation in the neonatal period ($P = 0.022$ and $P = 0.017$, respectively). Nevertheless, there was no significant association between the latter and low QRS voltage at ECG1 ($P = 0.338$), and abnormal repolarisation at ECG1 or ECG2 ($P > 0.999$ and $P = 0.365$, respectively).

Cardiac Imaging

Data regarding transthoracic echocardiography was available for 54 patients (96.4%) (**Table 4**). One (1.9%) developed asymmetric hypertrophy (HCM), mild mitral valve prolapse (MVP) and mild ascending aortic dilatation; additional genetic tests identified a variant of unknown significance in *TPM1* and *KCNQ1* genes. Five premature patients (9.3%) (median gestational age 34 [29.6–36.1] weeks), had a haemodynamically significant patent ductus arteriosus (PDA). No patients developed dilated cardiomyopathy or left ventricular systolic dysfunction.

Non-congenital Myotonic Dystrophy Type 1 Cohort

Table 1 contains baseline characteristics of patients with iDM1 and jDM1.

Nine (81.8%) non-cDM1 patients had an ECG1 which was abnormal in 6 (66.7%): 1st AVB and RBBB ($n = 1$, 16.7%), 1st AVB ($n = 1$, 16.7%), low QRS voltage and non-specific intraventricular conduction delay ($n = 2$, 33.3%), non-specific intraventricular conduction delay ($n = 1$, 16.7%), and non-specific intraventricular conduction delay, low QRS voltage and left axis deviation ($n = 1$, 16.7%). Two of the six patients (33.3%) that had an ECG2 had non-specific intraventricular conduction delay. One iDM1 patient (9.1%) had a small perimembranous ventricular septal defect and another an insignificant interatrial septal defect, both with no haemodynamic compromise.

TABLE 4 | Echocardiography data for congenital DM1 patients.

Echocardiography features	Study population ($n = 54$)
Left ventricular ejection fraction, % [IQR]	68.5 [62.5–72.0]
Left ventricular dimensions, z-score [IQR]	−1,8 [−0, 1–0, 0]
Echocardiographic abnormalities (total)	8 (14.8)
Pericardial effusion without haemodynamic compromise, *n* (%)	1 (1.9)
PDA (surgical closure), *n* (%)	3 (5.5)
PDA, VSD and left lower pulmonary vein stenosis, n (%)	1 (1.9)
Isolated PDA	2 (3.7)
PDA (interventional closure), *n* (%)	2 (3.7)
PDA and mild aortic root dilatation, *n* (%)	1 (1.9)
Isolated PDA	1 (1.9)
HCM, mild MVP and Aortic root dilatation, *n* (%)	1 (1.9)
Left aortic arch with right aberrant subclavian artery	1 (1.9)

HCM, Hypertrophic Cardiomyopathy; MVP, Mitral Valve Prolapse; PDA, Patent Ductus Arteriosus; VSD, Ventricular Septal Defect.

DISCUSSION

To the best of our knowledge, this is the largest study so far evaluating cardiac involvement and its progression in an exclusively pediatric cDM1 cohort. We have observed a high yield of electrocardiographic abnormalities and progression throughout follow-up in pediatric cDM1 patients, which has not been previously reported. Additionally, we demonstrated a potential risk of SCD at a young age among cDM1 patients.

Conduction Defects

Our analysis also demonstrates a high incidence of ECG abnormalities in cDM1 patients compared to a previous study by Ho et al. including pediatric DM1 patients (7). A potential explanation for this discrepancy could be that patients with cDM1 are more severely and prematurely affected compared with patients with milder forms of DM1 (non-cDM1).

Particularly, among ECG abnormalities, the major concern was related to conduction defects. Although we demonstrated progression of conduction defects, high degree conduction disease was rare with only one patient requiring pacing. We did not routinely perform EPS in our young patients in view of its invasive nature but we used it to assess conduction properties and confirm indication for pacing in a patient in the context of syncope and second degree AVB, according to international guidelines (Class I recommendation) (8).

First AVB has previously been reported as the most common conduction defect in adult DM1 patients (1, 21). Nevertheless, our data evidences a higher prevalence of 1st AVB in pediatric DM1 patients than adults and than a previous study by Sharma et al, from a cohort of pediatric cDM1 patients (22). This highlights the early conduction defects manifestations that cDM1 patients have, possibly in line with the more severe clinical expression described in the congenital onset compared to the other clinical forms. Moreover, the predominance of maternal inheritance in our cDM1 cohort reinforces the concept of an earlier and more severe phenotype from the systemic perspective and it can be speculated that cardiac abnormalities follow a similar pattern (3). Additionally, consistently with previous reports, in our cohort, 82.6% of the patients with a conduction defect were asymptomatic (23).

ECG Findings and Extracardiac Features

In this study, low QRS voltage and abnormal repolarisation were the first and second more frequent ECG abnormality at ECG2, respectively. This could be partially explained by long standing lung pathology and chest deformities of these patients as we found a statistically significant association between low QRS voltage at ECG2 and the need for non-invasive ventilation in the neonatal period. However, there was no significant association between the latter and the presence of abnormal repolarisation at ECG2. Nevertheless, due to its high prevalence in our study, these findings might be considered as an expression of myocardial involvement in these patients as diseases progresses. In this regard, there was a statistically significant difference between low QRS voltage prevalence at ECG2 compared to ECG1. Moreover, right-axis deviation and indeterminate axis were more frequent at ECG1 than at ECG2. This could be related to a higher prevalence of prematurity and need for ventilator support in cDM1 with possible electrical findings reflecting higher pulmonary pressures and lung pathology, with subsequent right heart involvement. This would be in keeping with, at least, partial regression of the findings as they got older and were weaned from support.

In our study, there was a trend toward a statistical significance between low QRS voltage and increased severity score, and low QRS voltage and mortality approached statistical significance. Additionally, the median severity assessed through systemic score was higher in deceased patients, which would be in keeping with the significance between low QRS voltage and severity score and mortality. Low QRS voltage had previously been associated with a more severe cardiac involvement in amyloidosis but this has not been proven in cDM1 patients (16). Low QRS voltage has also been reported associated with an increased risk of mortality in individuals apparently free of cardiovascular disease (16, 24). Further studies including larger sample sizes are warranted to confirm our findings.

Arrhythmias

Although arrhythmias are known to be the major cardiac manifestations of DM1, we did not document significant supraventricular or ventricular arrhythmias. Despite systematic ETT being recommended as Class IIB indication, we could only exercise a small number of patients due to their muscular impairment and inability to exercise with disease progression (8). Physical exercise has been previously reported to be an arrhythmogenic factor and it remains to be determined if the risk of malignant arrhythmia is driven by adrenergic stimuli and how that impacts a population that has a very low level of exercise (9). Another contributing factor could have been the lower age of our cohort, as arrhythmias are age-dependent in DM1 population, reported as occurring in the second decade of life (9).

Sudden Death

PR $\geq$ 200 ms, QRS $\geq$ 120 ms and QTc $\geq$ 450 ms have been described to be predictors of SCD in adult DM1 patients (21). In our cohort, none of the patients that died fulfilled these adult criteria. Complete heart block leading to asystole or ventricular arrhythmias had been documented as potential mechanisms leading to SCD (8). In our study, 3 out of the 4 deaths were sudden and unexpected, and an arrhythmia could not be ruled out as a cause of the death although mild ECG abnormalities were previously documented. Interestingly, all of them had low QRS voltage. Their deaths were unexplained as no autopsy was performed. Nevertheless, they raise concerns about the potential risk of SCD at a young age in this population given the small sample size and number of events observed.

Additional Cardiac Findings

In this study, the patient with HCM diagnosis was also heterozygous for a variant of uncertain significance in TPM1 and in KCNQ1 genes. Despite HCM having been rarely reported associated with DM1, it is difficult to determine the contribution of these two variants in his cardiac phenotype in the context of cDM1 diagnosis (5). Even if not common, an association between DM1 and dilated cardiomyopathy and heart failure has been reported later in life. None of our patients developed these two features, probably due to their age related penetrance in DM1 patients (8). MVP has been reported in 25-40% conversely to our findings, where 1.9% had MVP. Moreover, in our study, 9.3% of the patients that underwent echocardiography had a haemodynamically significant PDA. Although this finding has not been previously reported in DM1 patients, this is most likely due to the younger patients included and that all of them were ex-preterm babies.

Clinical Implications of Our Results

Our finding of a high prevalence of cardiac abnormalities and its progression throughout childhood in cDM1 patients stresses the vital importance of their regular clinical assessment, particularly to monitor the development of conduction defects as, together with ventricular arrhythmias, place DM1 patients at a higher risk of SCD (8). According to current guidelines, cardiac evaluation including examination, 12-lead ECG, echocardiogram and AECG monitoring at baseline are recommended as a Class IC indication, even in asymptomatic patients (8). Further follow-up with the same investigations are recommended as a Class IIa indication in patients with normal cardiac investigations at baseline (3, 8, 11). Our results support the validity of the investigations proposed by current guidelines as we have demonstrated that the ECG is almost invariably

abnormal, there is a potential for progression and higher degrees of AVB were recorded during AECG. The high prevalence of clinical events including syncope due to AV conduction disease (1/49, 2%) and unexplained deaths (3/49, 6.1%) stresses how screening is paramount and better risk stratification is still needed. We would recommend performing the same initial clinical evaluations as current guidelines with the addition of SAECG. We would suggest annual follow-up with the same investigations unless a progression or higher degree of AVB is observed. Performing an ETT will depend on the age range and/or physical capability of these patients.

LIMITATIONS

The study is limited by the small cohort of patients, probably due to the fact that cDM1 is a rare disease. Not all patients had an available baseline ECG nor a follow-up ECG. This lack of data could have had an impact on the detection of ECG abnormalities. Additionally, we were not able to compare non-cDM1 and cDM1 in terms of cardiac features due to the small sample size of the non-congenital group. As a tertiary center, non-cDM1 patients are not systematically referred to our Institution and are frequently followed-up locally, which would explain the smaller proportion on non-cDM1 patients seen in our clinic. Moreover, no post-mortem examination was available for the four deceased children, which limits our ability to infer the prevalence of SCD in the group. We created our own systemic score considering the 8 most representative clinical features of cDM1 in our cohort. This could have resulted in the omission of other relevant clinical features not widely presented by our patients. Additionally, the power of the statistical tests is limited by the small number of patients included. Finally, no correlation could be made between cardiac involvement and CTG repeat length as repeat size is not routinely assessed by UK laboratories. This limits the cardiac phenotype-genotype correlation. Although genotype-phenotype correlations in terms of severity of cardiac involvement and size of the CTG expansion have been advocated in adult groups, this remains controversial. No targeted study in the cDM1 population, where the length of the repeat is maximal, has been carried out to date.

CONCLUSION

This study demonstrates a high yield of cardiac conduction abnormalities with a progressive nature and potential for associated cardiac mortality due to dysrhythmias throughout childhood in an exclusively pediatric cDM1 cohort. Cardiac conduction disease is the most prevalent abnormality with 1st AVB demonstrated as the most frequent finding among cDM1 patients. Progression to higher degree of AVB was rare with only one patient requiring permanent pacing. There were four deaths despite the small cohort size, one due to progression of systemic disease but three were sudden and unexplained in otherwise stable children, and a sudden arrhythmic event could not be ruled out. Our findings stress the crucial role that regular and comprehensive cardiac follow-up of these patients plays starting from the onset of the disease. Further long-term prospective follow-up studies are needed to identify if electrocardiographic abnormalities can predict the risk of sudden cardiac events and namely sudden death. Genotype-phenotype correlations in terms of severity of cardiac involvement and size of the CTG expansion have been advocated in adult groups, this remains controversial. No targeted study in the cDM1 population, where the length of the repeat is maximal, has been carried out to date.

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 Research Board of Great Ormond Street Hospital. Written informed consent from the participants' 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

LB: drafted the manuscript, writing the bulk of the manuscript, and data collection. AH, JW, HW, and GN: data collection and critical revision of the manuscript. EF: data collection, statistical study, and critical revision of the manuscript. AM, FM, PM, SR, RQ, MS, GB, AS, LS, JK, and EC: critical revision of the manuscript. EC: coordinated and supervised data collection, editing, and responsible for the overall content. All authors have read and approved the final manuscript.

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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.2022.910660/full#supplementary-material

REFERENCES

1. Wahbi K, Babuty D, Probst V, Wissocque L, Labombarda F, Porcher R, et al. Incidence and predictors of sudden death, major conduction defects and sustained ventricular tachyarrhythmias in 1388 patients with myotonic dystrophy type 1. *Eur Heart J.* (2016) 38:751–8. doi: 10.1093/eurheartj/ehw569
2. Šabovič M, Medica I, Logar N, Mandić E, Zidar J, Peterlin B. Relation of CTG expansion and clinical variables to electrocardiogram conduction abnormalities and sudden death in patients with myotonic dystrophy. *Neuromuscul Disord.* (2003) 13:822–6. doi: 10.1016/S0960-8966(03)00138-X
3. Lau JK, Sy RW, Corbett A, Kritharides L. Myotonic dystrophy and the heart: a systematic review of evaluation and management. *Int J Cardiol.* (2015) 184:600–8. doi: 10.1016/j.ijcard.2015.03.069
4. Dogan C, De Antonio M, Hamroun D, Varet H, Fabbro M, Rougier F, et al. Gender as a modifying factor influencing myotonic dystrophy type 1 phenotype severity and mortality: a nationwide multiple databases cross-sectional observational study. *PLoS One.* (2016) 11:1–12. doi: 10.1371/journal.pone.0148264
5. Pelargonio G, Russo A., Dello Sanna T, De Martino G, Bellocci F. Myotonic dystrophy and the heart. *Heart.* (2002) 88:665–70. doi: 10.1136/heart.88.6.665
6. Ho G, Cardamone M, Farrar M. Congenital and childhood myotonic dystrophy: Current aspects of disease and future directions. *World J Clin Pediatr.* (2015) 4:66–80. doi: 10.5409/wjcp.v4.i4.66
7. Ho G, Carey KA, Cardamone M, Farrar MA. Myotonic dystrophy type 1: clinical manifestations in children and adolescents. *Arch Dis Child.* (2019) 104:48–52. doi: 10.1136/archdischild-2018-314837
8. Feingold B, Mahle WT, Auerbach S, Clemens P, Domenighetti AA, Jefferies JL, et al. Management of cardiac involvement associated with neuromuscular diseases: a scientific statement from the American Heart Association. *Circulation.* (2017) 136:200–31. doi: 10.1161/CIR.0000000000000526
9. Bassez G, Lazarus A, Desguerre I, Varin J, Laforêt P, Bécane HM, et al. Severe cardiac arrhythmias in young patients with myotonic dystrophy type 1. *Neurology.* (2004) 63:1939–41. doi: 10.1212/01.WNL.0000144343.91136.CF
10. European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association . *Europace.* (2013) 15:1070–118. doi: 10.1093/europace/eut206
11. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* (2015) 36:2793–867. doi: 10.1093/eurheartj/ehv316
12. Rijnbeek PR, Van Herpen G, Bots ML, Man S, Verweij N, Hofman A, et al. Normal values of the electrocardiogram for ages 16-90 years. *J Electrocardiol.* (2014) 47:914–21. doi: 10.1016/j.jelectrocard.2014.07.022
13. Rijnbeek PR, Witsenburg M, Schrama E, Hess J, Kors JA. New normal limits for the paediatric electrocardiogram. *Eur Heart J.* (2001) 22:702–11. doi: 10.1053/euhj.2000.2399
14. Surawicz B, Childers R, Deal BJ, Gettes LS. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. Part III: Intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee. *Circulation.* (2009) 119:235–40. doi: 10.1161/CIRCULATIONAHA.108.191095
15. DePace NL, Colby J, Hakki AH, Manno B, Horowitz LN, Iskandrian AS. Poor R wave progression in the precordial leads: Clinical implications for the diagnosis of myocardial infarction. *J Am Coll Cardiol.* (1983) 2:1073–9. doi: 10.1016/S0735-1097(83)80332-5
16. Mussinelli R, Salinaro F, Alogna A, Boldrini M, Raimondi A, Musca F, et al. Diagnostic and prognostic value of low QRS voltages in cardiac AL amyloidosis. *Ann Noninvasive Electrocardiol.* (2013) 18:271–80. doi: 10.1111/anec.12036
17. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation.* (2010) 121:1533–41. doi: 10.1161/CIRCULATIONAHA.108.840827
18. Rautaharju PM, Surawicz B, Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram. Part IV: The ST Segment, T and U Waves, and the QT Interval A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias. *J Am Coll Cardiol.* (2009) 53:982–91. doi: 10.1016/j.jacc.2008.12.014
19. Lopez L, Colan S, Stylianou M, Granger S, Trachtenberg F, Frommelt P, et al. Relationship of echocardiographic Z Scores adjusted for body surface area to age, sex, race, and ethnicity: the pediatric Heart Network Normal Echocardiogram Database. *Circ Cardiovasc Imaging.* (2017) 10:1–7. doi: 10.1161/CIRCIMAGING.117.006979
20. Evangelista A, Flachskampf F, Lancellotti P, Badano L, Aguilar R, Monaghan M, et al. European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. *Eur J Echocardiogr.* (2008) 9:438–48. doi: 10.1093/ejechocard/jen174
21. Petri H, Vissing J, Witting N, Bundgaard H, Kober L. Cardiac manifestations of myotonic dystrophy type 1. *Int J Cardiol.* (2012) 160:82–8. doi: 10.1016/j.ijcard.2011.08.037
22. Sharma A, Singh S, Mishra SK. Cardiac abnormalities in congenital and childhood Myotonic muscular dystrophy type 1. *Neuropediatrics.* (2017) 48:42–4. doi: 10.1055/s-0036-1597546
23. Choudhary P, Nandakumar R, Greig H, Broadhurst P, Dean J, Puranik R, et al. Structural and electrical cardiac abnormalities are prevalent in asymptomatic adults with myotonic dystrophy. *Heart.* (2016) 102:1472–8. doi: 10.1136/heartjnl-2015-308517
24. Usoro AO, Bradford N, Shah AJ, Soliman EZ. Risk of mortality in individuals with low QRS voltage and free of cardiovascular disease. *Am J Cardiol.* (2014) 113:1514–7. doi: 10.1016/j.amjcard.2014.02.006

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SARS-CoV-2 Associated Pediatric Inflammatory Multisystem Syndrome With a High Prevalence of Myocarditis – A Multicenter Evaluation of Clinical and Laboratory Characteristics, Treatment and Outcome

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Introduction: *Pediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-2 infection (PIMS –TS)* comprises a new disease entity having emerged after the COVID-19 outbreak in 2019.

Materials and Methods: For this multicenter, retrospective study children between 0 and 18 years with PIMS-TS between March 2020 and May 2021 were included, before availability of vaccination for children. Frequent SARS-CoV-2 variants at that period were the wildtype virus, alpha, beta and delta variants. Inclusion criteria were according to the PIMS-TS criteria, proposed by the Royal College of Pediatrics and WHO. Study aim was to review their clinical, laboratory and echocardiographic data with a focus on cardiac involvement.

Results: We report 45 patients, median age 9 years, 64% male. SARS-CoV-2 antibodies were positive in 35/41 (85%). PIMS occurrence followed local COVID-19 peak incidence periods with a time lag. The most common symptoms at presentation were fever (98%), abdominal pain (89%) and rash (80%). Fever history of > 5 days was associated with decreased left ventricular function (p = 0.056). Arterial hypotension and cardiac dysfunction were documented in 72% patients,

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increased brain natriuretic peptide in 96% and increased cardiac troponin in 64% of the children. Echocardiography revealed mitral valve regurgitation (64%), coronary abnormalities (36%) and pericardial effusions (40%). Increased NT-proBNP was significantly associated with the need of inotropics ($p < 0.05$), which were necessary in 40% of the patients. Treatment comprised intravenous immunoglobulin (93%), systemic steroids (84%) and acetylsalicylic acid (100%; 26/45 started with high dosages). For insufficient response to this treatment, five (11%) children received the interleukin-1 receptor antagonist anakinra. All patients were discharged with almost resolved cardiac signs.

Conclusion: Our analysis of non-vaccinated children with PIMS-TS demonstrates that a considerable number have associated myocarditis requiring intensive care and inotropic support. Most children showed adequate response to intravenous immunoglobulin and steroids and good recovery. Further evaluation of pediatric patients with COVID-19 associated diseases is required to evaluate the impact of new virus variants.

Keywords: COVID-19 associated pediatric inflammatory syndrome, myocarditis, cardiac decompensation, inotropic support, COVID-19, PIMS, echocardiograghy

INTRODUCTION

Pediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-2 infection (PIMS –TS) in Europe and *Multisystem Inflammatory Syndrome in Children (MIS-C)* in the United States comprises a new disease entity that emerged after the COVID-19 outbreak in 2019. Available literature from several countries reveals similarities to Kawasaki disease (KD), viral myocarditis and toxic shock syndrome, but also differences. Patients with PIMS-TS tend to be older than KD patients with a median age of 9 years. The majority of prior reported children had a COVID-19 infection 2–6 weeks before PIMS-TS and commonly presented with high fever, rash, and abdominal symptoms (1–6).

More than 70% of patients develop myocarditis with dyskinetic, impaired ventricular function, valve regurgitation, rhythm disturbance, and pericardial effusion. The coronary arteries may show perivascular echogenicity progressing to coronary aneurysms in up to 14% of the cases. Patients with PIMS-TS associated myocarditis are at increased risk for severe hypotension or cardiogenic shock, and may require intensive care treatment, inotropic support and rarely invasive cardiac support (7–10).

In the autumn of 2020 several Austrian pediatric departments noted an increasing occurrence of cases with a COVID-19 infection-associated inflammatory syndrome and myocarditis. The aim of this study was to evaluate PIMS-TS cases in Austria to describe clinical and laboratory characteristics at presentation with special focus on cardiovascular involvement, therapy and outcome.

Abbreviations: PIMS-TS, Pediatric inflammatory multisysteme syndrome-temporally associated with SARS-CoV-2; MIS-C, multisystem inflammatory syndrome in children; KD, Kawasaki disease; VSD, ventricular septum defect; ECG, electrocardiography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; CRP, C-reactive protein; IL-6, Interleukin-6; NT-proBNP: N-terminal pro B-type natriuretic PEPTIDE; IQR, Interquartile ranges.

MATERIALS AND METHODS

Study Population

The investigation included 45 consecutiv pediatric patients, age 0–18 years, diagnosed with PIMS-TS between March 2020 and May 2021 according to PIMS-TS diagnostic criteria by Royal College of Pediatrics and Child Health and WHO (11, 12). The cohort comprised all patients with PIMS-TS admitted to the Department of Pediatrics, Medical University of Vienna and eight secondary care pediatric departments in Vienna and Lower Austria. All departments had local ethics board approval for this data collection, data were deidentified, centrally connected to patient identification numbers.

Data Assessment

Clinical and diagnostic data were obtained from electronic medical records and entered in a case report form specifically designed for this study to ensure systematic data collection.

Data assessment included:

(i) Chart review regarding medical history and clinical status and medical treatment. "History of COVID-19 infection" was defined – according to WHO and RCPCH criteria as positive SARS-CoV-2 antigen or polymerase chain reaction (PCR) test or exposure to a positive tested person within the prior weeks (11, 12). "Asymptomatic COVID-19 infection prior to PIMS-TS diagnosis" applied to children who had SARS-CoV-2 antibodies at presentation and reported contact to a COVID-19 positive tested person within the prior weeks, but never had had symptoms.

(ii) Laboratory results: complete blood counts and chemistry including C-reactive protein (CRP), Interleukin-6 (IL-6), ferritin (documentation of normal or abnormal), and coagulation parameters. Cardio-specific biomarkers:

N-terminal pro-B type natriuretic peptide levels (NT-proBNP, measured by ChemiLumineszenz ImmunoAssay, Fa Roche, pg/mL), cardiac troponin T or I (TnT, TnI, high-sensitivity method; normal < 14 ng/L), documented as measured at the respective departments. Cardiac troponin was documented as normal or abnormal (no levels).

(iii) Microbiology: On admission all patients had a nasopharyngeal swab for viral polymerase chain reaction of SARS-CoV-2 done (PCR Genexpert Roche COBA 6800) and testing for SARS-CoV-2 nucleocapsid IgG antibodies to viral spike glycoprotein in this not vaccinated cohort (e.g., qualitative Elecsys® Anti-SARS-CoV-2 Test, Roche). Additionally, viral myocarditis work-up and bacterial cultures were performed. No COVID-19 antigen (rapid) tests were included.

(iv) Review of cardiac diagnostics included electrocardiography (ECG), echocardiography and cardiac magnetic resonance imaging (MRI). Further imaging comprised abdomen or kidney ultrasound, if performed based on clinical presentation.

Response to treatment was defined as decline of fever and abdominal pain, normalization of CRP and declining NT-pro BNP within 3–5 days of therapy initiation.

Statistics

Data on patient characteristics, clinical features, diagnostic results, therapy and outcome were summarized descriptively. Continuous variables were expressed as median, interquartile ranges (IQR), or minimum and maximum (min; max); categorical variables as numbers and percentages. For analysis of associations we used the Chi Quadrat Test and Students t-test, respectively.

RESULTS

Patient Characteristics

Forty-five patients with PIMS-TS were treated in the participating centers from March 2020 to May 2021 and included in the study. Their median age was 9 years, (IQR 4–12), 64% male. Further patient characteristics are given in **Table 1**. A history of COVID-19 infection was reported in 37/45 (82%). Thirty-nine/45 (87%) patients presented with PIMS-TS between October 2020 and January 2021 (n = 20) and February to May 2021 (n = 19), following local Austrian SARS-CoV-2 infection peaks, with a time lag of 3–6 weeks. The remaining 6/45 (13%) cases were reported between April and September 2020 (**Figure 1**).

TABLE 1 | Demographic data.

Characteristics	*N* (%)	Median (min; max)	Interquartile range (P25–P75)
Age, years		9 (1.2;18)	[4–12]
0–5	12 (27)		
6–10	13 (29)		
11–18	20 (44)		
Sex			
Male	29 (64)		
Female	16 (36)		
Weight (kg)		31.3 (11;79)	[19–50]
Body mass index (kg/m^2)		18	[16–20]
Comorbidity	6 (13%)		
Recurrent Bronchitis and prematurity	1		
VSD	1		
Hydronephrosis	1		
Latent tuberculosis	1		
Primary immune deficiency (cellular/humoral)	1		
Asthma, atopic dermatitis	1		
Presentation period			
April 2020 to September 2020	6 (13)		
October 2020 to January 2021	20 (44)		
February 2021 to May 2021	19 (43)		
Covid-19 positive history (weeks prior PIMS diagnosis)*	37 (82)		
0–2	1 (2)		
2–4	13 (29)		
4–6	13 (29)		
>6**	10 (22)		

**According to positivity of prior antigene or PCR tests or contact-history. **Maximum 8 weeks. VSD, ventricular septum defect.*

Clinical Presentation

Table 2 shows leading symptoms at admission. All patients presented in an impaired general condition, fever was present in 44/45 (98%) children, abdominal pain in 89%, and a polymorphic rash in 80% of the patients. Fever history of > 5 days was associated with decreased left ventricular function [11/15 (73%; p = 0.056)]. Further symptoms were cough (6%), pharyngitis (15%), and headache (4%). No serious primary respiratory symptoms were reported.

Cardiac Abnormalities

Table 3 illustrates the observed cardiac abnormalities. Cardiac dysfunction with severe arterial hypotension and shock was present in 31/45 (72%) children and required admission to an intensive care unit for 14/45 (31%) patients, seven of these required oxygenation, three of those patients were in cardiogenic shock and four children required oxygen because of pleural effusions and pulmonary edema. Chest x-ray revealed signs for pulmonary congestion (11%) and inflammatory changes (24%), but no patient required mechanical ventilation.

Cardiac work up revealed abnormal echocardiography in 40/45 (89%) patients, including left ventricular dysfunction (33%), mitral valve regurgitation (64%), pericardial effusions (15%), and echogenic walls of the coronary arteries (36%), no coronary aneurysms were detected. Additional pleural effusions

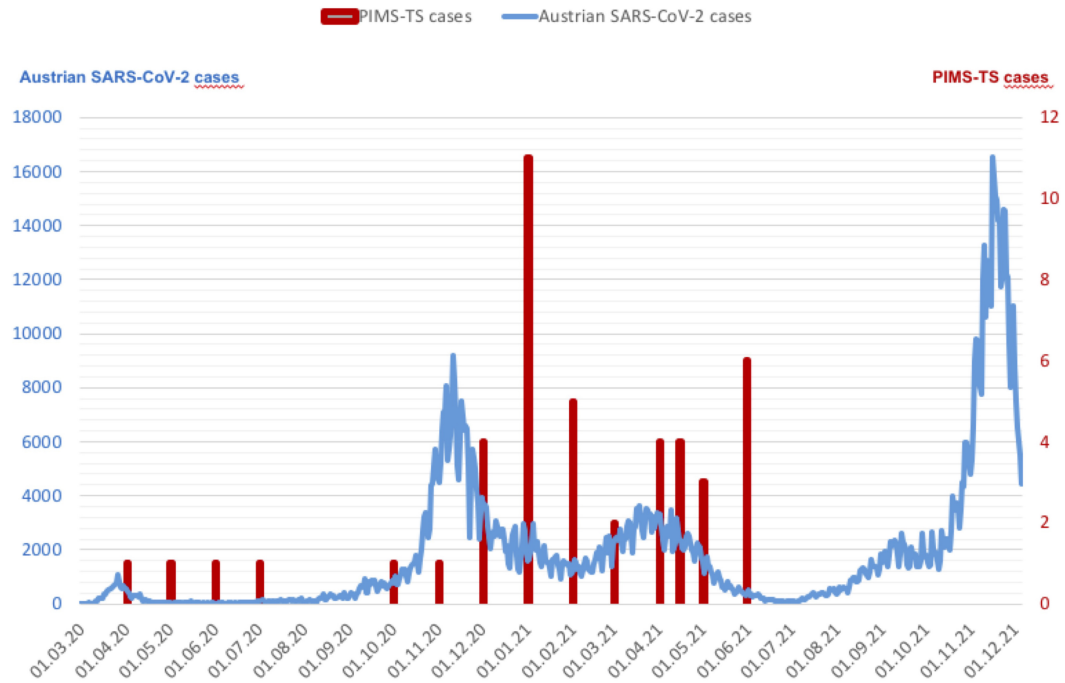

FIGURE 1 | The Graph demonstrates patients with PIMS-TS and Austrian COVID-19 cases (*blue curve*, data from Statistic Austria) (29). Of the 45 children 39/45 (87%) patients presented with PIMS-TS between October 2020 and January 2021 (n = 20) and February to May 2021 (n = 19). The remaining 6/45 (13%) cases were reported between April and September 2020 (*red bars*).

TABLE 2 | Signs and symptoms.

Signs and symptoms at presentation	*N* (%)
Impaired general condition	45 (100)
Fever	44 (98)
Gastrointestinal symptoms*	40 (89)
Rash	36 (80)
Pharyngitis, cough	9 (20)
Cerebral/head ache	2 (6)
Arterial hypotension	31 (72)

**Inclusive vomiting, diarrhea, and abdominal pain.*

TABLE 3 | Cardiac diagnostic.

Echocardiography and ECG	*N* (%)
Echocardiography generally abnormal	40 (89)
LV dysfunction, decreased LV ejection fraction	15 (33)
Mitral valve regurgitation	29 (64)
Coronary artery abnormalities	16 (36)
Additional pleural effusions	8 (18)
Isolated pleural effusions*	5 (11)
Electrocardiography	
Repolarisation abnormalities	12 (27)

*LV, left ventricular. *2 with combined pericardial and pleural effusions.*

were documented in 8/45 (18%) children. Another 5/45 (11%) patients with normal echocardiography results had pericardial effusions (in two patients a combination of pericardial-and pleural effusions) at presentation.

Seven patients had a cardiac MRI performed in the acute phase of PIMS-TS, two revealed pathological results (one had late enhancement of left ventricle posterior wall and one myocardial edema, no fibrosis).

ECG abnormalities were found in 12/45 (27%) children, 8% had ST elevations and 22% T inversion on left precordial leads lasting for 3–8 days. No relevant arrhythmias were detected.

Laboratory Results

Table 4 summarizes the results of the laboratory work up. The majority of patients (43/45; 96%) showed increased levels of NT-proBNP (median 8876 pg/ml; IQR 2677–10,556) and increased cardiac troponin in 29/45 (64%) patients. Most children (80%) had both cardiac biomarkers abnormal. Increased NT-proBNP was significantly associated with the need of inotropics ($p < 0.05$) (**Figure 2**). No other associations were found for abnormal NT-proBNP levels or troponin elevation. Markedly increased CRP was present in 37/45 (82%, IQR 14–27), increased Interleukin-6 in 16/35 (46%, IQR 31–1546), and abnormal ferritin in 31/42 (74%) children. Transient impairment of renal function with creatinine elevation was reported in 29% patients in the course of PIMS-TS.

SARS-CoV-2 testing at presentation revealed positive PCR from nasopharyngeal swab in 9/44 (20%) and COVID-19 IgG antibodies in 35/41 (85%) patients. A "positive COVID-19 history" was documented in 37/45 (82%) children, who all had confirmed COVID-19 IgG antibodies on admission

TABLE 4 | Laboratory results.

Laboratory results	Reference values	Abnormal at admission, *n* (%)	Median	Interquartile range (P25–P75)
Cardiac-biomarkers				
NT-proBNP, pg/ml	<125	43 (96)	6477	[2677–10556]
Cardiac troponins ng/L	<14	29 (64)		
Blood chemistry				
CRP, mg/dL	<0.5	37 (82)	19	[14–27]
Interleukin-6, pg/mL	<7	16 (46)	181	[31–1546]
Ferritin, mcg/L	6–60	31 (74)		
Creatinin, mg/dL	0.31–0.47	13 (29)		
Fibrinogen (Clauss), mg/dL	200–400	31 (69)	470	[280–550]
Covid-19 diagnostics at presentation				
SARS-CoV-2 PCR				
Positive		9/44 (20)		
Negative		35/44 (79)		
Not available		1		
SARS-CoV-2 antibodies				
Positive		35/41 (85)		
Negative		6/41 (15)		
Not available		4		

Für NT-proBNP, brain natriuretic peptide; CRP, C-reactive protein.

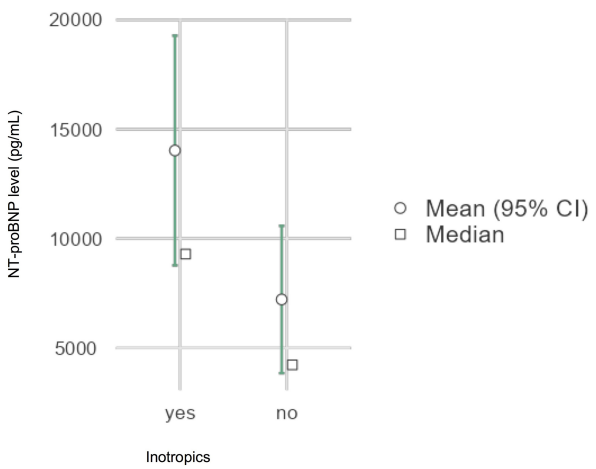

FIGURE 2 | Elevated NT-proBNP levels were associated with the need of inotropics, $p < 0.05$ Inotropics: milrinone ($n = 6$), noradrenalin ($n = 11$), dobutamine ($n = 1$). NT-proBNP: N-terminal-pro-B type natriuretic peptide.

(**Tables 1** and **4**). Out of 45 patients with PIMS-TS, 17 (38%) had "prior asymptomatic COVID-19 infection" with reported contact to a COVID-19 positive tested person within 2–6 weeks prior to admission, no symptoms or tests in the past, but positive SARS-CoV-2 antibodies at presentation/on admission.

Treatment

Table 5 summarizes the treatment of our cases. Severe myocardial dysfunction and arterial hypotension required therapy with inotropic agents in 18/45 (40%; milrinone: $n = 6$, dobutamine: $n = 1$, norepinephrine: $n = 11$).

Anti-inflammatory treatment comprised intravenous immunoglobulin 1–2 gram per kilogram bodyweight over 12–24 h given to all 42/45 (93%) but three children. Steroids were given in 38/45 (84%), of these 24/38% (63%) received methylprednisolone (10–30 mg per kg and day, over 3 days) and 16/38 (42%) prednisolone 2 mg/kg/day, two patients received both. Steroids were administered until fever cessation and then tapered over 2 weeks. Acetylsalicylic acid (aspirin) was given in all cases, 26/45 (58%) received high dosages (30 mg/kg/day) initially, followed by low dose (3–5 mg/kg/day) for 3 months in all but 6 patients, who received low dose aspirin for 6 weeks. For recurrent fever and persisting inflammation, 5/45 (11%) patients were treated with the recombinant Interleukin-1 receptor antagonist anakinra with 2–4 mg/kg/day over 3 days in 3 dosages and then reduced over 6 days, according to inflammation signs and symptoms. Baseline clinical and biochemical characteristics were indifferent in anakinra treated patients from the other PIMS patients. All but six children (87%) received prophylactic anticoagulation with enoxaparin subcutaneously. No thrombotic events were reported. Treatment response (decline of fever, symptoms and inflammation parameter) between 3 and 5 days after initiation of therapy was reported in 38/45 (84%). For three of the remaining seven patients the decision was made to administer another course of IVIG and four children received the above mentioned anakinra. All patients survived.

DISCUSSION

This study is a descriptive analysis of 45 consecutive patients with PIMS-TS admitted to nine pediatric departments in eastern Austria between March 2020 and May 2021. Almost all patients presented in reduced general condition with

TABLE 5 | PIMS treatment and outcome.

Treatment	*N* (%)
IVIG 1–2 grams/kg over 12–24 h	42 (93)
Corticosteroids	38 (84)
Methylprednisolon (10–30 mg/kg over 3 days)*	24 (53)
Prednisolon (2 mg/kg)	16 (35)
Acetylsalicylic acid	45 (100)
Primary high dose (30–50 mg/kg for 3–5 days)*	26/45 (58)
Low dose (3–5 mg/kg for 3 months)	39/45 (87)
Anakinra (2–4 mg/kg/day)	5 (11)
High fever and gastrointestinal symptoms, exanthema, konjuntivitis	5/5
Arterial hypotension, ICU	3/5; 2/5
Markedly elevated NT-pro BNP; CRP	5/5; 4/5
Prior IVIG	5/5
Prior prednisolone/methylprednisolone	2/5; 3/5
Inotropes	18 (40)
Milrinon	6 (13)
Dobutamine	1 (2)
Norepinephrine	11 (24)
Respiratory support	
Oxygen intranasal insufflation	7 (16)
Treatment response (improved clinical, laboratory, ECG and echocardiography) within 3–5 days after treatment start	38 (84)

*IVIG, intravenous immunoglobulin; ECG, electrocardiography; ICU: intensive care unit; CRP, C-reactive protein; IVIG, immunoglobulin. *Dosage according to local decision.*

fever, rash and gastrointestinal symptoms. Importantly, three quarters of the patients had cardiac involvement including arterial hypotension, cardiogenic shock, and with signs and symptoms of myocarditis.

The majority of our patients were diagnosed with PIMS-TS following the local Austrian SARS-CoV-2 infection peaks between October 2020 and January 2021 and February to May 2021, before approval of the vaccination for children. Their prior COVID-19 infection was most likely caused by the SARS-CoV-2 wild virus type B1 from spring 2020, which was followed by the British variant (B1.1.7, Alpha) in autumn 2020. The Beta variant (B.1.351) was seen between January and March 2021, thereafter the Delta variant (B.1.617.2) took over in May 2021 (dominant until December 2021).

Patients with PIMS-TS in our cohort were older, had myocarditis and circulatory dysfunction, contrary to KD (8). Additionally, laboratory signs indicated general inflammation and cytokine release as reflected by increased CRP, IL-6 and ferritin, consistent with the PIMS-TS and MIS-C criteria, but again different to KD (3, 5, 13). The prominent gastrointestinal symptoms, which in our population often delayed diagnosis, may have been caused by a gastrointestinal epithelitis as described by Yonker et al. (14). During the study period high fever, reduced condition and abdominal pain in combination with a COVID-19 history increased the suspicion index of PIMS-TS diagnosis to initiate early effective treatment.

In our analysis 72% of the patients presented with arterial hypotension, abnormal cardiac troponin and almost all patients had significantly increased NT-proBNP, indicating relevant myocardial stress. The initial shock situation presumably was a combination of cardiac dysfunction due to myocarditis and vasoplegia because of inflammation. In a majority of patients echocardiography revealed left ventricular dysfunction and mitral valve regurgitation, comparable to the multicenter European cohort study by Valverde et al. who summarized 286 patients after PIMS-TS with shock, myocarditis and cardiac dysfunction. Their patients (93%) also had raised cardiac troponin suggesting myocardial injury in the course of PIMS-TS (8).

Most of our patients had a combination of increased cardiac troponins, NT-proBNP and inflammation parameters, which have been described to be highly suggestive for myocarditis (8). Also in children troponin I and T poses a valid parameter of myocardial injury (15, 16).

Myocarditis is an inflammatory disease of the heart muscle with diverse causes, such as immunological or viral, that cannot be differentiated easily (17). Of our patients, 82% had a positive COVID-19 history and SARS-CoV-2 antibodies, suggestive of an possibly ongoing immunological process. Although an investigation demonstrated widespread antigenemia in several organs in the absence of nasopharyngeal virus material weeks after SARS-CoV-2 infection (14), another study suggested that persistent antigenemia is not a common contributor to MIS-C (18). We speculate that our unvaccinated patients may have developed an immunologically triggered multi-organ inflammation with cardiac involvement and signs of myocarditis after infection with the mentioned SARS-CoV-2 variants.This would be consistent with international epidemiological studies from the United Kingdom, United States and France reporting PIMS-TS with myocarditis 4–6 weeks after local infection peaks. Their patients also had increased cardiac troponins and positive SARS-CoV-2 antibodies, but negative COVID-19 PCR, also indicating a post-viral immunologically triggered process followed by cardiac dysfunction (2, 19, 20). In contrast, Belhadjer et al. published a case series of 35 children with PIMS-TS and significant ventricular dysfunction (28% required extracorporeal membrane oxygenation) with only mild troponin elevation. However, 88% had positive COVID-19 PCR, indicating a rather direct viral induced myocarditis (7). It remains to be seen if later variants of the SARS-CoV-2 virus will also cause PIMS-TS or similar syndromes with cardiac affection.

The majority of our patients received anti-inflammatory treatment with corticosteroids, either prednisolone or methylprednisolone pulse therapy (dosages varied between the pediatric departments) and immunoglobulins. According to available data at the time of the study, management and treatment of patients with PIMS-TS was based on guidelines for related syndromes like KD, toxic shock syndrome and macrophage-activation syndrome (21). More recent literature confirmed a benefit of IVIG and steroids compared to IVIG alone with regard to cardiac function and general outcome (22, 23). One explanation for the good response to steroids

might be biological similiarities to toxic shock syndrome, involving the T-cells, as recently described by Sacco et al. (24). Furthermore, recently appeared evidence supports early start of anti-inflammatory treatment (25, 26). Our patients showed excellent response with improved blood pressure to initial volume administration, immunomodulatory and anti-inflammatory treatment. This might be the reason why despite of a high proportion of patients with arterial hypotension (72%) only 40% required inotropes. All patients were discharged with improved cardiac function and general condition, no patient died. We confirm a high morbidity but low mortality in patients with PIMS-TS, as described in other cohorts (9, 27).

The long-term management after PIMS-TS in general and particularly in patients with coronary involvement is not well established. Physical sparing, sports ban for at least 3 months and regular follow-up by a pediatric cardiologist have usually been recommended. Follow-up investigations should comprise echocardiography and, in some cases cardiac MRI and cardiopulmonary exercise test before restarting physical activity (28).

Our study has some limitations. The data collection was retrospective but we went through much efforts to identify all patients presenting with PIMS-TS to the participating hospitals. SARS-Cov2 mutations were not documented consistently, and of the 9 patients with positive PCR incomplete information concerning Ct values are available. As this was an observational, retrospective study, diagnostic work up was per local institutional standards with excellent documentation. For uniform local data collection some of the results (such as ferritin) were only documented as "normal" or "abnormal," which affected quality of analysis. Treatments were not standardized and therefore varied between the centers. Echocardiography and cardiac evaluation in the different departments was performed by pediatric cardiologists.

CONCLUSION

In our analysis of unvaccinated Austrian children with PIMS-TS three quarters of the patients had cardiac involvement with significant myocarditis and circulatory dysfunction requiring inotropic support and intensive care management. Our data confirm the excellent response to intravenous immunoglobulins and steroids resulting in clinical improvement and discharge of the children with almost resolved cardiac signs. Follow-up of our patient series is ongoing to detect long term complications of this new disease entity. Further evaluation of pediatric patients with COVID-19 associated diseases is required to evaluate the impact of emerging virus variants.

What is already known on this topic

- Multisystem inflammatory syndromes in children can involve several organs. Kawasaki disease (KD) is a well-known inflammatory disease, where an acute vasculitis can cause a mild and transient myocarditis.
- A new COVID-19 associated multisystem inflammatory syndrome (PIMS-TS in Europe, MIS-C in USA) shows several similarities but also different features compared to KD, including the older age and more severe cardiac involvement.
- Several international investigations demonstrated a temporal association between local SARS-CoV-2 infection peaks with an increasing incidence of PIMS-TS cases.

What this study adds

- For a better understanding of this new disease it is useful to collect as much information as possible with regard to the considerable number of children who developed PIMS-TS associated cardiac impairment.
- Our study adds more valuable information concerning the clinical picture of PIMS-TS and signs of an associated myocarditis.
- This study contributes data from Middle Europe concerning PIMS-TS after infection with SARS-Cov-2 wild-virus, before availability of the vaccination for children.

How this study might affect research, practice or policy

The increasing evidence and understanding of the new PIMS-TS and its distinction from KD improves quality and tempo of diagnosis.

Because of the high prevalence of cardiac involvement in the course of PIMS-TS, early identification of children who require immediate cardiac (inotropic) support and anti-inflammatory treatment is crucial to improve outcome of this severe complication.

DATA AVAILABILITY STATEMENT

De-identified patient datasets will be available upon request to the corresponding author.

AUTHOR CONTRIBUTIONS

KT, BK, and IM-B conceived and designed the study. BK and KT conducted analysis and produced the tables. KT produced the initial draft, editing, and submission. CM did additional editing. All authors take full responsibility for data collection, data analysis, interpretation and submission of the study.

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REFERENCES

1. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. (2020) 324:259–69. doi: 10.1001/jama.2020.10369
2. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. (2020) 383:334–46. doi: 10.1056/NEJMoa2021680
3. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. (2020) 369:m2094. doi: 10.1136/bmj.m2094
4. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. (2020) 395:1607–8. doi: 10.1016/S0140-6736(20)31094-1
5. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. (2020) 395:1771–8. doi: 10.1016/S0140-6736(20)31103-X
6. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, et al. Treatment of multisystem inflammatory syndrome in children. *N Engl J Med*. (2021) 385:11–22.
7. Belhadjer Z, Meot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation*. (2020) 142:429–36.
8. Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in europe. *Circulation*. (2021) 143:21–32. doi: 10.1161/CIRCULATIONAHA.120.050065
9. Miller AD, Zambrano LD, Yousaf AR, Abrams JY, Meng L, Wu MJ, et al. Multisystem inflammatory syndrome in children-United States, February 2020-July 2021. *Clin Infect Dis*. (2021) 2021:ciab1007.
10. Kurz H, Gombala T. Multisystem inflammatory syndrome in children (MIS-C)-A case series in December 2020 in Vienna, Austria. *Front Pediatr*. (2021) 9:656768. doi: 10.3389/fped.2021.656768
11. RCPCH. *Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19*. (2020). Available online at: https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance (accessed May 22, 2020)
12. WHO. *Multisysteme Inflammatory Syndrome in Children and Adolescents with COVID-19. Scientific Brief*. Geneva: WHO (2020).
13. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis*. (2020) 79:999–1006.
14. Yonker LM, Gilboa T, Ogata AF, Senussi Y, Lazarovits R, Boribong BP, et al. Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier. *J Clin Invest*. (2021) 131:e149633. doi: 10.1172/JCI149633
15. Clerico A, Aimo A, Cantinotti M. High-sensitivity cardiac troponins in pediatric population. *Clin Chem Lab Med*. (2022) 60:18–32. doi: 10.1515/cclm-2021-0976
16. Franzini M, Lorenzoni V, Masotti S, Prontera C, Chiappino D, Latta DD, et al. The calculation of the cardiac troponin T 99th percentile of the reference population is affected by age, gender, and population selection: a multicenter study in Italy. *Clin Chim Acta*. (2015) 438:376–81. doi: 10.1016/j.cca.2014.09.010
17. Canter CE, Simpson KE. Diagnosis and treatment of myocarditis in children in the current era. *Circulation*. (2014) 129:115–28. doi: 10.1161/CIRCULATIONAHA.113.001372
18. Sigal GB, Novak T, Mathew A, Chou J, Zhang Y, Manjula N, et al. Measurement of SARS-CoV-2 antigens in plasma of pediatric patients with acute COVID-19 or MIS-C using an ultrasensitive and quantitative immunoassay. *medRxiv*. (2021). [Preprint].
19. England PH. *Coronavirus (COVID-19) Statistics and Analysis*. (2020). Available online at: https://www.gov.uk/guidance/coronavirus-covid-19-statistics-and-analysis (accessed July 16, 2020)
20. Belot A, Antona D, Renolleau S, Javouhey E, Hentgen V, Angoulvant F, et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. *Euro Surveill*. (2020) 25:2001010. doi: 10.2807/1560-7917.ES.2020.25.22.2001010
21. Harwood R, Allin B, Jones CE, Whittaker E, Ramnarayan P, Ramanan AV, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *Lancet Child Adolesc Health*. (2021) 5:133–41. doi: 10.1016/S2352-4642(20)30304-7
22. Son MBF, Murray N, Friedman K, Young CC, Newhams MM, Feldstein LR, et al. Multisystem inflammatory syndrome in children - initial therapy and outcomes. *N Engl J Med*. (2021) 385:23–34. doi: 10.1056/NEJMoa2102605
23. Ouldali N, Toubiana J, Antona D, Javouhey E, Madhi F, Lorrot M, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. *JAMA*. (2021) 325:855–64. doi: 10.1001/jama.2021.0694
24. Sacco K, Castagnoli R, Vakkilainen S, Liu C, Delmonte OM, Oguz C, et al. Immunopathological signatures in multisystem inflammatory syndrome in children and pediatric COVID-19. *Nat Med*. (2022). [Online ahead of print]. doi: 10.1038/s41591-022-01724-3
25. Brisca G, Consolaro A, Caorsi R, Pirlo D, Tuo G, Campanello C, et al. Timely recognition and early multi-step antinflammatory therapy may prevent ICU admission of patients with MIS-C: proposal for a severity score. *Front Pediatr*. (2021) 9:783745. doi: 10.3389/fped.2021.783745
26. German DGPI guidelines. *Stellungnahme der DGPI, API, DGKJ, DGPK, GPOH, GKJR, GPP und STAKOB zur Klinik, Diagnostik und Therapie von Kindern mit COVID-19 – Update Februar 2022*. (2022). Available online at: https://dgpide/klinik-diagnostik-therapie-kinder-mit-covid-feb-2022/ (accessed February 14, 2022).
27. Matsubara D, Chang J, Kauffman HL, Wang Y, Nadaraj S, Patel C, et al. Longitudinal assessment of cardiac outcomes of multisystem inflammatory syndrome in children associated with COVID-19 infections. *J Am Heart Assoc*. (2022) 11:e023251. doi: 10.1161/JAHA.121.023251
28. Theocharis P, Wong J, Pushparajah K, Mathur SK, Simpson JM, Pascall E, et al. Multimodality cardiac evaluation in children and young adults with multisystem inflammation associated with COVID-19. *Eur Heart J Cardiovasc Imaging*. (2021) 22:896–903. doi: 10.1093/ehjci/jeaa212
29. Home page SA. *Covid-19 Cases*. Home page, SA, South Australia. (2021). Available online at: https://de.statista.com/statistik/daten/studie/1150777/umfrage/entwicklung-der-taeglichen-fallzahl-des-coronavirus-in-oesterreich/.

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Physical Activity in Fontan Patients Relates to Quality of Life and Sleep Quality

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Background and Aim: Fontan patients tend to have reduced physical exercise capacity. This study investigates physical activity (PA) and its relationship to exercise capacity, heart rates, cardiac function, biomarkers, health-related quality of life (HRQoL), and sleep quality.

Methods: Cardiovascular magnetic resonance (CMR), exercise testing (CPET), 24 h-ECG, and blood samples were prospectively performed in 38 patients, age 13 (11–16) years. PA was assessed by accelerometer during 7 consecutive days. HRQoL was self-assessed with KIDSCREEN-27 and SF-36 according to patients' age; sleep quality with Pediatric Sleep Questionnaire (PSQ) and Pittsburgh Sleep Quality Index (PSQI).

Results: Daily moderate to vigorous physical activity (MVPA) was in median (IQR) 40 (28–57) mins; 7/38 (18%) patients reached the recommended 60 mins/day of MVPA. MVPA did not correlate with gender, age, single ventricle morphology, time from Fontan, heart rate, ventricular volumes, and ejection fraction at CMR, biomarkers, or CPET. Physical wellbeing ($r = 0.33$, $p = 0.04$), autonomy ($r = 0.39$, $p = 0.03$), and social support ($r = 0.43$, $p = 0.009$) assessed using the KIDSCREEN-27, and both physical ($r = 0.57$, $p = 0.03$) and mental ($r = 0.54$, $p = 0.04$) domains of the SF-36 questionnaire correlated with daily minutes of MVPA. PSQI global sleeping score ($r = -0.7$, $p = 0.007$), and PSQ scales for behavior ($r = -0.36$; $p = 0.03$) correlated with daily minutes of MVPA.

Conclusion: Only 18% of the Fontan patients meet the recommendation for daily MVPA. Measures of exercise capacity, cardiac function or chronotropic competence are not correlated to daily physical activity. In contrast, HRQoL and sleep quality seem to be associated with regular physical activity.

Keywords: single ventricle, Fontan, physical activity, quality of life, sleep quality

INTRODUCTION

Treatment of patients with a single ventricle consists of a staged procedure, the last step being the Fontan operation (1). In the last decades relevant developments in surgical, interventional, and medical therapies lead to a dramatical raise in survival rate of Fontan patients. Nevertheless because of the unphysiological hemodynamics of the Fontan circulation, morbidity remains important during mid- and long-term follow-up (1). It is well known that objective exercise capacity in Fontan patients is significantly decreased compared to normal subjects (2–5). The postulated reasons for this are various and include surgical factors, cardiac factors, such as systolic and diastolic dysfunction, morphology of the dominant ventricle, abnormal chronotropic response, diseased pulmonary vasculature, as well as lung dysfunction, cachexia, and decreased muscle mass (1). Guidelines for physical activity (PA) and sport participation in Fontan patients generally recommend light- to moderate intensity activity (6, 7). Some degree of PA is also recognize to help for peer and family socialization (8), reaching of normal developmental milestones, and decreasing the risk for sedentary lifestyles (9). Moreover, training programs for Fontan patients positively influence their objective exercise capacity (10) and self-reported as well as proxy-reported health-related quality of life (HRQoL) (10, 11).

In previous studies the reported PA level in Fontan patients failed to reach the current PA recommendations for the healthy population (2–5, 12–15). Only few authors have marginally assessed the effects of PA on quality of life (HRQoL) and sleep quality (11, 16).

The purpose of this study was to determine PA levels in a cohort of children, adolescents, and young adults with a Fontan physiology, and to focus on the relationship between PA and patient characteristics, cardiac function, exercise capacity, heart rates, serum biomarkers, and particularly HRQoL, and sleep quality.

METHODS

Study Design and Patients' Selection

This is a single centre, prospective, observational study (2019–2021) in a cohort of 38 Fontan patients, children and young adults. The patients were identified from the cardiac electronic database of our institution. Inclusion criteria were ability to perform cardiopulmonary exercise testing (CPET) and to undergo cardiovascular magnetic resonance (CMR) without the need for sedation, as well as written informed consent of the subject or his/her legal guardian. Exclusion criteria were younger age, any contraindication for CMR or pregnancy. Every test was performed following the clinical standards of our institution. All tests were performed within a maximal time interval of 6 months to each other.

Physical Activity

Physical activity was measured using an accelerometer (ActiGraph® GT3X+, Pensacola, Florida, USA) for 7 consecutive days, during a regular school/work week and including both weekdays and weekends) (17). Participants were asked to wear the device 24 h/day on the right hip. Participants with a wear time more than 4 days and longer of 10 h/day were included in the study. Activity was analyzed during the timeframe from 06:00 am to 10:00 pm using the manufacturer's software (ActiLife 6.13.4). The time during which the patients wear or non-wear the accelerometer was calculated with an automatic algorithm as reported by Choi et al. (18). The accelerometer registered accelerations with a frequency of 100 Hz and an epoch lengh 60 s. The total vector magnitude in counts was calculated from the three axes of movement (horizontal, vertical, and diagonal). The activity intensity was analyzed and categorized in accordance with Evenson's Actigraph cut-off points (moderate intensity PA was defined as >2,296 counts/min and vigorous PA as >4,012 counts/min) (17, 19). Time spent in activity of a defined intensity (light, moderate, or vigorous) was provided by Actilife by summing minutes in a day where the count met the criterion for that intensity. Moderate to vigorous physical activity (MVPA) was categorized as inactive (<60 mins of MVPA per day) or active (≥60 mins of MVPA per day) according to the World Health Organization guidelines (20). Moderate physical activity corresponds to activities such as brisky walking or biking with a light effort. Vigorous physical activity corresponds to activities such as jogging, hiking, or playing a team sport (20). Normal values regarding PA in Fontan patients are lacking.

Bioparameters

Ventricular volumes and function (ejection fraction) were measured by CMR using a 1.5 T scanner (Signa HDxt and MRI 450 or GE Signa Artist GE Medical Systems, Milwaukee, WI, USA) and a 32-channel phased array cardiac coil. Steady state free precession (SSFP) cine images were acquired in a horizontal and vertical long-axis plane, as well as in a short-axis plane covering the entire single ventricle. The SSFP parameters were as follows: retrospective cardiac gating, 40 phases/cardiac cycle, TE 1.5–1.8 ms, TR 2.8–3.1 ms, flip angle 45°, bandwidth 125 kHz, matrix 224 × 224, number of excitations 1, field of view 250–350, views per segment 4–10 according to heart rate. In-plane resolution was 1–1.5 mm and true temporal resolution was <25 ms.

Blood-sample for cardiac biomarkers were collected the same day as the CMR scan, aliquoted into freezer vials, and stored at −80°C. All samples were frozen and thawed only once before analysis. NTproBNP and growth differentiation factor 15 (GDF-15) were measured in plasma by an ISO 15189 accredited diagnostic laboratory using a Cobas e411 analyser according to the manufacturer's instructions using commercial reagents (Roche, Rotkreuz, Switzerland) with coefficients of variation of 1.1% (139 ng/L) and 3.1% (1,322 ng/L), respectively. Protein delta homolog 1 (DLK-1) and insulin-like growth factor-binding protein 7 (IGFBP-7) were measured by ELISA in serum and were analyzed on a Synergy HT Multi-Detection Microplate Reader (BioTek, Winooski, VT, USA) according to the manufacturer's instructions with coefficients of variation in our samples ($n = 5$) of 13.8% (34.5 μg/L) and 10.5% (57 μg/L) respectively. These biomarkers were chosen based on previous data of the literature for (21–23).

24 h ECG and accelerometer registrations were started the same day of the CMR scan. Cardiopulmonary exercise test was performed on a cycle ergometer with a ramp protocol in accordance with our institutional standards (24). Resting parameters were defined as the mean values of the raw data acquired during 3 mins in a sitting position without cycling; the peak parameters were the mean values of the raw data acquired during the 30-sec time interval at maximal exercise (peakVO_2).

Health-Related Quality of Life and Sleep Quality

In patients older than 16 years the self-perceived HRQoL was evaluated using the questionnaire 36-item short-form (SF-36) The SF-36 questionnaire covers physical, mental and social aspects using eight categories of questions with scores ranging from 0 (bad) to 100 (best) and subscales with 2 to 10 entries, and has been validated in various categories of patients (25). Reference values for the normal adult population have been published (26).

Children younger than 16 years completed the KIDSCREEN-27 test, which is a short version of the original KIDSCREEN-52, together with their parents or guardians. The 27-item questionnaire assesses 5 HRQoL dimensions: Physical wellbeing, psychological wellbeing, arent relations and autonomy, social support and peers, and school. Each item is scored on a 5-point scale (from 1 = "not at all" to 5 = "very much"). For each dimension, a scoring algorithm is used to calculate "T-scores" scaled with reference values of 50±10 (27).

Evaluation of sleep quality was performed in children <16 years of age with a Pediatric Sleep Questionnaire (PSQ) (27), with their parents being asked to complete the questionnaire. The total sleep-related breathing disorder (SRBD) scale evaluates symptoms such as snoring, apneas, difficulty breathing during sleep, daytime sleepiness, inattentive or hyperactive behavior. The SRBD scale is divided in 3 subscales: 4-items for *Sleepiness*, 4-items for *Snoring*, and 6-items for *Attention/hyperactivity*. Every positive answer gives one point and a positive PSQ scoring; the cut-off for each sub-scale is 0.33, with a mean score of ≥0.33 being considered positive and a mean score <0.33 negative.

Patients older than 16 years completed the Pittsburgh Sleep Quality Index (PSQI) (28). This is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. The sum of 7 component scores results in a global score and the cut-off for pathology is set by 5 points. The German-language versions were used for all instruments.

Statistics and Ethics

Statistical analysis was performed using SPSS 27.0.0 (SPSS Inc, IBM Company, Chicago Illinois/USA). Continuous variables are expressed as median (IQR), categorical data as counts (percentages). For normally distributed continuous variables, Levene's test for equality of variance was used to analyse if the variability in the two groups was significantly different and group comparison of was performed using two-sample *t*-tests. Kolmogorov-Smirnov analyses were used for group comparisons of non-normally distributed continuous variables. Ordinal, nominal, and dichotomic variables were evaluated with contingency tables and chi-square-tests. Correlations between continuous variables were tested using Pearson's (for the normally distributed variables) or Spearman's (for the non-normally distributed variables) correlations. Binomial logistic regression was used for dichotomic variables. Significance was defined by values of $p < 0.05$.

The study followed the ethical guidelines of the declaration of Helsinki for medical research involving human subjects. The study was approved by the local ethical authorities (KEK: 2018-01878).

TABLE 1 | Patients' characteristics.

Cardiac anatomy	*n*	%
Left single ventricle	18	47
Double inlet left ventricle	8	21
Tricuspid atresia	4	10
Pulmonary atresia with intact ventricular septum	3	8
Dysbalanced atrioventricular septal defect	3	8
Right single ventricle	20	53
Hypoplastic left heart syndrome complex	13	34
Double outlet right ventricle	6	16
Dysbalanced atrioventricular septal defect	1	3

RESULTS

Patients and Cardiac Parameters

A total of 38 Fontan patients, 15 (39%) females, were included in the study. Median (IQR) age was 13.1 (11.0–16.2) years, weight 46.5 (32.3–60.6) kg, height 152 (140–166) cm, and BMI 18.3 (17.4–21.6) kg/m². Twenty (53%) patients had a single right ventricle, being hypoplastic left heart syndrome the most frequent diagnosis (13 patients, 34%of all patients). Patients cardiac anatomies are presented in **Table 1**. Age at Fontan surgery was 2.6 (2.2–2.9) years and time interval from Fontan surgery 10.9 (8.3–12.2) years. The surgical technique of total cavopulmonary connection consisted of an extracardiac tunnel in all patients. Cardiac medication was taken by 19 patients (50%) and consisted of an ACE-inhibitor in 9 (23%), diuretics in 6 (15%) and sildenafil in 4 (10%) sildenafil. Anticoagulation consisted of aspirin in 35 (92%) and warfarin in three (7%) patients.

At time of the study, two (5%) patients were treated for protein loosing enteropathy, and one (2.5%) for plastic bronchitis. Eight (21%) patients had a previous history of chylothorax, CMR measurements of ventricular volumes resulted in end-diastolic volume of 116.0 (81.7–136.0) ml/m^2 and end-systolic volume of 51.5 (31.5–66.7) ml/m^2. Median ejection fraction (EF) was 51.2 % (48.6–58.6), with 15 patients (39%) having an EF < 50%.

Serum cardiac biomarkers showed following values: GDF-15 502.2 (450.9–569.3) pg/mL, DLK-1 1.16 (0.41–2.82) ng/mL, IGFBP-7 101.4 (80.9–117.6) ng/mL, and NT-pro-BNP 59 (37–126) ng/L. NT-pro-BNP was within the range of normality, while for the other parameters validated normal values do not exist yet.

Median heart rate (HR) measured during 24 h-ECG was 80 bpm (75–89), maximal HR was 149 bpm (137–164). A sinus or

TABLE 2 | Physical activity levels of all patients.

Physical activity (min/7 days)	Median (IQR)
Light	2,287 (1,761–2,568)
Moderate	177 (140–246)
Vigorous	47 (31.5–81)
Physical activity, total of 7 days	
Sedentary (%)	56.6 (50.2–63.4)
Light (%)	39.3 (32.9–43.7)
Moderate (%)	3.3 (2.3–4.6)
Vigorous (%)	0.76 (0.53–1.51)
Moderate-to-vigorous physical activity	
Total, 7 days (minutes)	249 (188–323)
Total, 7 days (%)	4.3 (3.4–6.2)
Minutes/day	40 (29–55)
> 60 mins/day, *n* (%)	7 (18)

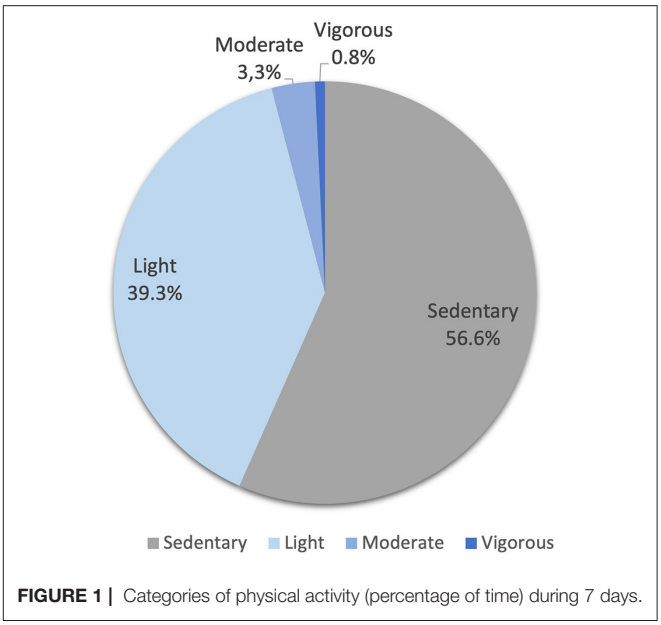

FIGURE 1 | Categories of physical activity (percentage of time) during 7 days.

atrial rhythm was present in 31 patients (79%), a combination of sinus and junctional rhythm in 4 (10%), and solely junctional rhythm in 3 (8%). A history of supraventricular arrhythmias was reported in 4 (10%) patients, but none of them was under antiarrhythmic medication at time of the study.

CPET showed, as expected, reduced exercise capacity with a peakVO_2 of 28.7 (25.3–31.7) ml/kg/min. Maximal HR was 169 bpm (158–181) and maximal work was 2.1 (2.0–2.7) Watt/kg.

Physical Activity

Levels and duration of PA are summarized in **Table 2**. The respective percentage (%) of light, moderate, and vigorous PA are shown in **Figure 1**. Overall the patients were sedentary during 56.6 (50.2–63.4) % of the time. Only 7 (18%) patients reached the cut-off of 60 min/day of MVPA for being defined as "active" according to the WHO guidelines. MVPA was registered in only 4.3 % of the total time (7 days), which corresponded to an average of 40 (29–55) min/day.

Health-Related Quality of Life and Sleep Quality

The KIDSCREEN-27 questionnaire was completed by 31 pediatric patients and the SF-36 test by 7 young adults. The results of the KIDSCREEN-27 (T-scores) and SF-36 (%predicted) tests are summarized in **Table 3**. Overall, the patients self-reported a good HRQoL. In the KIDSCREEN only the T-scores for the category physical wellbeing and social support & peers were lower than the expected value of 50. In the SF-36 vitality was in median only 61.7% of the expected value, while general health, physical functioning, and mental health were only slightly below the norm of 100%.

Thirty-one children and their parents completed PSQ and 7 adults the PSQI (**Table 4**).

The total PSQ score for obstructive sleep-related breathing disorders, as well as the subscale for snoring and that for sleepiness were in the normal range, i.e., <0.33. Nevertheless high scores (>0.33) were found in 12 (39%) patients for the total score, in four (13%) for snoring and in 10 (32%) for sleepiness.

The overall score for inattentive / hyperactive behavior was borderline with a value of 0.33 (0.17–0.67). Correspondingly, a score > 0.33 was obtained in 17 (55%) patients.

TABLE 3 | Results of the SF-36 and KIDSCREEN-27 questionnaires and correlation with MVPA/day.

Test	Score	MVPA/day	
KIDSCREEN-27 (*n* = 31)	***T*-scores**	***p***	**r**
Physical wellbeing	47.08 (42.53–52.43)	**0.05**	0.33
Psychological wellbeing	53.07 (46.53–59.51)	0.30	0.18
Parent relations & autonomy	53.25 (49.47–56.58)	**0.03**	0.37
Social support & peers	49.79 (44.40–53.23)	**0.01**	0.44
School environment	54.40 (48.09–58.16)	0.08	0.29
Questionnaire SF-36 (*n* = 7)	**% predicted**	***p***	**r**
Physical functioning	93.94 (73.06–94.45)	**0.04**	0.56
Physical role functioning	101.74 (78.48–101.74)	**0.05**	0.53
Bodily pain	109 (109–109)	0.16	0.40
General health	91.42 (74.74–99.65)	**0.03**	0.58
Vitality	61.73 (34.29–96.02)	**0.04**	0.55
Social role functioning	106.18 (99.54–106.18)	0.08	0.48
Emotional role functioning	105.36 (70.24–105.36)	0.08	0.49
Mental health	93.96 (84.73–100.33)	**0.04**	0.56
Component summaries:			
Physical	93.96 (84.73–100.33)	**0.03**	0.57
Mental	107.45 (96.76–110.28)	**0.04**	0.55
Total	96.21 (88.89–102.23)	0.07	0.49

Statistically significant correlations are marked in bold.

TABLE 4 | Results of the PSQ and PSQI questionnaires.

Test	Score	Patients	MVPA/day	
PSQ ($n = 31$)		**>0.33**	**p**	**r**
Obstructive sleep-related breathing disorders	0.21 (0.13–0.47)	12 (39)	0.13	0.26
Subscale for snoring	0 (0–0.33)	4 (13)	0.06	0.50
Subscale for sleepiness	0.25 (0–0.5)	10 (3)	0.06	0.32
Subscale for inattentive/hyperactive behavior	0.33 (0.17–0.67)	17 (55)	**0.03**	**−0.36**
PSQI ($n = 7$)		**>5**	**p**	**r**
Global score	4 (2.25–5.57)	4 (57)	**0.01**	−0.71

PSQ, Pediatric sleep questionnaire; PSQI, Pittsburgh Sleep Quality Index. The results of expressed as median (IQR) or n (%), as appropriate. The statistically significant correlations are marked in bold.

Similarly the overall global PSQI score for sleep quality and disturbances was normal, but a pathologic high scorer resulted in 4 (57%) patients.

Predictors of Physical Activity Levels

No significant correlation was found between daily minutes of MVPA were and gender, age, BMI, single ventricle morphology, age at Fontan operation, time from Fontan operation, ventricular volumes and ejection fraction, serum biomarkers, heart rate and cardiac rhythm, CPET parameters, cardiac medication or any complications and/or sequelae.

Physical Activity Levels and Quality of Life and Sleep

Daily minutes of MVPA showed a positive correlation with three sub-classes of the KIDSCREEN-27, namely physical wellbeing ($p = 0.05$, $r = 0.33$), parent relations & autonomy ($p = 0.03$, $r = 0.37$), and social support & peers ($p = 0.01$, $r = 0.44$). The SF-36 questionnaire showed a positive correlation between daily minutes of MVPA and five categories of both, physical health and mental health, as shown in **Table 3**.

Daily minutes of MVPA correlated with lower PSQI global score ($p = 0.01$, $r = -0.71$), and better scores for the subscale for inattentive/hyperactive behavior of the PSQ ($p = 0.03$, $r = -0.36$).

DISCUSSION

In this study we have assessed the physical activity measured by accelerometer in 38 young Fontan patients and its relationship to somatic and cardiac parameters, as well as its influence on HRQoL and sleep quality. In addition to other published data on PA in Fontan patients (2–5, 12–15), our results add information about the interaction with novel serum biomarkers and the influence of PA on HRQol and sleep quality.

Physical Activity and Somatic Parameters

Notably, the median MVPA value measured in our cohort was 40 (29–55) min/day, and only 7 (18%) patients achieved a MVPA $\geq$ 60 min/day, defined by the WHO as a sufficiently active life style (12). In the largest cohort published so far, McCrindle et al. studied the PA level in 108 children and adolescents (7–18 years) and found that only 38% of the subjects achieved the age-specific physical activity recommendations (4). Similar findings than ours have been described by other authors with daily MVPA of 42 and 50 min/day respectively (2, 3). In contrast Hedlund et al. in a similar population and same accelerometer technique than in our study, reported an average MVPA of 148 min/day and 38% of the patients reaching a MVPA $\geq$ 60min/day (15). Most interestingly no difference was observed between Fontan teenagers and healthy teenagers in two studies with an internal age-matched control group (3, 15). Thus, the review of the literature suggests that most Fontan patients, but not all, present with reduced levels of physical activity. The reasons for lower PA remain unclear. We could not identify any clinical factors related to decreased PA levels. One may question if accelerometery is an ideal method for assessing PA levels in Fontan patients, even though activity measurement by accelerometer is a wellestablished and validated method in the pediatric population. One additional question can be if the WHO guidelines are an appropriate benchmark for patients with an unphysiological circulation. Our results and these considerations can be helpful for the design of future prospective studies.

Our results did not show any significant decrease in MVPA with increasing age, as it has been described by others (2, 4, 5, 15). The reasons for this can probably be found in the size and age distribution of the study groups (2, 4, 5, 15). A gender difference has been described by McCrindle et al. but not by others (2, 4, 5). We did not identified any anatomical or surgical characteristics affecting PA levels, nor did other authors for ventricular morphology (14, 15), time interval from Fontan completion (14), and/or type of Fontan connection (4, 5). Some have reported that a diagnosis different than hypoplastic left heart syndrome (4), older age at Fontan completion (2, 14), and fewer procedures prior to Fontan were related to higher PA levels.

Serum cardiac biomarkers have been associated with reduced objective exercise capacity and poor clinical outcome in Fontan patients (21–23). This is the first study testing novel biomarkers, such as GDF-15, DLK-1 and IGFBP-7, in relation to PA, and we did not observe any correlation. Similarly to Müller et al. we also did not find any correlation between NT-pro-BNP and PA levels (5).

It is well known that severe cardiac abnormalities have a major impact on objective exercise capacity (12). Some authors have also shown that patients with a higher exercise capacity have a more active daily life measured by accelerometer (3, 5, 12). Surprisingly we did not find any correlation between CPET parameters and MVPA. Interestingly, McCrindle et al. (4) in their larger patients cohort also described a lack of correlation between PA and objective exercise capacity. In this context we believe that several other factors may influence the time spent doing physical exercise in Fontan patients; these may include an extremely cautious medical counseling regarding selected sports (particularly in patients receiving anticoagulation), which may be understood as general dissuasion from sport by certain families, anxious parents blocking their children from sportive activities, patients self-perception and subjectively reduced exercise capacity (in comparison to peers) yielding to a behavior avoiding frustration, and lack of personal motivation (2–5, 10). All these factors/ behaviors can be influenced by cultural, socio-economic and familial structure, as well as geographical factors. Parental overprotection has been recognized to be an important issue for exercise limitation, as 50% of patients with congenital heart disease reported that their parents limit their physical activities (11). Reduced self-efficacy, particularly in adolescents and young adults, may also impact their degree of participation in PA (29). The reported decrease of PA with increasing age and the lack of difference between Fontan patients and control adolescents reported in some studies (3, 15) may question the concept of a fix cut-off for definition of ideal MVPA over the ages.

Recent reviews on structured exercise training in Fontan patients have described how regular physical activity is safe and beneficial for these patients. However it is important to note that punctual short-term interventions like a time-limited training program did not lead to a permanent improvement of MVPA (11, 30). These observations suggest that interventions aiming to improve PA levels should be established early during treatment of single ventricle lesions and be supported by postsurgical rehabilitation programs.

Health-Related Quality of Life

As survival of single ventricle patients keeps improving, their quality of life represents an important goal to be targeted in the long term. Our study confirms a good HRQoL reported by the majority of Fontan patients (31). We have demonstrated that higher PA levels were associated with higher scores in many categories of both, the self-reported SF-36 and parents-reported KIDSCREEN-27. Interestingly, in the perceived HRQoL PA levels not only influenced the plain physical sphere, but also the general perception of health status and social wellbeing, which included parents relation and social support and peers in children, and mental health in adolescents and young adults. Few other authors also reported a positive correlation between PA levels and the self-reported psychosocial functioning and general health (4, 5). In contrast other studies did not observe any association between PA levels and parent-reported HRQoL (32, 33). Even though data are not completely consistent, our results suggests that specific interventions targeted to increase PA levels may have some beneficial effects not only on physical aspects but also on peer and family socialization and patients cognitive development (8, 9).

Sleep Quality

In Fontan patients sleep disturbances have been related to a reduced HRQoL and neurodevelopmental impairment (34). Our patients reported sleep disturbances and inattentive or hyperactive behavior in up to 30–57%, depending on the specific item. Daily minutes of MVPA were correlated with a lower incidence of sleep disturbances, similarly as it was described by Hedlund et al. (16). Therefore, PA may have a positive effect on sleep quality and reduce hyperactive behavior in Fontan patients.

LIMITATION

As a single center study on a rare cardiac condition, our results report on a limited number of subject, and statistical analysis may present some limitations. Moreover, the cohort may have a patients selection bias regarding age of the patients and comorbidity factors. We included children from an age, in which they were able to perform CPET and CMR without need for sedation; therefore, we could not cover the full age spectrum starting just after Fontan completion. Patients with a pacemaker have not been included because of the contraindication for undergo CMR. We have not included a control population; this would have provided the study with a valid group comparison for PA levels. Moreover, an appropriate use of the accelerometer could not be monitorized, as this was based on a short introduction and on reciprocal trust; some degree of monitor tampering cannot be completely excluded. The data acquired did not allow for analysis of the influence of familiar, saisonal, geographical factors or medical advice on the effective PA of the patients (2, 4, 14).

CONCLUSIONS

Only a minority of Fontan patients (18%) meets the recommendation for daily physical activity. Measures of exercise capacity, cardiac function, or chronotropic competence are not correlated to daily MVPA. In contrast levels of PA are related to quality of life, not only in the physical but also in the mental domains.

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 Kantonale Ethikkommission Kanton Zurich, Switzerland. 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

AC designed the study, was primarily involved in data acquisition, and data analysis and drafted the manuscript. KF and CP was involved in data acquisition and data analysis. RJ provided knowledge and technical support in data acquisition (accelerometer) and data analysis. FB and BB was involved in study design, data acquisition, and data analysis. EV designed the study, was involved in data analysis, drafting, reviewing, and revising the manuscript. All authors reviewed the manuscript.

REFERENCES

1. Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. *Heart.* (2016) 102:1081–6. doi: 10.1136/heartjnl-2015-307467
2. Longmuir PE, Corey M, Faulkner G, Russell JL, McCrindle BW. Children after fontan have strength and body composition similar to healthy peers and can successfully participate in daily moderate-to-vigorous physical activity. *Pediatr Cardiol.* (2015) 36:759–67. doi: 10.1007/s00246-014-1080-6
3. Härtel JA, Herberg U, Jung T, Winkler C, Breuer J, Müller N. Physical activity and heart rate monitoring in Fontan patients–should we recommend activities in higher intensities?. *PLoS ONE.* (2020) 15:e0228255. doi: 10.1371/journal.pone.0228255
4. McCrindle BW, Williams RV, Mital S, Clark BJ, Russell JL, Klein G, et al. Physical activity levels in children and adolescents are reduced after the Fontan procedure, independent of exercise capacity, and are associated with lower perceived general health. *Arch Dis Child.* (2007) 92:509–14. doi: 10.1136/adc.2006.105239
5. Müller J, Christov F, Schreiber C, Hess J, Hager A. Exercise capacity, quality of life, and daily activity in the long-term follow-up of patients with univentricular heart and total cavopulmonary connection. *Euro Heart J.* (2009) 30:2915–20. doi: 10.1093/eurheartj/ehp305
6. Hirth A, Reybrouck T, Bjarnason-Wehrens B, Lawrenz W, Hoffmann A. Recommendations for participation in competitive and leisure sports in patients with congenital heart disease: a consensus document. *Eur J Cardiovasc Prev Rehabil.* (2006) 13:293–9. doi: 10.1097/00149831-200606000-00002
7. Graham TP, Driscoll DJ, Gersony WM, Newburger JW, Rocchini A, Towbin JA. Task Force 2: congenital heart disease. *J Am Coll Cardiol.* (2005) 45:1326–33. doi: 10.1016/j.jacc.2005.02.009
8. Ginsburg KR, American Academy of Pediatrics Committee on Communications, American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health. The importance of play in promoting healthy child development and maintaining strong parent-child bonds. *Pediatrics.* (2007) 119:182–91. doi: 10.1542/peds.2006-2697
9. Kantomaa MT, Purtsi J, Taanila AM, Remes J, Viholainen H, Rintala P, et al. Suspected motor problems and low preference for active play in childhood are associated with physical inactivity and low fitness in adolescence. *PLoS One.* (2011) 6:e14554. doi: 10.1371/journal.pone.0014554
10. Takken T, Hulzebos HJ, Blank AC, Tacken MHP, Helders PJM, Strengers JLM. Exercise prescription for patients with a Fontan circulation: current evidence and future directions. *NHJL.* (2007) 15:142–7. doi: 10.1007/BF03085970
11. Sutherland N, Jones B, d'Udekem Y. Should we recommend exercise after the fontan procedure? *Heart Lung Circulat.* (2015) 24:753–68. doi: 10.1016/j.hlc.2015.03.005
12. Arvidsson D, Slinde F, Hulthén L, Sunnegårdh J. Physical activity, sports participation and aerobic fitness in children who have undergone surgery for congenital heart defects. *Acta Paediatrica.* (2009) 98:1475–82. doi: 10.1111/j.1651-2227.2009.01369.x
13. Duppen N, Etnel JR, Spaans L, Takken T, van den Berg-Emons RJ, Boersma E, et al. Does exercise training improve cardiopulmonary fitness and daily physical activity in children and young adults with corrected tetralogy of Fallot or Fontan circulation? a randomized controlled trial. *Am Heart J.* (2015) 170:606–14. doi: 10.1016/j.ahj.2015.06.018
14. Longmuir PE, Tyrrell PN, Corey M, Faulkner G, Russell JL, McCrindle BW. Home-based rehabilitation enhances daily physical activity and motor skill in children who have undergone the fontan procedure. *Pediatr Cardiol.* (2013) 34:1130–51. doi: 10.1007/s00246-012-0618-8
15. Hedlund ER, Lundell B, Villard L, Sjöberg G. Reduced physical exercise and health-related quality of life after Fontan palliation. *Acta Paediatr.* (2016) 105:1322–8. doi: 10.1111/apa.13544
16. Hedlund ER, Villard L, Lundell B, Sjöberg G. Physical exercise may improve sleep quality in children and adolescents with Fontan circulation. *Cardiol Young.* (2019) 29:922–9. doi: 10.1017/S1047951119001136
17. Trost SG, Pate RR, Freedson PS, Sallis JF, Taylor WC. Using objective physical activity measures with youth: how many days of monitoring are needed? *Med Sci Sports Exerc.* (2000) 32:426–31. doi: 10.1097/00005768-200002000-00025
18. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and non-wear time classification algorithm. *Med Sci Sports Exerc.* (2011) 43:357–64. doi: 10.1249/MSS.0b013e3181ed61a3
19. Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. *J Sports Sci.* (2008) 26:1557–65. doi: 10.1080/02640410802334196
20. WHO. *Global Recommendations on Physical Activity for Health [Internet].* Geneva: World Health Organization; (2010) (WHO Guidelines Approved by the Guidelines Review Committee). Available online at: http://www.ncbi.nlm.nih.gov/books/NBK305057/ (accessed July 6, 2021).
21. van den Bosch E, Bossers SSM, Kamphuis VP, Boersma E, Roos-Hesselink JW, Breur JMPJ, et al. Associations between blood biomarkers, cardiac function, and adverse outcome in a young fontan cohort. *JAHA [Internet].* (2021) 10:5. doi: 10.1161/JAHA.119.015022
22. Hager A, Christov F, Hess J. Increase in N-Terminus-Pro-B-Type Natriuretic Peptide During Exercise of Patients With Univentricular Heart After a Total Cavopulmonary Connection. *Pediatric Cardiology.* (2012) 33:764–9. doi: 10.1007/s00246-012-0210-2
23. Raedle-Hurst TM, Koenigstein K, Gruenhage F, Raedle J, Herrmann E, Abdul-Khaliq H. Growth differentiation factor 15–an early marker of abnormal function of the Fontan circuit in patients with univentricular hearts. *Am Heart J.* (2010) 160:1105–12. doi: 10.1016/j.ahj.2010.08.033
24. Takken T, Bongers BC, van Brussel M, Haapala EA, Hulzebos EHJ. Cardiopulmonary exercise testing in pediatrics. *Annals ATS.* (2017) 14:S123–8. doi: 10.1513/AnnalsATS.201611-912FR
25. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* (1992) 30:473–83. doi: 10.1097/00005650-199206000-00002
26. Bullinger M, Morfeld M, Kohlmann T, Nantke J, van den Bussche H, Dodt B, et al. [SF-36 health survey in rehabilitation research. findings from the North German Network for Rehabilitation Research, NVRF, within the rehabilitation research funding program]. *Rehabilitation (Stuttg).* (2003) 42:218–25. doi: 10.1055/s-2003-41645
27. Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric Sleep Questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problemsq. *Sleep Med.* (2000) 12:23. doi: 10.1037/t24052-000
28. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4
29. Bar-Mor G, Bar-Tal Y, Krulik T, Zeevi B. Self-efficacy and physical activity in adolescents with trivial, mild, or moderate congenital cardiac malformations. *Cardiol Young.* (2000) 10:561–6. doi: 10.1017/S1047951100008829
30. Scheffers LE, Berg LE vd, Ismailova G, Dulfer K, Takkenberg JJ, Helbing WA. Physical exercise training in patients with a Fontan circulation: a systematic review. *Eur J Prev*

Cardiolog. (2020) 20:4748732094286. doi: 10.1177/2047487320942869
31. Marshall KH, D'Udekem Y, Sholler GF, Opotowsky AR, Costa DSJ, Sharpe L, et al. Health-related quality of life in children, adolescents, and adults with a fontan circulation: a meta-analysis. *JAHA [Internet].* (2020) 9:172. doi: 10.1161/JAHA.119.014172
32. Hedlund ER, Lundell B, Söderström L, Sjöberg G. Can endurance training improve physical capacity and quality of life in young Fontan patients? *Cardiol. Young.* (2018) 28:438–46. doi: 10.1017/S1047951117002360
33. Hedlund E, Lundell B. Endurance training may improve exercise capacity, lung function and quality of life in Fontan patients. *Acta Paediatr.* (2022) 111:17–23. doi: 10.1111/apa.16121
34. Knobbe K, Partha M, Seckeler MD, Klewer S, Hsu C-H, Edgin J, et al. Association between sleep disturbances with neurodevelopmental problems and decreased health-related quality of life in children with fontan circulation. *J Am Heart Assoc.* (2021) 10:e021749. doi: 10.1161/JAHA.121.021749

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The German EMPATHIC-30 Questionnaire Showed Reliability and Convergent Validity for Use in an Intermediary/General Pediatric Cardiology Unit: A Psychometric Evaluation

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Background: Family-Centered Care is a useful framework for improving care for hospitalized children with congenital heart disease. The EMpowerment of PArents in THe Intensive Care-30 (EMPATHIC-30) questionnaire is a widely accepted tool to measure parental satisfaction with Family-Centered Care. Psychometric properties of the EMPATHIC-30 have been evaluated in neonatal and pediatric intensive care units, but not in pediatric cardiac care units. Therefore, our aim was to assess the psychometric properties of the German EMPATHIC-30 in an intermediary/general pediatric cardiology unit.

Methods: We used data from a quality management survey comprising the German EMPATHIC-30, a sociodemographic questionnaire and four general satisfaction items. Data were collected at the intermediary/general pediatric cardiology unit of a specialized heart center in Germany ($n = 366$). We split the data randomly into two subsets. In the first subset, we assessed internal consistency reliability with McDonald's omega and Cronbach's alpha, and convergent validity using Spearman's rank correlation. Furthermore, we explored the internal structure with Principal Component Analysis (PCA). In the second subset, we validated the resulting structure using Confirmatory Factor Analysis (CFA).

Results: The reliability estimates exceeded 0.70 for all five domain scores and 0.90 for the full-scale score. Convergent validity between EMPATHIC-30 domain scores/ the full-scale score and the four general satisfaction items was adequate ($r_s = 0.40$–0.74). The PCA suggested three components, accounting for 56.8% of the total variance. Cross-validation via CFA showed poor model fit ($\chi^2 = 1545.78$, $\chi^2/df = 3.85$, CFI = 0.70, TLI = 0.66, RMSEA = 0.13), indicating that the EMPATHIC-30 shows no clear and generalizable factor structure in this sample.

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Discussion: The German version of the EMPATHIC-30 exhibited reasonable psychometric properties in an intermediary/general pediatric cardiology unit. Follow-up studies should investigate the factor structure of the EMPATHIC-30 in other pediatric inpatient care settings.

Keywords: congenital heart disease, family-centered care, pediatric cardiology, psychometric properties, internal consistency reliability, convergent validity, construct validity

INTRODUCTION

Congenital Heart Disease (CHD) is defined as a structural defect of the heart or intrathoracic vessels (1). With a global prevalence of 9.41 per 1,000 births, it represents the most common birth defect worldwide (2, 3). In Europe, ∼36 000 children are born with a CHD each year and around 28% of them have moderate to complex heart defects, requiring interventional or surgical treatment (4). During hospitalization, they are exposed to a myriad of stressors, such as separation from their parents, a stressful environment with bright lights and loud noises, restricted mobility, and disrupted sleep. Research shows that children with CHD are at risk for neurodevelopmental impairment, as well as emotional, social, and behavioral difficulties (5–7). Distress during hospitalization may contribute to these challenges (7, 8). Hence, optimizing the hospital environment potentially is an effective strategy to improve neurodevelopmental and psychosocial outcomes of children with CHD, for which Family-Centered Care (FCC) provides a useful framework (9).

Family-Centered Care is an international standard of healthcare provision based on a mutually beneficial partnership among the healthcare providers, patients, and their families (10, 11). In pediatrics, FCC emphasizes the parents as their child's primary source of emotional, social, and developmental support and acknowledges them as integral part of the healthcare team (12). Specific FCC interventions either target the parents (e.g., educational programs, participation of parents in medical rounds), the parent-child dyad (e.g., promoting skin-to-skin contact), or the health-care ecosystem as a whole (e.g., structural implementation of a primary nursing model) (13). Most studies investigating the effects of FCC interventions on child and parent wellbeing have been conducted in Neonatal Intensive Care Units (NICUs), with positive effects reported for physical wellbeing, stress regulation, sleep, and neurodevelopmental outcomes of the child, parent-child attachment, and parental mental wellbeing (14–17). A meta-analysis of randomized controlled trials showed that FCC interventions improve physical health outcomes in premature infants (e.g., weight gain), while their parents experience less anxiety, depression, and stress (18). Despite the positive effects of FCC interventions in neonatology, studies investigating FCC in children with CHD are scarce. However, several authors argue that FCC practices may be similarly beneficial in this population (19–21).

Measuring the subjective experience of provided care is crucial for advances in this area of research, especially when FCC principles are not structurally implemented yet (22). In order to measure parent satisfaction with FCC, the EMpowerment of PArents in THe Intensive Care (EMPATHIC) questionnaire is frequently used (23). Latour et al. (24, 25) originally developed the questionnaire for Pediatric Intensive Care Units (PICUs), based on expert opinions from over 300 PICU nurses and physicians, as well as over 600 parents of children discharged from a PICU. The original scale comprises 65 items, with each item reflecting care aspects from one of the following five domains: Information, Organization, Parental Participation, Care and Cure, and Professional Attitude (23). The domains were identified in qualitative analyses and evaluated quantitatively, by using Confirmatory Factor Analysis (CFA), with separate models for each domain. The authors subsequently developed a shortened version of the questionnaire, the EMPATHIC-30, to improve user friendliness (26). The number of items was reduced by means of multiple regression analysis, resulting in 30 items. In the past years, the EMPATHIC-30 gained international popularity and has been translated from Dutch into various languages, including English, Spanish, Turkish, and German (27–30).

In the original publication of the EMPATHIC-30, Latour et al. (26) found high internal consistency reliability estimates for the five domain scores and the full-scale score. Gill et al. (27) tested the questionnaire's psychometric properties in Australian PICUs, NICUs, and general pediatric wards and reported similar values for the internal consistency reliability (27). Above that, the questionnaire showed adequate convergent validity, as assessed by moderate to strong correlations between each of the domain scores and four general satisfaction items, pointing toward applicability of the questionnaire in these care settings. Orive et al. (28) investigated internal consistency reliability and convergent validity of the questionnaire in Spanish PICUs, with similar results. Only few studies have investigated the construct validity of the questionnaire by using factor analysis. Factor analysis is a statistical method to identify latent variables, which explain covariation amongst a set of measured variables (31). It is therefore an essential approach to generate and evaluate hypotheses about the underlying construct an instrument aims to measure (32). Tiryaki et al. (29) investigated psychometric properties of the EMPATHIC-30 in Turkish NICUs and conducted a CFA in a sample of 238 parents. The authors found a moderate model fit of the final factor solution. However, the factor structure was not reported and thus remains unclear. The German version of the EMPATHIC-30 has not been evaluated psychometrically (30). Furthermore, while the EMPATHIC-30 has been extensively evaluated in different care settings, it has not been psychometrically tested for use in pediatric cardiology units.

Therefore, our aim was to evaluate the psychometric properties, specifically internal consistency reliability, convergent validity, and factor structure of the German EMPATHIC-30 at an intermediary/general pediatric cardiology unit. In order to assess internal consistency reliability, we used McDonald's omega. Although controversially discussed in the literature, we additionally present the classical Cronbach's alpha, to allow for direct comparison to other studies (33, 34). To assess convergent validity, we investigated the relationship between the domain scores and the full-scale score with four general satisfaction items, comparable to the methodology of above-mentioned studies. Furthermore, we investigated the factor structure of the questionnaire, following a two-step procedure. In the first step, we explored the internal structure of the questionnaire on half of the data using Principal Component Analysis (PCA) rather than Exploratory Factor Analysis (EFA). While both PCA and EFA are variable reduction techniques, EFA assumes an underlying construct, which is not measured directly, and PCA reflects a linear combination of variables. We used PCA to explore the internal structure of the questionnaire, because our focus was to explore the structure in total item variance including error, without making assumptions on latent constructs, as these were unknown for the current context (35). In a second step, we used three separate CFA on the other half of the data: The first CFA was conducted to validate the structure resulting from the PCA. The second CFA was conducted to investigate a one-component solution, motivated by potential unidimensionality of the scale. The third CFA was conducted to investigate a five-component solution motivated by the five domains of the EMPATHIC-30.

MATERIALS AND METHODS

Study Design and Setting

For the psychometric evaluation of the EMPATHIC-30 questionnaire, we used data from a quality management survey comprising the German EMPATHIC-30, a socio-demographic questionnaire, four general satisfaction items and open commentary fields. Data were collected at the intermediary/general pediatric cardiology unit of the German Heart Center Berlin. With its 24 monitored beds and 1,200 yearly admissions, the unit provides specialized care to patients of all ages, ranging from infants to adults, with varying degrees of CHD. This study was approved by the Medical Ethics Committee Charité Virchow (Nr EA2/032/20).

Procedures

All parents of children with CHD hospitalized at the ward were invited to participate in the quality management survey. Participation was voluntary and anonymous. At discharge, doctors handed out a paper and pencil version of the survey together with a return envelope. After completing the survey, parents returned it in a mailbox on the ward. Data collection took place between August 2019 and June 2021.

Materials

The German EMPATHIC-30 questionnaire comprises 30 statements spanning five domains: Information (5 items), Organization (5 items), Parental Participation (6 items), Care and Cure (8 items), and Professional Attitude (6 items). Every statement is rated on a six-point scoring-scale ranging from 1 "certainly no" to 6 "certainly yes," or rated 0 for the answer alternative "not applicable."

Sociodemographic information was obtained through a purpose-designed questionnaire. It contains one item to specify the respondent (with options "mother," "father," "both mother and father," and "other relatives" with the option of open-ended specification), as well as items relating to age of the child, place of birth and mother tongue of the parents, length of hospital stay, type of and reason for admission, and undertaken medical procedures.

Four general satisfaction items were included in the survey: Two items are rated on the same six-point scale as the EMPATHIC-30 questionnaire: "We would recommend this unit or ward," "We would be happy to return to this unit or ward". Two more items are rated on a ten-point scale, ranging from "very bad" to "excellent": "Overall performance of doctors" as well as "Overall performance of nurses" (23). Furthermore, commentary fields were included in the survey about general experiences made during admission, hospital stay, and discharge.

Statistical Analyses

Statistical analyses were carried out using SPSS 27 (SPSS Inc, Chicago, Illinois). Non-linear and linear PCA were conducted in SPSS. AMOS, an SPSS extension module, was used for the CFA.

Data Preparation and Preliminary Analyses

Handling of Answer Alternative "Not Applicable"

Non-linear Principal Component Analysis (CATPCA) was performed to determine the best linear replacement values for observed scores in each item individually, for the scores 0 up to 6 (0 corresponding to the answer alternative "not applicable") (36). Based on transformation plots from nominal optimal scaling, the scores 0 and 6 got assigned a similar quantification; both answer categories had an equivalent interpretation by participants. This was consistent with previous findings by Latour et al. (23). Scores on the answer category "not applicable" were therefore recoded to the highest value of the scale (i.e., 6). In addition, the transformation plots revealed that the answer categories functioned as near-equally spaced linear scale; models with nominal transformation and with numerical transformation after recoding yielded 0.8% difference in explained variance. All subsequent linear analyses were performed using the recoded scores.

Handling of Missing Data

Returned questionnaires with ≥75% of missing items were excluded from analysis. One third of respondents presented at least one missing value and the total percentage of missing data points was 2.3%. Missing data can affect the estimation and interpretation of PCA (37). Little's Missing Completely at Random (MCAR) test was significant, indicating that missings are not missing completely at random, thus indicating a potentially systematic difference between missing and observed values (38). Therefore, multiple imputation, a proven statistical

method to estimate missing values, was used on the recoded scores. Missing scores were estimated in 25 sets, applying Markov Chain Monte Carlo sampling and predictive mean matching (39). Results of the statistical analyses were pooled for the imputed data sets whenever possible.

Data Split for Separate Estimation and Validation

The data set was randomly split in half, creating two subsets (A, B) to perform 2-fold cross-validation. All statistical structure and content analyses were performed on set A. Set B was used only as validation set for the confirmatory evaluation of the internal structure via CFA.

Descriptive Statistics

Descriptive statistics of the EMPATHIC-30 scores as well as sociodemographic characteristics of the sample are reported (means and standard deviations for quantitative variables, absolute frequencies and percentages for categorical variables). To check for successful randomization, descriptive statistics for the full set, analysis set A, and validation set B, as well as test statistics for the comparison between set A and B are provided.

Internal Consistency Reliability

The internal consistency reliability of the German EMPATHIC-30 questionnaire on domain and full-scale level was assessed with McDonald's omega. Cronbach's alpha was computed additionally. Values greater than 0.70, 0.80, and 0.90 reflect acceptable, good, and excellent reliability, respectively (40).

Convergent Validity

To examine convergent validity of the questionnaire, we used Spearman's rank correlation test for non-normally distributed data, as assessed visually and through significant Shapiro Wilk tests ($p < 0.01$). We assessed the relationship between the domain scores/ the full-scale score and the four overall satisfaction statements. Based on findings from other validation studies, we expected moderate to strong correlation coefficients, ranging from 0.40 up to 0.79, indicating adequate convergent validity (41).

Internal Structure

Principal Component Analysis

We conducted a PCA to explore the internal structure of the questionnaire. An oblique rotation should be applied, which reorients the components in order to simplify the mathematical model and interpretation by allowing for intercorrelations between the components. However, this rotation is not implemented for multiply imputed data. Therefore, we conducted a two-step procedure. First, we performed a PCA on the unimputed data set A to determine the number of components. Pairwise deletion was selected to handle missing values. The suitability of the data was assessed with the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity. In this exploratory stage, the KMO value is interpreted as an approximation of the ratio of potential common variance compared to the total variance in the data and thus provides information if subsequent factor analysis is suitable. Final component extraction was based on the combined Monte Carlo Parallel Analysis and examination of the scree plot (42). Oblique rotation allowing for intercorrelations between the components was applied in this step. For items with cross-loadings, the component on which the item loaded higher was selected. Loadings under 0.30 (<10% shared variance between item and component) were considered as negligible and therefore not considered for inclusion in the component structure. Second, we used the results of this PCA to motivate the number of components in a second PCA on the imputed data set A by using Generalized Procrustes Analyses in the subroutine by Wingerde et al. (43). This subroutine imposed a pre-specified number of components and orthogonal rotation of the component loadings, ignoring intercorrelations between the components.

Confirmatory Factor Analysis

We conducted three separate factor analyses on set B of the sample. First, we conducted a CFA to validate the component structure resulting from the two-step PCA. Second, we conducted a CFA based on a one-component model to investigate potential unidimensionality of the questionnaire. Third, we conducted a CFA based on a five-component model to investigate the validity of the five domains of the EMPATHIC-30 (Information, Organization, Parental Participation, Care and Cure, and Professional Attitude). In the CFA measurement models, correlation between the components is allowed. As combining the results of multiply imputed data is not possible in AMOS, we conducted the analyses on the data with missing values using Full Information Maximum Likelihood Estimation and compared model estimates for robustness. To assess model fit, we used the following fit indices: model-Chi-squared test divided by the degrees of freedom (χ^2/df), Comparative Fit Index (CFI), Tucker Lewis Index (TLI), and Root Mean Square Error of Approximation (RMSEA). Cut-off values were: $\chi^2/df < 3$, CFI of at least 0.90, TLI of at least 0.95, and RMSEA < 0.08 (44, 45). A second evaluation of robustness of findings was performed by repeating the same analyses on the other half of the data (set A).

RESULTS

A total of 475 questionnaires were returned between August 2019 and June 2021. The response rate was 68% (percentage of returned questionnaires vs. distributed copies). To ensure homogeneity of the data set, we only included questionnaires filled out by parents. As a result, we excluded 91 questionnaires filled out by adult patients, as well as nine questionnaires filled out by relatives other than parents. Upon first exploration of data, we excluded three more questionnaires with comments in the commentary fields reflecting very high satisfaction, but with lowest possible scores on EMPATHIC-30 items, potentially indicating a mix up between highest and lowest scores. Above that, we excluded six questionnaires with ≥75% missing items. The final number of questionnaires included in the analysis was 366, resulting in 183 questionnaires each for analysis set A and validation set B.

TABLE 1 | Characteristics of children and parents in set A, B, and the full sample.

Characteristics	Set A		Set B		Full sample		*P*-value
	n	%	*n*	%	*n*	%	
Questionnaire completed by							
Mother	136	76.4	15	64.6	251	70.5	0.017[a]*
Father	23	12.9	25	14	48	3.5	
Both	19	10.7	38	21.3	57	15.6	
Country of birth							
Germany	166	91.2	154	84.2	320	87.7	0.093[a]
Other	15	8.2	25	13.7	40	11	
Both[1]	1	0.5	4	2.2	5	1.4	
Mother tongue							
German	148	83.1	143	79	291	81.1	0.548[a]
Other	24	13.5	32	17.7	56	15.6	
Both[1]	6	3.4	6	3.3	12	3.3	
First admission							
Yes	95	52.5	99	54	194	53.6	0.673[a]
No	86	47.5	82	45.3	168	46.4	
Type of admission							
Planned	165	91.7	174	97.2	339	94.4	0.055[a]
Unexpected	13	7.2	5	2.8	18	5	
Both	2	1.1	0		2	0.6	
Medical procedures[2]							
Cardiac surgery	88		103		191		0.154[a]
Heart catheterization	93		79		172		0.102[a]
Medication	19		20		39		0.851[a]
Other	13		13		26		0.988[a]
Age of the child in years							
Mean (SD)	5.32 (6.63)		4.98 (6.25)		5.15 (6.43)		0.589[b]
Length of stay in days							
Mean (SD)	6.32 (8.86)		7.92 (24.15)		7.13 (18.28)		0.784[b]

*SD, standard deviation. Total number of respondents vary because of missing data. [1]Different answer for either parent when questionnaire filled out by both. [2]Multiple answers were possible. [a]Pearson's Chi-square test. [b]Mann-Whitney U-test. * Statistically significant (p <0.05).*

Descriptive Statistics

The child and parent characteristics are presented in **Table 1**. No significant differences between set A and set B were observed for any of the characteristics, except for the item specifying the respondent, in which a significant shift of mother-only to both parents was seen ($X_{2\ (2,\ 356)} = 8.17$, $p = 0.017$). As the proportion of mothers giving their input does not differ in both sets, we view this difference as negligible. Therefore, we consider the reported characteristics of each set representative for the whole group. Below, we present the characteristics of set A, as this set drives the main psychometric analysis. Most children of participating families were either infants ($n = 53$, 29.6%), toddlers ($n = 30$, 16.8%) or preschoolers ($n = 39$, 21.8%) and the mean age was 5.32 years (SD = 6.63). Seventy-six percent of the questionnaires were completed by mothers. The majority of participants were born in Germany ($n = 166$, 91.2%) and native German speakers ($n = 148$, 83.1%). Only 7% of hospital admissions were unexpected and the mean length of hospital stay was 6.32 days (SD = 8.86), ranging from 1 to 105 days.

Parents gave high ratings on the EMPATHIC-30 and all except four items showed mean scores above 5 (**Table 2**). On the domain level, mean scores ranged from 5.19 (SD = 0.84) for the domain Organization up to 5.45 (SD = 0.76) for the domain Professional Attitude. The "not applicable" response was given most frequently for the item "The unit could easily be reached by telephone" ($n = 42$, 23%).

Internal Consistency Reliability

McDonald's omega on the domain level ranged from 0.75 (Organization) to 0.87 (Professional Attitude; Care and Cure) and reached 0.95 for the full-scale. Cronbach's alpha on the domain level was only slightly lower and ranged from 0.73 (Organization) to 0.85 (Professional Attitude). The findings are presented in **Table 3**.

Convergent Validity

As shown in **Table 4**, the correlations between the EMPATHIC-30 domain scores and scores on the four overall satisfaction

TABLE 2 | EMPATHIC-30 means and standard deviations for set A, B and the full sample.

Items	Set A		Set B		Full sample	
	Mean	SD	Mean	SD	Mean	SD
Information						
Disease treatment	5.52	0.97	5.49	0.97	5.50	0.97
Examination	5.49	0.92	5.56	0.79	5.52	0.86
Drugs	4.99	1.23	5.19	1.13	5.09	1.19
Daily talks with doctor	5.37	1.07	5.46	1.11	5.41	1.09
Daily talks with nurse	5.59	0.94	5.63	0.99	5.61	0.97
Organization						
Clean	5.55	0.89	5.64	0.78	5.59	0.84
Reachable	5.75	0.65	5.80	0.61	5.78	0.63
Noise	4.94	1.27	5.09	1.21	5.02	1.24
Space	4.70	1.51	4.83	1.47	4.76	1.47
Efficiency	5.09	1.20	5.13	1.22	5.11	1.21
Parental participation						
Decision-making	5.20	1.17	5.30	1.13	5.25	1.15
Encouraged to stay close	5.22	1.18	5.24	1.30	5.23	1.24
Stay close	5.55	0.92	5.59	0.96	5.57	0.94
Asked about experiences	4.75	1.51	4.60	1.67	4.68	1.59
Confidence in doctor	5.65	0.84	5.73	0.75	5.69	0.79
Confidence in nurse	5.59	0.87	5.67	0.76	5.63	0.82
Care and cure						
Teamwork	5.45	0.93	5.46	0.87	5.45	0.90
Pain treatment	5.57	0.91	5.57	0.88	5.57	0.90
Child comfort doctor	5.49	0.91	5.51	0.95	5.50	0.93
Child comfort nurse	5.65	0.76	5.61	0.84	5.63	0.80
Responsible doctor	5.00	1.49	5.12	1.38	5.06	1.43
Responsible nurse	5.41	1.25	5.44	1.09	5.43	1.17
Discharge doctor	5.27	1.25	5.37	1.21	5.32	1.23
Discharge nurse	5.34	1.15	5.44	1.11	5.39	1.13
Professional attitude						
Admission	5.42	0.95	5.26	1.14	5.34	1.05
Hygiene	5.57	0.90	5.60	0.88	5.59	0.89
Privacy	5.07	1.26	5.12	1.21	5.10	1.23
Respect	5.56	0.86	5.65	0.85	5.61	0.86
Sympathy doctor	5.54	0.94	5.61	0.88	5.58	0.91
Sympathy nurse	5.56	0.94	5.64	0.84	5.60	0.89
General satisfaction items						
Recommend ward	5.56	0.87	5.56	0.89	5.56	0.88
Readmission to ward	5.57	0.90	5.54	0.98	5.56	0.94
Overall rating doctor	9.06	1.49	9.12	1.63	9.09	1.56
Overall rating nurse	9.07	1.44	9.00	1.62	9.03	1.53

SD, standard deviation. Descriptive statistics were computed on the unimputed data. The answer category 0 ("not applicable") was treated as missing value.

statements ranged from $r_{s(183)} = 0.40$, $p < 0.01$ between the domain Organization and satisfaction statement "Readmission to ward," to $r_{s(183)} = 0.68$, $p < 0.01$ between the domain Care and Cure and satisfaction statement "Overall rating doctors." The lowest correlations were found for the domain Organization, with correlations under 0.50 for all satisfaction statements. Similarly, the correlations between the full-scale score and scores on the four overall satisfaction statements ranged from $r_{s(183)} = 0.62$, $p < 0.01$ for the statement "Readmission to ward" to $r_{s(183)} = 0.74$, $p < 0.01$ for the statement "Overall rating doctors." All correlations were significant and moderate to high, according to expectation. For an overview of correlations between the domain scores, see **Table 5**.

TABLE 3 | Internal consistency reliability of the EMPATHIC-30 domain scores and full-scale score ($n = 178$).

	Mean (SD)	Cronbach's alpha, mean over imputed data sets (range)	McDonald's omega, mean over imputed data sets (range)
Domain scores			
Information	5.41 (0.75)	0.78 (0.77–0.79)	0.80 (0.79–0.80)
Organization	5.19 (0.84)	0.73 (0.72–0.73)	0.75 (0.75–0.76)
Parental participation	5.34 (0.82)	0.83 (0.81–0.84)	0.84 (0.83–0.85)
Care and cure	5.49 (0.80)	0.85 (0.84–0.85)	0.87 (0.86–0.87)
Professional attitude	5.45 (0.76)	0.85 (0.85–0.86)	0.87 (0.86–0.87)
Full-scale score	5.36 (0.70)	0.95 (0.95–0.95)	0.95 (0.95–0.95)

SD, standard deviation.

TABLE 4 | Spearman's rank correlation coefficient between domain scores/ full-scale score and scores on the overall satisfaction items ($n = 183$).

	Recommend ward	Readmission to ward	Overall rating doctors	Overall rating nurses
Domain scores				
Information	0.57	0.53	0.60	0.54
Organization	0.43	0.40	0.46	0.41
Parental participation	0.62	0.58	0.63	0.54
Care and cure	0.58	0.56	0.68	0.67
Professional attitude	0.63	0.57	0.64	0.61
Full-scale score	0.67	0.62	0.74	0.69

All correlations significant ($p < 0.01$), two-tailed.

TABLE 5 | Spearman's rank correlation coefficient between domain scores ($n = 183$).

	Information	Organization	Parental participation	Care and cure	Professional attitude
Information	1.00				
Organization	0.49	1.00			
Parental participation	0.69	0.52	1.00		
Care and cure	0.70	0.52	0.70	1.00	
Professional attitude	0.63	0.52	0.67	0.69	1.00

All correlations significant ($p < 0.01$), two-tailed.

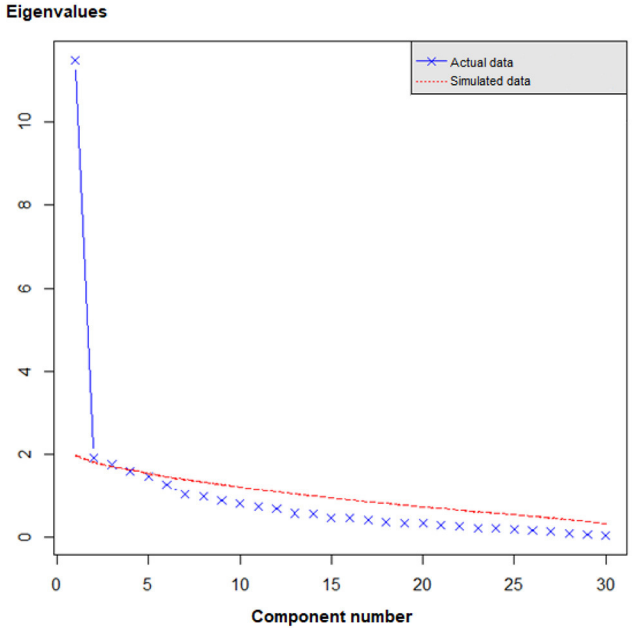

FIGURE 1 | Scree plot. Actual data: unimputed complete case observed data from set A. Simulated data: simulated random data from Monte Carlo Parallel Analysis. The strongest inflection in the empirical data is observed after the first component, suggesting unidimensionality. The lines cross between component 3 and 4, indicating that three *components* based on actual observed data provided more substantive information compared to three components based *on purely random* data. Four or more components should therefore not be extracted from the observed data.

Internal Structure

Principal Component Analysis

For the first PCA on unimputed data, sampling adequacy was ascertained by a KMO value of 0.89 and a significant Bartlett's test of sphericity ($\chi^2 = 3734.43$, $p < 0.01$). The comparison of empirical data to simulated random data through Monte Carlo Parallel Analysis suggested a three-component solution, explaining 56.8% of the total variance, with each component accounting for the following percentages: 43.7, 7.5, and 5.6%. In the scree plot (**Figure 1**), we observed the strongest inflection after the first component, which visually supports unidimensionality of the scale. The obliquely rotated component loadings for the three-component solution based on the first PCA are presented in the **Supplementary Table**. The correlations between the components were ranging from 0.28 to 0.46. The orthogonally rotated combined component loadings from the imputed data in the second PCA showed a similar three-component solution; except for two items (Professional Attitude - Admission, Organization - Efficiency) all of them loaded on the same respective components. Both items showed strong associations with more than one component in either version of the PCA and seemed to contribute mainly to the intercorrelations among the components. The comparison between component loadings for the first, oblique PCA and second, orthogonal PCA are presented in the **Supplementary Table**, found in the **Supplementary Material**.

Confirmatory Factor Analysis

The first CFA was conducted to validate the fit of the three-component solution. As the results of both alternative PCAs showed a comparable three-component solution, we chose to start with a CFA model based on results from the second PCA (on imputed data with orthogonal rotation). However,

TABLE 6 | Model fit statistic for the respective CFA models.

	χ^2	χ^2/df	CFI	TLI	RMSEA
Three-component model	1545.78	3.85	0.70	0.66	0.13
Three-component model, revised	1640.05	5.05	0.73	0.70	0.09
One-component model	1642.17	4.05	0.68	0.63	0.13
Five-component model	1561.97	3.95	0.70	0.64	0.13

CFA, Confirmatory Factor Analysis; χ^2, model-Chi-squared; df, degrees of freedom; CFI, Comparative Fit Index; TLI, Tucker Lewis Index; RMSEA, Root Mean Square Error of Approximation.

TABLE 7 | Variance explained by each factor for the respective CFA models.

	F_1	F_2	F_3	F_4	F_5
Three-component model	0.30	0.32	0.14		
Three-component model, revised	0.47	0.67	0.72		
One-component model	0.35				
Five-component model[a]	0.51	0.42	0.73	0.54	0.44

CFA, Confirmatory Factor Analysis; F, factor. [a]Five-component model: F_1 Information, F_2 Organization, F_3 Parental Participation, F_4 Care and Cure, F_5 Professional Attitude.

model fit was poor ($\chi^2 = 1545.78$, $\chi^2/df = 3.85$, CFI = 0.70, TLI = 0.66, RMSEA = 0.13). The model was then further revised using Lagrange Multiplier Tests (LM test), evaluating several alterations aiming at reducing large correlation residuals. The best fitting solution was found after first removing four items and then applying LM test improvements, yet overall model fit remained poor ($\chi^2 = 1640.05$, $\chi^2/df = 5.05$, CFI = 0.73, TLI = 0.70, RMSEA = 0.09).

The alternative model specifying pure unidimensionality showed poor goodness of fit, with $\chi^2 = 1642.17$, $\chi^2/df = 4.05$, CFI = 0.68, TLI = 0.63, RMSEA = 0.13. The five-factor model aiming to evaluate the validity of the five domains also showed poor goodness of fit ($\chi^2 = 1561.97$, $\chi^2/df = 3.95$, CFI = 0.70, TLI = 0.64, RMSEA = 0.13).

Model fit statistics for the respective CFA models are summarized in **Table 6**. Variance explained by the factors for each CFA model are presented in **Table 7**. To eliminate lack of power or collateral bias between set A and B as potential cause for finding the current results, we have repeated the same analyses on the other half of the data set. These analyses yielded equivalent results, supporting the robustness of our findings.

DISCUSSION

In this study, we evaluated the psychometric characteristics of the German version of the EMPATHIC-30 for use in intermediary/general pediatric cardiology units. Furthermore, we extended the psychometric assessment in comparison to previous studies by evaluating the internal structure of the questionnaire in this care setting.

On average, parents gave high ratings for their satisfaction with FCC. The McDonald's omega values in our study indicated acceptable to good reliability for the items within the five domains and excellent reliability for the full-scale score. These values are consistent with the findings of other EMPATHIC-30 studies (26–29). We found adequate convergent validity as shown by moderate to strong correlations between the five domains scores/ the full-scale score and the four general satisfaction items. Our results fall in line with previous publications, reporting correlation coefficients in the same order of magnitude (23, 27, 28). Future studies should extend these findings by investigating convergent validity based on methodology that is more elaborate, such as the use of other standardized instruments measuring parent satisfaction with care, as well as by incorporating assessments of discriminant validity.

We used PCA to assess the internal structure of the German version of the EMPATHIC-30. The analyses from the first PCA revealed a three-component structure with an explained variance over 50%. The first component explains beyond 40%, which supports the unidimensionality of the scale and may indicate that the questionnaire adequately measures the construct of interest (satisfaction with FCC) in our population. The three-component structure resulting from the first PCA (conducted on complete case data and allowing for intercorrelations between components) is very similar to the three-component structure resulting from the second PCA (conducted on imputed data, ignoring intercorrelations between components): only two out of 30 items load differently. Considering that the correlations among the components were close to negligible in the first PCA, rotation seems to have a minor impact on the interpretation of the internal structure, which may not be true for missing data (37). Therefore, we are inclined to view the three-component structure resulting from the second PCA as the best approximation of the questionnaire's internal structure in our sample. Although the three-component solution differs from the expected five-component structure, it is plausible and interpretable. Based on the semantic content of the respective items, we label the first component as "Perception and respect of the family's needs," the second component as "Involvement of and collaboration with the parents," and the third as "Communication and organization." However, despite the interpretability of the three components, the cross-validation of the three-component solutions via CFA resulted in poor fit indices. Model revisions did not significantly improve the model fit. A one-component solution to test for unidimensionality also showed a poor fit to the real data. Although the first component captures over 40% of the total variance in PCA, the true score variance seems to be relatively small compared to the random error variance. Additionally, we validated the five-component solution based on the original domains of the EMPATHIC-30, which indicated a poor fit to the real data. According to the poor model fit indices, all tested component models seem to be an oversimplification of the true structure of the questionnaire.

Our findings suggest that the EMPATHIC-30 has no clear and generalizable factor structure in our population. The ambiguous internal structure found in our study needs to be interpreted in light of the construction of the EMPATHIC questionnaires. In the original publication of the EMPATHIC-65, the five domains were defined during expert group sessions and item groupings into the respective domains were performed consensus based (24).

While the authors used CFA to evaluate the unidimensionality of each domain (assessing whether the items within every domain measured the same construct), they did not evaluate the underlying factor structure of the questionnaire (23). For the development of the shortened EMPATHIC-30 questionnaire, multiple regression analysis was used to evaluate statistical performance of the items, which might explain the divergence between the conceptual and the data-driven structure of the questionnaire (26). Furthermore, scores on the EMPATHIC-30 were high on average, with relatively small standard deviations. Accordingly, the parents in our sample were highly satisfied and the limited variation may contribute to the unclear factor structure. Still, our data showed sufficient true score variation to find three interpretable dimensions. The non-zero but not very high correlations between domain scores support this claim rather than support a true unidimensional structure. Replication studies may shed light on the question whether the unclear factor structure is sample specific. For instance, individual characteristics may influence interpretation of the items and subsequently, the way items divide into latent factors. Investigating the data-driven internal structure vs. theoretically postulated structure by conducting studies in different cultural settings and (sub-) populations may therefore be an interesting avenue for follow-up research. While we did not find strong support for the five-factor structure, we consider the domains informative, especially as they were thoroughly developed through expert panels. Nevertheless, FCC reflects a multi-faceted construct and we need more conceptual work to explain expert consensus on the one hand, and unclear factorial structure on the other, especially in light of the fact that the questionnaire assesses the subjective experience, as opposed to objective criteria for FCC.

Our study warrants some limitations. This is an analysis of quality management data from a single intermediary/general pediatric cardiology unit. Participation of other pediatric cardiology centers would allow for a more robust interpretation of results and in a prospective study design, additional measurements should be included for psychometric evaluation, specifically allowing for an assessment of discriminant validity. Furthermore, based on our results, differential analyses considering population characteristics like age range, duration of stay, and complexity of disease may be important to further increase our insights into the internal structure of the questionnaire.

To sum up, the German EMPATHIC-30 has no clear and simple factor structure in our population, while showing adequate reliability and convergent validity as assessed with four general satisfaction items. Accordingly, the EMPATHIC-30 is a suitable instrument to measure FCC in intermediary/general pediatric cardiology wards. However, follow-up studies are needed to further investigate the factor structure of the questionnaire. To our knowledge, this is the first study to assess psychometric properties of a standardized assessment of satisfaction with FCC in this population. Identifying care aspects that need to be improved during hospitalization is crucial in order to meet the developmental needs of children with CHD.

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 Medical Ethics Committee Charité Virchow (Nr EA2/032/20). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HF, KS, JL, RR, and AG contributed to the conception of the study. HF, RR, and AG developed the data analysis plan. MJ and AG prepared the dataset. RR and AG performed the statistical analysis. AG wrote the first draft of the manuscript. HF and RR reviewed the first version and wrote sections of the manuscript. All the 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.2022.901260/full#supplementary-material

REFERENCES

1. Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births. incidence and natural history. *Circulation.* (1971) 43:323–32. doi: 10.1161/01.CIR.43.3.323
2. Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol.* (2019) 48:455–63. doi: 10.1093/ije/dyz009
3. Van Der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* (2011) 58:2241–7. doi: 10.1016/j.jacc.2011.08.025
4. Dolk H, Loane M, Garne E, European Surveillance of Congenital Anomalies (EUROCAT) Working Group. Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005. *Circulation.* (2011) 123:841–9. doi: 10.1161/CIRCULATIONAHA.110.958405

5. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American heart association. *Circulation.* (2012) 126:1143–72. doi: 10.1161/CIR.0b013e318265ee8a
6. Howell HB, Zaccario M, Kazmi SH, Desai P, Sklamberg FE, Mally P. Neurodevelopmental outcomes of children with congenital heart disease: a review. *Curr Probl Pediatr Adolesc Health Care.* (2019) 49:100685. doi: 10.1016/j.cppeds.2019.100685
7. Clancy T, Jordan B, de Weerth C, Muscara F. Early emotional, behavioural and social development of infants and young children with congenital heart disease: a systematic review. *J Clin Psychol Med Settings.* (2020) 27:686–703. doi: 10.1007/s10880-019-09651-1
8. McGauran M, Jordan B, Beijers R, Janssen I, Franich-Ray C, de Weerth C, et al. Long-term alteration of the hypothalamic-pituitary-adrenal axis in children undergoing cardiac surgery in the first 6 months of life. *Stress.* (2017) 20:505–12. doi: 10.1080/10253890.2017.1349748
9. Ryan KR, Jones MB, Allen KY, Marino BS, Casey F, Wernovsky G, et al. Neurodevelopmental outcomes among children with congenital heart disease: at-risk populations and modifiable risk factors. *World J Pediatr Congenit Heart Surg.* (2019) 10:750–8. doi: 10.1177/2150135119878702
10. *Institute for Patient- and Family-Centered Care*. Available online at: https://www.ipfcc.org/ (accessed November 2, 2021).
11. Davidson JE, Aslakson RA, Long AC, Puntillo KA, Kross EK, Hart J, et al. Guidelines for family-centered care in the neonatal, pediatric, and adult ICU. *Crit Care Med.* (2017) 45:103–28. doi: 10.1097/CCM.0000000000002169
12. Committee on Hospital Care and Institute for Patient-and Family-Centered Care. Patient-and family-centered care and the pediatrician's role. *Pediatrics.* (2012) 129:394–404. doi: 10.1542/peds.2011-3084
13. Franck LS, O'Brien K. The evolution of family-centered care: from supporting parent-delivered interventions to a model of family integrated care. *Birth Defects Res.* (2019) 111:1044–59. doi: 10.1002/bdr2.1521
14. Feldman R, Rosenthal Z, Eidelman AI. Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. *Biol Psychiatry.* (2014) 75:56–64. doi: 10.1016/j.biopsych.2013.08.012
15. Lv B, Gao XR, Sun J, Li TT, Liu ZY, Zhu LH, et al. Family-centered care improves clinical outcomes of very-low-birth-weight infants: a quasi-experimental study. *Front Pediatr.* (2019) 7:138. doi: 10.3389/fped.2019.00138
16. Als H, Duffy FH, McAnulty GB, Rivkin MJ, Vajapeyam S, Mulkern RV, et al. Early experience alters brain function and structure. *Pediatrics.* (2004) 113:846–57. doi: 10.1542/peds.113.4.846
17. Welch MG, Myers MM, Grieve PG, Isler JR, Fifer WP, Sahni R, et al. Electroencephalographic activity of preterm infants is increased by family nurture intervention: a randomized controlled trial in the NICU. *Clin Neurophysiol.* (2014) 125:675–84. doi: 10.1016/j.clinph.2013.08.021
18. Ding X, Zhu L, Zhang R, Wang L, Wang TT, Latour JM. Effects of family-centred care interventions on preterm infants and parents in neonatal intensive care units: a systematic review and meta-analysis of randomised controlled trials. *Aust Crit Care.* (2019) 32:63–75. doi: 10.1016/j.aucc.2018.10.007
19. Torowicz D, Lisanti AJ, Rim JS, Medoff-Cooper B. A developmental care framework for a cardiac intensive care unit: a paradigm shift. *Adv Neonatal Care.* (2012) 12:S28–32. doi: 10.1097/ANC.0b013e318265aeef
20. Lisanti AJ, Vittner D, Medoff-Cooper B, Fogel J, Wernovsky G, Butler S. Individualized family-centered developmental care: an essential model to address the unique needs of infants with congenital heart disease. *J Cardiovasc Nurs.* (2019) 34:85–93. doi: 10.1097/JCN.0000000000000546
21. Peterson JK. Supporting optimal neurodevelopmental outcomes in infants and children with congenital heart disease. *Crit Care Nurse.* (2018) 38:68–74. doi: 10.4037/ccn2018514
22. Dall'Oglio I, Mascolo R, Gawronski O, Tiozzo E, Portanova A, Ragni A, et al. A systematic review of instruments for assessing parent satisfaction with family-centred care in neonatal intensive care units. *Acta Paediatr.* (2018) 107:391–402. doi: 10.1111/apa.14186
23. Latour JM, van Goudoever JB, Duivenvoorden HJ, Albers MJIJ, Van Dam NAM, Dullaart E, et al. Construction and psychometric testing of the EMPATHIC questionnaire measuring parent satisfaction in the pediatric intensive care unit. *Intensive Care Med.* (2011) 37:310–8. doi: 10.1007/s00134-010-2042-y
24. Latour JM, Hazelzet JA, Duivenvoorden HJ, van Goudoever JB. Construction of a parent satisfaction instrument: perceptions of pediatric intensive care nurses and physicians. *J Crit Care.* (2009) 24:255–66. doi: 10.1016/j.jcrc.2008.06.002
25. Latour JM, van Goudoever JB, Duivenvoorden HJ, van Dam NA, Dullaart E, Albers MJ, et al. Perceptions of parents on satisfaction with care in the pediatric intensive care unit: the EMPATHIC study. *Intensive Care Med.* (2009) 35:1082–9. doi: 10.1007/s00134-009-1491-7
26. Latour JM, Duivenvoorden HJ, Tibboel D, Hazelzet JA, EMPATHIC Study Group. The shortened EMpowerment of PArents in THe Intensive Care 30 questionnaire adequately measured parent satisfaction in pediatric intensive care units. *J Clin Epidemiol.* (2013) 66:1045–50. doi: 10.1016/j.jclinepi.2013.02.010
27. Gill FJ, Wilson S, Aydon L, Leslie GD, Latour JM. Empowering parents of australian infants and children in hospital: translation, cultural adaptation, and validation of the EMpowerment of PArents in the intensive care-30-AUS questionnaire. *Pediatr Crit Care Med.* (2017) 18:e506–13. doi: 10.1097/PCC.0000000000001309
28. Pilar Orive FJ, Basabe Lozano J, López Zuñiga A, López Fernández YM, Escudero Argaluza J, Latour JM. Spanish translation and validation of the EMPATHIC-30 questionnaire to measure parental satisfaction in intensive care units. *An Pediatr.* (2018) 89:50–7. doi: 10.1016/j.anpede.2017.08.006
29. Tiryaki O, Zengin H, Çinar N, Umaroglu MM, Latour JM. Turkish adaptation and validation of the EMpowerment of PArents in THe Intensive Care (EMPATHIC-30) questionnaire to measure parent satisfaction in neonatal intensive care units. *Front Pediatr.* (2020) 8:421. doi: 10.3389/fped.2020.00421
30. Nagl-Cupal M, Lippoldt J. *Übersetzung und kulturelle Adaptierung eines Instruments zur Messung von Family-Centered Care aus der Perspektive von Eltern bzw*. nahen Familienmitgliedern Unpublished manuscript Faculty of Nursing Science, University of Vienna (2016).
31. Bandalos DL, Finney SJ. Factor analysis: exploratory and confirmatory. *In: The Reviewer's Guide to Quantitative Methods in the Social Sciences*. New York, NY: Routledge (2018). p. 98–122. doi: 10.4324/9781315755649-8
32. Tavakol M, Wetzel A. Factor Analysis: a means for theory and instrument development in support of construct validity. *Int J Med Educ.* (2020) 11:245–7. doi: 10.5116/ijme.5f96.0f4a
33. Sijtsma K. On the use, the misuse, and the very limited usefulness of Cronbach's alpha. *Psychometrika.* (2009) 74:107–20. doi: 10.1007/s11336-008-9101-0
34. Dunn TJ, Baguley T, Brunsden V. From alpha to omega: a practical solution to the pervasive problem of internal consistency estimation. *Br J Psychol.* (2014) 105:399–412. doi: 10.1111/bjop.12046
35. Abdi H, Williams LJ. Principal component analysis. *Wiley Interdiscip Rev Comput Stat.* (2010) 2:433–59. doi: 10.1002/wics.101
36. Linting M, van der Kooij A. Nonlinear principal components analysis with CATPCA: a tutorial. *J Pers Assess.* (2012) 94:12–25. doi: 10.1080/00223891.2011.627965
37. Van Ginkel JR, Kroonenberg PM, Kiers HA. Missing data in principal component analysis of questionnaire data: a comparison of methods. *J Stat Comput.* (2014) 84:2298–315. doi: 10.1080/00949655.2013.788654
38. Little RJ. A test of missing completely at random for multivariate data with missing values. *J Am Stat Assoc.* (1988) 83:1198–202. doi: 10.1080/01621459.1988.10478722
39. van Ginkel JR, Linting M, Rippe RC, van der Voort A. Rebutting existing misconceptions about multiple imputation as a method for handling missing data. *J Pers Assess.* (2020) 102:297–308. doi: 10.1080/00223891.2018.1530680
40. Taber KS. The use of Cronbach's alpha when developing and reporting research instruments in science education. *Res Sci Educ.* (2018) 48:1273–96. doi: 10.1007/s11165-016-9602-2
41. Akoglu H. User's guide to correlation coefficients. *Turk J Emerg Med.* (2018) 18:91–3. doi: 10.1016/j.tjem.2018.08.001
42. Watkins M. *Monte Carlo PCA for Parallel Analysis (Computer Software).* State College, PA: Ed & Psych Associate (2000).

43. van Wingerde B, van Ginkel J. SPSS syntax for combining results of principal component analysis of multiply imputed data sets using generalized procrustes analysis. *Appl Psychol Meas.* (2021) 45:231–2. doi: 10.1177/0146621621990757
44. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Struct Equ Model.* (1999) 6:1–55. doi: 10.1080/10705519909540118
45. Matsunaga M. How to factor-analyze your data right: do's, don'ts, and how-to's. *Int J Psychol Res.* (2010) 3:97–110. doi: 10.21500/20112084.854

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Pregnancy Outcomes in Women With Mechanical Valve Prostheses Using Vitamin K Antagonist Therapy: The Experience of the Salam Centre for Cardiac Surgery in Sudan

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Pregnancy and childbirth on anticoagulants after mechanical heart valve replacement present a high risk of complications for both mother and baby. On top of pregnancy worsening the mother's cardiac function, anticoagulant therapy itself is a crucial problem. A safe and effective anticoagulation regimen for both mother and fetus is not possible. The most effective drugs for preventing valve thrombosis are VKAs, whose dosage needs to be adjusted with frequent INR checks. Moreover, VKAs can have embryopathic and teratogenic action. Patients in follow-up and anticoagulant treatment at the Salam Centre for Cardiac Surgery in Sudan live spread out over a large area where transport to the Center is generally difficult; pregnancy treatment has, therefore, been adapted to the limitations of reality. Pregnancy is discouraged and contraception and therapeutic abortion are recommended, but this guidance frequently goes unheeded. Here we describe maternal and fetal outcomes in 307 consecutive pregnancies recorded by staff at the oral anticoagulant clinic (OAC) from April 2017 to November 2021. Out of 307 pregnancies, there were 15 maternal deaths (4.9%), 24 thrombotic events (7.8%) and 22 major bleedings (7.2%). Fifty pregnancies (16.3%) were terminated by therapeutic abortion. Only 47.6% of pregnancies had good maternal and neonatal outcomes. Data clearly show that, due to the complexity of pregnancy in women with mechanical heart valves and the scarcity of tertiary healthcare services in the area where patients live, maternal mortality is at an unacceptable level and requires a structured, multi-disciplinary intervention.

Keywords: anticoagulants-therapeutic use, pregnancy, mechanical heart valves, humanitarian medicine, Warfarin, maternal death, Salam Centre for Cardiac Surgery

INTRODUCTION

Mechanical heart valves (MHVs) replacing destroyed natural ones are life-saving for patients with advanced rheumatic heart disease (RHD). The downside of this surgical approach is the resultant need for life-long anticoagulant treatment, to limit the risk of thrombosis around the MHV, which can lead to severe valve dysfunction, embolism and stroke. Anticoagulant treatment has crucial intrinsic risks: if the dose is too low, the MHV function is put at risk of enhanced clotting; if the dose is too high, bleeding may occur spontaneously or after trauma. Both risks may be life-threatening, so careful management of anticoagulant therapy is essential. For long-term systemic anticoagulant treatment, Warfarin, a vitamin K antagonist (VKA) approved nearly 70 years ago, is still the drug of choice (1, 2). Warfarin is effective and cheap, but the treatment is complex and sometimes cumbersome. Patient compliance, frequent blood tests to check prothrombin time and international normalized ratio (INR), and dose adjustments are imperative (1, 2).

Moreover, VKAs are characterized by a significant, dose-dependent, placental drug transfer, (3) which can lead to embryo-/fetotoxicity and teratogenicity, (4) frequently leading to miscarriage, stillbirth and congenital malformations (Warfarin syndrome) (5–9). Intrauterine hemorrhage may also occur and lead to permanent damage. The balance between the need for anticoagulation to avoid or limit severe complications from MHV dysfunction and stroke for the mother, on the one hand, and a smooth pregnancy producing a healthy baby, on the other, is very fine. Some progress has been made in this field with the introduction of low molecular weight heparin (LMWH) in specific periods or throughout the pregnancy (1–3). This alternative anticoagulant treatment does not cross the placental barrier and is not dangerous for the child. However, it is reported to be less effective in preventing thrombosis in mothers, particularly where the dose cannot be adjusted weekly according to the level of factor anti-Xa activity (1, 2, 10, 11). Despite the limited data available from randomized controlled trials, the recent guidelines (1) recommend anticoagulation with LMWH and factor anti-Xa activity monitoring in the first trimester in patients requiring Warfarin doses of >5 mg/day; after the 36th week, a shift to LMWH is imperative regardless of the daily dose of warfarin. The unavailability of frequent anti-Xa activity monitoring and the high cost of LMWH in medium- and low-income countries (MLICs) make it challenging to follow these recommendations.

Our patients come from Sudan and neighboring states, most of which are low-income countries (LICs) with very limited healthcare systems that cannot support pregnant patients in need of anticoagulation. Moreover, many women live far from where they can get blood tests, counseling, drug prescription and drug supply and these difficulties greatly amplify the risk in pregnancies with anticoagulation compared to the same situation in high-income countries (10).

Women with MHVs treated with anticoagulants are at a high risk of death during pregnancy, at delivery and in puerperium; pregnancy is therefore strongly discouraged before surgery and at discharge after surgery. However, women are often eager to see their pregnancy through and, in some cases, are forced to do so due to social and family pressure.

Avoiding pregnancy as well as supporting pregnant women remain frequent and difficult tasks at the *Salam* Centre for Cardiac Surgery in Khartoum. This study aims to describe and analyze the outcome of pregnancies in women on anticoagulants in follow-up treatment at the *Salam* Centre and discuss possible improvements in the clinical path.

METHODS

The *Salam* Centre for Cardiac Surgery (12), a humanitarian project by the NGO EMERGENCY in collaboration with the Sudanese government, has been operating in Khartoum since 2007.

The Center offers surgical treatment free of charge for RHD and congenital heart disease to patients from Sudan and neighboring countries. Between the opening of the *Salam* Centre in 2007 and November 2021, 3,552 women underwent valve surgery and had one or two mechanical heart valves implanted, therefore requiring life-long anticoagulant treatment.

Patients scheduled for this type of surgery had pre-operative assessment and counseling for pregnancy (strongly discouraged) and contraception (strongly recommended). Counseling about contraception and pregnancy is repeated in the OAC at discharge. In case of pregnancy referred at the follow-up visit, therapeutic interruption is encouraged. In case of refusal, the following steps are implemented: full cardiac assessment is provided; Warfarin therapy is continued, with the addition of 100 mg of Aspirin per day (2): INR checks and dose adjustments are made every 2 weeks until the 36th week. At the 36th week, VKA is switched to full-dose LMWH. Patients have to rely on hospitals other than the *Salam* Centre for delivery and obstetric care. After delivery, VKA therapy is recommenced, and the patient is submitted for full cardiac assessment as soon as possible. However, patients often adhere only partly to this program, especially those living in regions far from the Center.

Data Collection

In this retrospective study of routinely collected data, all consecutive pregnancies from April 2017 to November 2021 in patients with MHV implants and follow-up at the *Salam* Centre were included. The Center runs the OAC in collaboration with the Italian federation of anticoagulant clinics (FCSA). It provides all patients, free of charge, with counseling, management of anticoagulant treatment, INR checks and other necessary blood tests, VKA dose adjustment and rescue treatments in collaboration with cardiologists and cardiac surgeons (12).

Data on cardiac procedures, prescribed Warfarin doses, pregnancy outcomes, cardiologic follow-up, vital status and complications in patients during and after pregnancy [major (13, 14) and clinically relevant bleeding, thrombosis and embolism] were stored, together with the INR and warfarin prescriptions, in the dedicated software Parma® (Werfen Italy).

Survival is reported as survival during pregnancy up to 6 weeks after delivery (according to the definition of maternal

TABLE 1 | Maternal outcome in pregnant women with MHV: overall and in strata of pregnancies outcome.

	Maternal death*	Major bleeding ¥	Thrombosis†
	N (%; 95% CI)	*N* (%; 95% CI)	*N* (%; 95% CI)
All pregnancies ($n = 307$)	15 *(4.9)* *(4.9; 2.8–7.9)*	22 *(7.2)* *(4.5–10.7)*	24 *(7.8)* *(5.1–11.4)*
Therapeutic abortion ($n = 50$)	3 *(6.0)* *(1.3–16.6)*	6 *(12.0)* *(4.5–24.3)*	8 *(16.0)* *(7.2–29.1)*
Miscarriage/Fetal demise <28 weeks ($n = 70$)	2 *(2.9)* *(0.4–9.9)*	9 *(12.9)* *(6.1–23.0)*	4 *(5.7)* *(1.6–14.0)*
Delivery >28 weeks/Post-partum ($n = 180$)	3 *(1.7)* *(0.4–4.8)*	7 *(3.9)* *(1.6–7.9)*	12 *(6.7)* *(3.5–11.4)*
P-values§	*0. 196*	*0.019*	*0.090*

**Seven women died during pregnancy.*

¥ 17 metrorrhagia, one hemorrhagic stroke, four other causes requiring blood transfusion.

† 23 valve thrombosis, one ischemic stroke.

§ Fisher exact Test for maternal death and thrombosis, Chi-Square for major bleeding.

mortality); the outcome of "late maternal mortality" (maternal death between 6 weeks and 1 year post-partum) has been evaluated for the sub-group of patients with 1 year of follow-up after birth. Fetal/neonatal outcomes concern survival; no data about congenital malformations is available. Uncertainties regarding the outcome of babies are reported as unknown.

Statistical Analysis

All data were entered and stored on Microsoft Excel files. Descriptive analyses are presented as frequencies, proportions, means and standard deviations, medians and interquartile ranges (IQR) where appropriate to characterize patients and their clinical outcomes. Proportions are compared using the $\chi 2$ test or Fisher Test, depending on variables distribution. For maternal outcomes occurred up to 6 weeks after delivery (i.e., major bleeding, thrombosis and maternal mortality), 95% confidence intervals (95% CI), are also presented. SAS 9.4 software (Inc., Cary, NC, USA) was used for all analysis.

ETHICS

The institutional, scientific ethics board of the University of Milan has approved this study and, due to the nature of retrospective chart reviews, waived the need for informed consent from individual patients.

RESULTS

Between April 2017 and November 2021, 307 pregnancies in 253 women were assessed at the OAC of the *Salam* Centre. All patients had mechanical heart valve prostheses: 15 isolated aortic valve prostheses (AVPs), 163 isolated mitral valve prostheses (MVPs) and 75 combined MVPs and AVPs. The average individual weekly dose of Warfarin was 43.1 ± 18.7 mg, while 40% of the women were prescribed a dose above 5 mg/day.

The median elapsed time from the operation to the first reported pregnancy is 4.5 years, ranging from one to 12 years.

Most women (206, 81.4%) had only one pregnancy, 47 (18.6%) patients had more than one pregnancy (40 had two, seven had three). Therefore, we analyzed the outcome of 253 pregnant women (mean age 28.1 years ± 6.6, range 14–50) and 307 pregnancies. There were no losses in the follow-up (FU) during pregnancy; nevertheless, 11 patients were lost to follow-up after delivery, namely 2 did not attend the 6 week-FU and 9 the 1 year-FU.

According to the definition of maternal death (up to 6 weeks after birth), the overall maternal survival was 95.1%; we reported 15 maternal deaths/307 pregnancies (4.9%), corresponding to 5.9 deaths/100 women. In the sub-group for which a follow-up 1 year after birth was available (234), we recorded nine further late maternal deaths (3.8%).

Maternal deaths, major bleeding and thrombosis are reported in **Table 1**, for all pregnancies and in strata of pregnancies outcome. Causes of death (mainly reported to us by relatives) are lacking in most cases: five valve thrombosis (three with documented diagnosis, two suspected), one intracranial bleeding, three infections and six unknown causes. Only major bleeding showed a significant different distribution according to pregnancy outcome, with a higher frequency after spontaneous or therapeutic abortion (12 and 12.9%, respectively), than after delivery (3.9%). On one occasion, it was responsible for maternal death. Thrombosis leading to death was more frequent than hemorrhage (33.3 vs. 6.7%). The therapeutic interruption was complicated by bleeding in 12% of the cases (**Table 1**); nevertheless, no significant association is found between the two events. Therapeutic interruption is related to thrombosis and blocked valves ($P < 0.05$) as most of the women (75%) were directed to perform an abortion once discovered the thrombosis. Only two patients had thrombosis after abortion as a proper bridging may have been omitted, or the intervention may have been performed outside hospitals.

TTR calculated with the Rosendaal method shows a median TTR of 28% (13–46) during pregnancy, a value considered particularly low, especially when compared to the TTR before pregnancy (44%, 25–59). Moreover, a significant association was found between TTR > 46% (IV Quartile) and a reduced incidence of adverse events such as thrombosis and bleeding (*P*-value 0.0128).

A limited number (153/307, 49.8%) of pregnancies resulted in babies born alive (**Table 2**).

Only 133 out of the 236 (56.4%) women, who survived pregnancy and the first 6 weeks post-partum, gave birth to at least one alive baby (119 to one, 13 to two, and one to three babies); 104 mothers failed to do so, while three babies born alive lost their mothers at birth.

As for termination of pregnancy on the recommendation of cardiologists, it was agreed to by 37 patients (28.5%) counseled in the first trimester of each pregnancy and by 8 (15.4%) in the second trimester (OR 2.18, CI 0.95–5.37 *P*-value = 0.09).

TABLE 2 | Fetal outcome.

	Overall *N* (%)	One pregnancy *N* (%)	Two or three pregnancies *N* (%)
All pregnancies	307	206	101
Born alive	153 *(49.8)*	112 *(54.4)*	41 *(40.6)*
Therapeutic abortion (TA)	50 *(16.3)*	30 *(14.6)*	20 *(19.8)*
All pregnancies–excluding TA	257	176	81
Born alive	153 *(59.5)*	112 *(63.6)*	41 *(50.6)*
Miscarriage/Fetal demise <28 weeks	70 *(27.2)*	39 *(22.2)*	31 *(38.3)*
Stillbirth/neonatal death	24 *(9.3)*	16 *(9.1)*	8 *(9.9)*
Maternal death during pregnancy	7 *(2.7)*	7 *(4.0)*	0 *(0)*
Unknown	3 *(1.2)*	3 *(1.7)*	0 *(0)*

DISCUSSION

To become a mother is a natural desire all over the world. In many medium- and low-income countries, and indeed high-income ones, the importance placed on women having children, and the social pressure on them to do so, is very strong. In Sudan and neighboring countries, having children, often many children, is a sign of prestige for women; not having children is often seen as indicative of a lack of values by women's families and society, and can impact very heavily on their self-esteem and quality of life. Moreover, in LICs, having a lot of children can be a substitute for the weak support provided by the national welfare system to elderly and fragile family members.

Most women taking anticoagulants after heart surgery and mechanical valve implants have to live with this reality. Many of them are very young and have had difficult lives even before surgery. Streptococcal infection, rheumatic fever and RHD are mostly found among the poorest, and illness hinders schooling and acquisition of skills. Heart surgery and mechanical valves save lives, but they make life-long treatment a necessity and any return to normality only partial, with a higher risk of complication-related morbidity and mortality.

During the observation period, 253 women who had been referred to the OAC for VKA management due to MHVs became pregnant despite repeated advice to avoid doing so. When prevention fails, therapeutic interruption is recommended to pregnant women (and frequently refused). A significantly higher adherence to recommendations (even if not statistically significant) has been noticed in patients who received counseling in the first trimester of pregnancy; they had therapeutic abortions in almost three times as many cases as women counseled in the second trimester. This can be due to factors related to both women's attitude (intentional delay in informing the cardiologist, in order to preserve their pregnancy; increased confidence in a smooth pregnancy as the months go by) and significant difficulties finding doctors/facilities willing to interrupt pregnancies in the second trimester of pregnancy. Pregnant women refusing abortion have a complete cardiological visit; administration of VKA is continued as the most effective and safest anticoagulation treatment for the mother, especially as weekly anti-Xa activity monitoring and dose adjustment are not possible (1). The prescribed dose of Warfarin is in 40% of the ladies higher than the threshold of 5 mg/day and the risk of fetal damage (15, 16) is expected to be more frequent. However, our limited data, with many values missing, do not allow conclusions on this point.

Nearly half (154/307, 50.2%) of all pregnancies are unsuccessful. Only 133/236 (56.4%) mothers gave birth to at least one live baby. Nearly one out of five mothers (19.8%) repeatedly tried to have a child, but only 41 children were born alive after their collective 101 pregnancies. The price paid by these mothers is very high in terms of suffering, frustration and survival (**Table 1**): we registered 15 maternal deaths/307 pregnancies (4.9%).

The most frequent and life-threatening complications were valve thrombosis, which might have been caused by low compliance to oral anticoagulant treatment (OAT) once the patients became aware they were pregnant. Indeed, information on the embryo-/fetotoxicity of VKAs can lead to patients giving up the medication prescribed for them or taking it irregularly. Haemorrhagic complications occurred mostly around delivery or miscarriage/therapeutic abortion. Haemorrhagic complications had lower mortality strictly speaking, but sometimes led shortly after to thrombosis because of improper anticoagulation management after bleeding in hospitals, where medical staff are not trained to find the balance between the risk of bleeding and thrombosis.

In fact, rather than a potential improvement from complicated and costly anticoagulation strategies with probable but uncertain benefits to both mothers and babies, (17) the lack of competent clinical support from tertiary care centers (1, 2) is the most pressing of our patients' needs. Maternal mortality (4.9%) is much higher than in the ROPAC cohort (18) (1.4% of 212 patients, most of them from M-LICs, but not from sub-Saharan Africa). However, a comparison has limited value as their observation period is much shorter (follow-up until 1 week after delivery); pregnancies, however, ending with a baby being born alive were only 58%, not too far from our 50.3% (59.5% considering only pregnancies without women who had therapeutic abortion).

In the ROPAC (18) cohort, over 40% of pregnant women experienced severe complications, but most were treated and survived. Higher, but still far from our mortality rate, are the data from the metanalysis by Lawley et al. (19) on 256 patients with MHVs; they report a maternal mortality of 1.8 (CI 0.5–3.7) deaths/100 pregnancies. Once again, comparison with our data is limited, as no details about length of post-partum follow-up are reported. We register 4.9 deaths/100 pregnancies, which is above the upper limit of the confidence interval.

It emerges very clearly that we have to improve maternal survival before all else. Safeguarding mothers' lives must become our principal commitment. Where long-term anticoagulation cannot be avoided, and contraception is not accepted, a

nationwide obstetric support network seems the only solution; the *Salam* Centre can advise hospitals on anticoagulation management in case of hemorrhage or thrombosis provided there is a mutual relationship of trust. A similar network is in place for cardiology but is needed also for obstetrics.

More efforts could be made to improve women's awareness about health issues related to pregnancy. Standardized counseling, focusing on self-engagement, can strengthen relationships between patients and caregivers, improve adherence to therapy and contraceptive indications, and ensure timely communication about pregnant status.

STRENGTHS AND LIMITATIONS OF THE STUDY

We report on a very large, single-center experience of treatment for mothers taking anticoagulants after heart-valve surgery in sub-Saharan Africa. The analysis and the findings may help point the way to effective solutions for improving outcomes.

On the other hand, it is clear that there are many limitations, primarily due to the retrospective nature of the study and the difficulties in obtaining information from other hospitals or patients/relatives about patients' outcomes. This is particularly evident when it comes to causes of death and assessment of child morbidity.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Milan. Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: The institutional ethics board of the University of Milan due to the nature of retrospective chart reviews, waived the need for informed consent from individual patients.

AUTHOR CONTRIBUTIONS

NE organized and supervised the Oral Anticoagulant Clinic, contributed to the study concept, data collection, interpretation, writing, and supervision. SG contributed to the data cleaning, managed the database, contributed to interpretation, and contributed language revision. SH contributed to data collection and interpretation. ML contributed to the study concept, writing, and supervision. LC contributed to the statistical analysis. GP contributed to the study design and supervision. RB contributed to the design, elaboration of the data, writing, and supervision. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková R, Michele De Bonis M, et al. Guidelines for the management of cardiovascular diseases during pregnancy'. *Eur Heart J*. (2018) 7:3165–241. doi: 10.1093/eurheartj/ehy340
2. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. "2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines." *J Am Coll Cardiol*. (2021) 77:e35–71. doi: 10.1161/CIR.0000000000000932
3. Bavry AA, Arnaoutakis GJ. Perspective to 2020 American College of Cardiology/American Heart Association (ACC/AHA) guideline for the management of patients with valvular heart disease.' *Circulation*. (2021) 143:407–9. doi: 10.1161/CIRCULATIONAHA.120.051501
4. van Driel D, Wesseling J, Sauer PJ, Touwen BC, van der Veer E, Heymans HS. 'Teratogen update: fetal effects after in utero exposure to coumarins overview of cases, follow-up findings, and pathogenesis'. *Teratology*. (2002) 66:127–40. doi: 10.1002/tera.10054
5. Chetot T, Mouette-Bonnet M, Taufana S, Fourel I, Lefebvre S, Benoit E, et al. 'Differences in teratogenicity of some vitamin K antagonist substances used as human therapeutic or rodenticide are due to major differences in their fate after an oral administration'. *Toxicol Lett*. (2020) 333:71–9. doi: 10.1016/j.toxlet.2020.07.034
6. Becker MH, Genieser NB, Finegold M, Miranda D, Spackman T. 'Chondrodysplasis punctata: is maternal warfarin therapy a factor?' *Am J Dis Child*. (1975) 129:356–9. doi: 10.1001/archpedi.1975.02120400056013
7. Hall JG, Pauli RM, Wilson KM. 'Maternal and fetal sequelae of anticoagulation during pregnancy'. *Am J Med*. (1980) 68:122–40. doi: 10.1016/0002-9343(80)90181-3
8. WarkanyJ. 'A warfarin embryopathy?' *Am J Dis Child*. (1975) 129:287–8. doi: 10.1001/archpedi.1975.02120400005001
9. Walfisch A, Koren G. 'The "Warfarin Window" in pregnancy: the importance of half-life'. *J Obstet Gynaecol Can*. (2010) 32:988–9. doi: 10.1016/S1701-2163(16)34689-8
10. D'Souza R, Ostro J, Shah PS, Silversides CK, Malinowski A, Murphy KE, et al. 'Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis'. *Eur Heart J*. (2017) 38:1509–16. doi: 10.1093/eurheartj/ehx032
11. Wang J, Li K, Li H, Zhu W, Sun H, Lu C. 'Comparison of anticoagulation regimens for pregnant women with prosthetic heart valves: a meta-analysis of prospective studies'. *Cardiovasc Ther*. (2017) 35:e12292. doi: 10.1111/1755-5922.12292
12. Miccio R, Quattrociocchi M, Valgoi L, Chatenoud L, Lentini S, Giovanella E, et al. 'Treating children with advanced rheumatic heart disease in Sub-Saharan Africa: the NGO EMERGENCY's project at the Salam Centre for cardiac surgery in Sudan. *Front Pediatr*. (2021) 9:704729. doi: 10.3389/fped.2021.704729
13. Schulman S, Kearon C, Subcommittee on control of anticoagulation of the Scientific and Standardization Committee of the International

Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. (2005) 3:692–4 doi: 10.1111/j.1538-7836.2005.01204.x

14. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost.* (2015) 13:2119–26. doi: 10.1111/jth.13140
15. Hassouna A, Allam H. Limited dose warfarin throughout pregnancy in patients with mechanical heart valve prosthesis: a meta-analysis. *Interact Cardiovasc Thorac Surg*. (2014) 18:797–806. doi: 10.1093/icvts/ivu009
16. Xu Z, Fan J, Luo X, Zhang W-B, Ma J, Lin Y-B, et al. Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a systematic review and meta-analysis. *Can J Cardiol*. (2016) 32:1248.e1–1248.e9. doi: 10.1016/j.cjca.2015.11.005
17. Malhamé I, Othman M, Casais P, D'Souza R, Wald RM, Silversides CK, et al. 'Communication from the ISTH SSC subcommittee on women's health issues in thrombosis and haemostasis: a survey on anticoagulation for mechanical heart valves in pregnancy'. *Thromb Haemost.* (2021) 19:859–64. doi: 10.1111/jth.15213
18. van Hagen IM, Roos-Hesselink JW, Ruys TP, Merz WM, Goland S, Gabriel H, et al. Pregnancy in women with a mechanical heart valve: data of the european society of cardiology registry of pregnancy and cardiac disease (ROPAC). *Circulation.* (2015) 132:132–42. doi: 10.1161/CIRCULATIONAHA.115.015242
19. Lawley CM, Lain SJ, Algert CS, Ford JB, Figtree GA, Roberts CL. Prosthetic heart valves in pregnancy, outcomes for women and their babies: a systematic review and meta-analysis. *BJOG.* (2015) 12:1446–55. doi: 10.1111/1471-0528.13491

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Discordant Post-natal Patterns in Fetuses With Heterotaxy Syndrome: A Retrospective Single-Centre Series on Outcome After Fetal Diagnosis

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Objective: Cardiac and extra-cardiac anomalies in 46 pre-natally diagnosed cases of heterotaxy were compared to post-natal anatomical patterns in order to reveal discordant findings. Second, the outcome of these fetuses was evaluated.

Methods: Fetuses with heterotaxy, diagnosed in a tertiary referral centre, were analysed retrospectively. Based on the foetal abdominal situs view, right atrial isomerism (RAI) and left atrial isomerism (LAI) were defined as foetal sub-types. Post-natally, discordant anatomical patterns for broncho-pulmonary branching, atrial appendage morphology, and splenic status were further clarified with CT scans. In summary, the spectrum of pre-natally and post-natally detected cardiac and extra-cardiac anomalies is systematically reviewed. Necessary surgical interventions and mid-long-term outcomes were compared between the two sub-types in surviving infants.

Results: A total of 46 fetuses with heterotaxy were included; LAI was diagnosed in 29 (63%) fetuses and RAI was diagnosed in 17 (37%) fetuses. Extra-cardiac anomalies were noted in 35% of fetuses. Seven out of the 29 fetuses (24%) with LAI had atrio-ventricular block (AVB) and four of these cases presented with hydrops. Twenty nine out of the 46 participating fetuses (63%) were live births, with 62% in the LAI group and 65% in the RAI group. Five fetuses were lost to follow-up. At the age of 1 year, the overall survival of live births [estimate (95% CI)] was 67% (48; 92%) in patients with LAI and 55% (32; 94%) in patients with RAI. At the age of 5 years, the estimates were 67% (48; 92%) in the LAI group and 46% (24–87%) in the RAI group. The median survival (first quartile; third quartile) was 11.1 (0.1; 14) years for patients with LAI and 1.3 (0.09; NA) years for patients with RAI. Of 17 children who had undergone cardiac surgery, five (29%) children achieved a bi-ventricular repair and 12 (70%) children achieved a uni-ventricular palliation. Three were primarily palliated, but converted to bi-ventricular thereafter. Foetal subtype definition of heterotaxy based on the abdominal situs and

post-natal thoracic imaging studies showed a discordant pattern of broncho-pulmonary branching and atrial appendage anatomy in 40% of our live-born children.

Conclusion: Heterotaxy is a rare and complex condition with significant morbidity and mortality related to severe cardiac and extra-cardiac associations. Accurate pre-natal diagnosis can help identify the fetuses at risk and allow for timely intervention in a multi-disciplinary setting. Further studies are warranted to shed light on the exact sub-type definition in fetuses with heterotaxy and the presence of discordant post-natal patterns.

Keywords: heterotaxy, isomerism, discordant pattern, foetal echocardiography, cardiac surgery, outcome

INTRODUCTION

Heterotaxy syndrome (HS) is a rare congenital disorder with an incidence of 1 in 5,000–7,000 live births (1), characterised by an abnormal arrangement of structures relative to the left-right axis of the foetal body (2, 3), including the atrial appendages and the internal thoraco-abdominal organs. The left and right atria can be identified by the morphology of the atrial appendage, which has a specific pattern of pectinate muscles, referring to a right atrium and a left atrium. The normal arrangement, with asymmetrically arranged thoracic and abdominal organs, is called "situs solitus." Both the nomenclature and classification are a matter of discussion. As a result, the International Society for Nomenclature of Paediatric and Congenital Heart Disease proposed a definition in 2007 (4) to facilitate the precise use of the term, which will be used in this study. The definition of HS usually implies the description of two groups based on the morphology of the symmetrical side: left atrial isomerism (LAI) and right atrial isomerism (RAI). Historically, LAI and RAI have been distinguished based on certain features such as the presence or absence of a spleen (5). However, while there seems to be no pathognomonic pattern in each group, certain associated patterns have been described to occur more often in the respective groups (2, 4, 6).

In LAI, there are usually two morphological left atrial appendages, bilateral bi-lobed lungs, long bronchi on both the sides, and a situs anomaly of the abdominal organs, typically along with balanced congenital heart defects (CHDs), an interrupted inferior vena cava (IVC), and non-cardiac conditions such as malrotation of the intestines and polysplenia and biliary atresia (6).

In RAI, two morphological right atrial appendages can be found, as well as bilateral tri-lobed lungs, two short bronchi on both the sides, together with typically severely unbalanced CHD involving abnormal drainage of the pulmonary veins and abnormal intra-abdominal location of the aorta and the IVC; asplenia is also found in the majority of cases (6). Most of the post-natal features defining the HS subtypes (RAI vs. LAI), such as broncho-pulmonary branching, atrial appendage arrangement, and splenic status, are difficult to visualise in foetal scanning. To visualise the normal abdominal situs arrangement, a cross-sectional view of the foetal abdomen is obtained. In situs solitus, the aorta and the stomach bubble can be seen to the left of the spine, while the IVC is anterior and to the right (7). Deviations from this arrangement raise the suspicion of HS (8). Identification of the subtype in the foetus relies mainly on the 184 position of the IVC and the aorta in the abdominal situs view (8, 9). Interruption of IVC is seen in the majority of cases with LAI, whereas a juxtaposition of the IVC and the aorta is present in the majority of cases with RAI (8, 10). The thoracic situs is usually concordant with the abdominal situs, but cases with discordance have been described (4). Additional observations may point to a particular subtype. For example, the presence of total anomalous pulmonary venous drainage (TAPVD) is more likely in RAI (11). In LAI, the intra-cardiac anatomy can be normal, but this is very rare in right isomerism. Recent studies have shown that the currently used foetal HS definition is not always congruent with post-natal findings (12–14). Yim et al. reported a discordance of broncho-pulmonary branching, atrial appendage arrangement, and splenic status in more than one-fifth of patients with HS (13). Houyel et al. found non-classic patterns in 27 (44%) out of 61 foetal specimens (14). Accurate foetal diagnosis of included anomalies is crucial for counselling families about post-natal inter-disciplinary management. Ascertainment of the cardiac defect is important, as the post-natal prognosis is largely determined by the cardiac course (15–17). However, associated non-cardiac anomalies, especially anomalies of the mid-line spectrum (18), also influence morbidity and mortality. This is supported by recently published data on foetal MRI in the same HS cohort (19). Children with HS often exhibit a complex peri-natal and long-term course with significant morbidity and mortality (8–11, 20–24). However, recent studies report better outcomes, due to improved post-natal care (1, 17, 24, 25).

This study aimed to: (1) assess post-natal concordance or discordance of the sub-type of HS (LAI vs. RAI), (2) describe the spectrum of associated cardiac, non-cardiac, and chromosomal anomalies, and (3) examine pre- and peri-natal mortality and morbidity, as well as long-term outcomes in a cohort of live-born children with pre-natal diagnosis of HS in a single tertiary referral centre.

MATERIALS AND METHODS

Study Population and Design

This is a retrospective cohort study of foetal and paediatric patients collected from the databases of the Department for Obstetrics and Gynaecology, Division of Paediatric Cardiology, and Department of Paediatric and Adolescent Medicine of the Medical University of Vienna. The ethical committee

of the Medical University of Vienna approved the study protocol (1306/2020). Fetuses diagnosed with HS and a cardiac malformation between January 1998 and December 2019 were included. The pre-natal diagnoses were made with a variety of imaging investigations such as detailed foetal echocardiography (FE), obstetric ultrasound (US), and foetal MRI according to the published guidelines (7, 26, 27). The foetal MRI results of 27 fetuses of the 46 fetuses have been already reported (19). Post-natal verification was feasible with autopsy reports, post-mortem MRI (pm MRI), US, echocardiography, and CT.

Clinical data on the foetal and post-natal course (including time of interventions/surgery) and outcome at last follow-up were obtained from patients' records, echocardiography reports, imaging reports, and autopsy reports. Fetuses diagnosed with HS whose subgroup could not be determined were excluded from the study. Type of HS was diagnosed with FE on the abdominal situs view: the presence of an interrupted IVC with azygos continuity was found to most likely suggest LAI and juxtaposition of the aorta and IVC in combination with a cardiac malformation and abnormal cardiac or abdominal organ situs most likely suggested RAI (8, 9, 11). Complete atrio-ventricular block (AVB) was defined as atrial rates faster than ventricular rates with dissociation between the two. Hydrops was diagnosed when abnormal fluid accumulations were present in more than two compartments of the foetal body. Foetal cardiac defects were defined based on the anatomy and haemodynamic circulation (uni-ventricular/bi-ventricular). In the year 2009, a new leadership team in paediatric cardiology and paediatric heart surgery started a new era of care at the paediatric heart centre in Vienna. Thus, two time periods regarding long-term outcomes were separately evaluated (1998–2009 vs. 2010–2021). Available CT scans of live-born children and available post-mortem MRI in terminated cases were evaluated regarding concordance or discordance of broncho-pulmonary branching and atrial appendage arrangement. The splenic status was assessed with the post-natal US. Broncho-pulmonary branching was defined as situs solitus, situs inversus, LAI, and RAI. LAI was defined as the pulmonary artery coursing backwards over the upper lobar bronchus (epbronchial pulmonary artery-hyparterial bronchus) (13, 28). RAI was defined as the descending branch of the pulmonary artery coursing backwards below the upper lobar bronchus (hypo-bronchial pulmonary artery-eparterial bronchus) (13, 28). Atrial appendage arrangement was defined as two morphological left appendages in LAI and two morphological right appendages in RAI using the pectinate muscles and shapes as landmarks (29, 30). The splenic status was described in post-natal US either by the morphology (regular, abnormal shaped) or by the number (polysplenia or asplenia) (13).

Statistical Analysis

Demographic, anatomic, procedural, and outcome data were included in the analysis. Qualitative variables are summarised as frequencies (percentage) and metric variables are summarised as medians (range), if not stated otherwise. The uni-variate Cox regression models (R-package survival 3.2-10) were applied with the survival time in years as a dependent variable. An estimate for the hazard ratio (HR) with 95% confidence limits and the p-value (H0:HR = 1) is reported. The Kaplan–Meier curves were plotted for LAI and RAI separately. Median survival (first quartile Q1; third quartile Q3) is reported, as well as the Kaplan–Meier estimates with 95% confidence limits at different time points, respectively. Statistical analysis was performed with R 4.0.5. A value of $P < 0.05$ was considered statistically significant. Due to the explorative character of the study, we did not adjust for multiple testing. The interpretation of the p-values is descriptive.

RESULTS

Prenatal Cohort

During the study period, 48 fetuses met the inclusion criteria of prenatally diagnosed HS. The flowchart of the study population is shown in **Figure 1**. Two fetuses were excluded from further analysis (classification of LAI or RAI could not be established). A total of 46 fetuses (29 LAI, 63%; 17 RAI, 37%) were included for in-depth evaluation. The clinical characteristics of the study population are shown in **Table 1**. Termination of pregnancy (TOP) only occurred from 2003 to 2018 in 7/29 (24%) fetuses with LAI and 5/17 (29%) fetuses with RAI. For ongoing pregnancies, no intrauterine death occurred in the cohort. In total, five fetuses were lost to follow-up during pregnancy with no available outcome data.

Cardiac Malformations

A detailed description of the summary of foetal and postnatal cardiac findings is shown in **Table 2**. Abnormal atrio-ventricular connection or significant hypoplasia of the left or right ventricle was present in 10 out of 29 (10/29, 34%) fetuses with LAI and in 13/17 (76%) fetuses with RAI and a complete atrio-ventricular septal defect (AVSD) was diagnosed in 9/29 (31%) fetuses with LAI and in 10/17 (59%) fetuses with RAI. Anomalies of the pulmonary venous drainage were present in 2/29 (7%) fetuses with LAI and 9/17 (53%) fetuses with RAI. Nine fetuses (9/46, 20%; all with LAI) had no intra-cardiac defect. 20/29 (69%) fetuses with LAI were expected to require open-heart surgery due to the complex cardiac defect in the first year of life. Foetal arrhythmia was only identified in the LAI group: 7/29 (24%) fetuses with LAI had a higher degree of AV block.

Extra-Cardiac Malformations

Extra-cardiac anomalies are given in **Table 3**. Anomalies of abdominal organ locations were present in all the cases. An example of a foetal MRI image is shown in **Figure 2**. There were 7/29 (24%) fetuses with LAI who had asplenia, 13/29 (45%) fetuses had polysplenia, and 5/29 (17%) fetuses had a regular spleen. Of the fetuses with RAI 12/17 (71%) had asplenia and 4/17 (24%) had a regular left-sided spleen There were no polysplenia cases in our fetuses with RAI. In 4/46 (9%) fetuses, it was not possible to determine the presence or absence of a spleen (3 LAI, 1 RAI). Extra-cardiac anomalies (apart from the situs and spleen) were present in 16/46 (35%) of the fetuses. Twenty fetuses (10/29, 34% LAI; 10/17, 59% RAI) had abnormal findings in the central nervous system

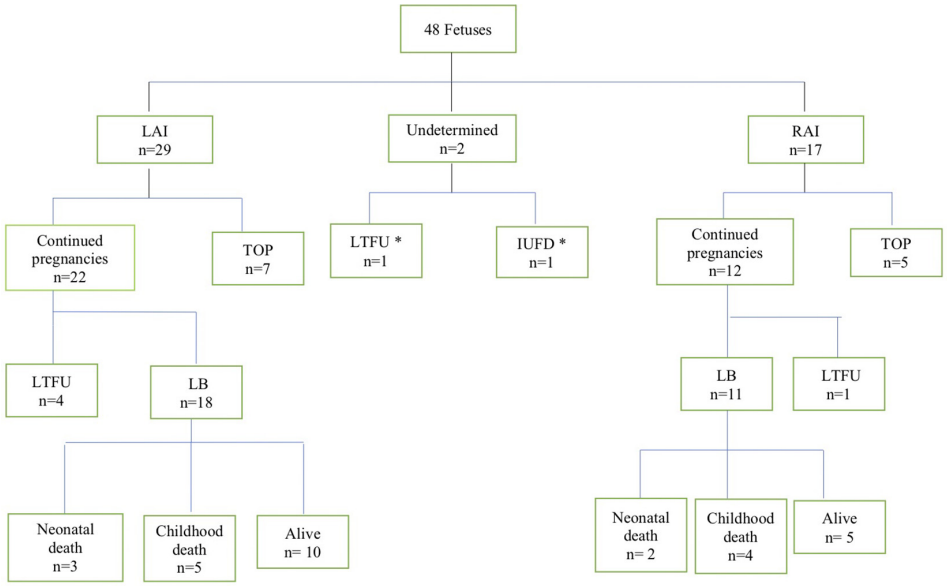

FIGURE 1 | Flowchart of patients with the pre-natal diagnosis of heterotaxy in this cohort. LAI, left atrial isomerism; RAI, right atrial isomerism; TOP, termination of pregnancy; LTFU, lost to follow up; IUFD, intrauterine fetal demise; LB, livebirth. *These two fetuses were excluded from further analysis.

TABLE 1 | Clinical characteristics of the study population.

No of patients included	**46**
Maternal age at diagnosis (mean)	30 (Range 17–42) years
Gestational age at diagnosis (mean)	23 (Range 12–36) weeks
Gender known	40/46
Male sex	23/40 (58%)
Left atrial isomerism (LAI)	29/46 (63%)
Right atrial isomerism (RAI)	17 (38%)
Genetic assessment	**31/46 (67%)**
Karyotype	27 (58%)
Karyotype including microarray	1
Non-invasive prenatal testing (Trisomies 21, 18, 13)	1
Next generation sequencing	1
Postnatal chromosomal investigation	1

and cranio-facial anomalies. Gastro-intestinal anomalies were present in 21/46 (46%) fetuses (17/29, 59% LAI; 4/17, 24% RAI). Malrotation of the intestines was noted in 9/29 (31%) LAI cases and 3/17 (18%) RAI cases. Anomalies of the urinary tract were seen in 10/46 (22%) cases. Verification of pre-natal non-cardiac findings (imaging or autopsy) was possible in 39/46 (85%) fetuses. Pre-natal imaging findings were confirmed in 29/39 (74%) and post-natal imaging revealed additional non-cardiac malformations not previously detected on pre-natal US or MRI in 10/39 (26%) cases.

Genetic Evaluation

Genetic testing was performed in 67% (31/46) of the fetuses and the majority had a normal karyotype. One foetus was diagnosed with Bardet–Biedl syndrome, one foetus was diagnosed with micro-deletion 22q11, and one child tested positive for asphyxiating thoracic dysplasia 3 (ATD3) or Jeune syndrome post-natally.

Post-natal Cohort

Overall, 18/29 (62%) fetuses with LAI and 11/17 (65%) fetuses with RAI were live born. The median birth weight was 3,290 g (range 1,950–5,300 g) in the LAI group and 3,178 g (range 2,464–3,567 g) in the RAI group. Median gestational age at delivery was 38 weeks in both the groups (range LAI 32–42 weeks, range RAI 35–40 weeks). A description of clinical data of foetal and neonatal deaths after prenatal diagnosis is shown in **Supplementary Table 1**.

Follow-ups were available between 1 day and 18 years after birth. At 1 year of age, the overall survival [estimate (95% CI)] was 67% (48; 92%) in patients with LAI and 55% (32; 94%) in patients with RAI. At 5 years of age, the estimates were 67% (48; 92%) in the LAI group and 46% (24; 87%) in the RAI group. Median survival (Q1; Q3) was 11.1 (0.1; 14) years for patients with LAI and 1.3 (0.09; NA) years for patients with RAI. The survival rate of live births with LAI (95% CI) was 67% (0.48; 0.92) at 10 years and 22% (0.04; 1) at 15 years. The survival rate of live births with RAI (95% CI) was 46% (0.24; 0.87) at 10 years and 46% (0.24; 0.87) at 15 years.

Figure 3 shows the Kaplan–Meier survival curve for 29 live-born children with HS. There was no significant difference in the survival rate between the LAI and RAI groups [HR (95% CI): 0.84 (0.29; 2.44), $p = 0.75$]. In addition, there was no difference in the era-specific outcome [HR (95% CI): 1.01 (0.31; 3.37), $p = 0.98$]. Gestational week (GW) at delivery was the only variable with a statistically significant effect on survival [HR (95% CI): 0.62 (0.47; 0.82), $p = 0.0009$]. Detailed information on mid-long-term survivors is given in **Supplementary Table 2**.

TABLE 2 | Distribution of cardiovascular malformations among fetuses with left atrial isomerism (LAI) and right atrial isomerism (RAI).

	LAI (*n* = 29)	RAI (*n* = 17)
Systemic venous anomalies		
Interrupted inferior vena cava	18 (62)	1 (6)
Bilateral superior vena cava	9 (31)	5 (29)
Single left superior vena cava	0	1 (6)
Pulmonary venous anomalies		
Total anomalous pulmonary venous connection	2 (7)	9 (53)
Partial anomalous pulmonary venous connection	5 (18)	3 (18)
Septation defects		
Isolated ventricular septal defect	1 (4)	1 (6)
Common atrium	1 (4)	4 (23)
Complete atrio-ventricular septal defect	9 (31)	10 (59)
Anomalies of the ventricles		
Hypoplastic left ventricle/single right ventricle	3 (11)	3 (18)
Hypoplastic right ventricle/single left ventricle	3 (11)	4 (23)
Single ventricle morphology	4 (14)	6 (35)
Ventriculo-arterial connection anomalies		
Transposition/malposition of the great arteries	6 (21)	9 (53)
Double-outlet right ventricle	5 (18)	6 (35)
Double-outlet left ventricle	2 (7)	0
Truncus arteriosus communis	0	1 (6)
Outflow tract obstructions		
Pulmonary stenosis/atresia	8 (28)	14 (82)
Aortic stenosis/atresia	4 (14)	3 (18)
Coarctation of the aorta	8 (28)	1 (6)

Data are given as number (percent). Some fetuses had more than one cardiac anomaly.

Discordant Anatomical Patterns Compared to Initial Pre-natal Diagnosis

Investigation of discordant or concordant post-natal patterns after a foetal diagnosis of HS was possible in 11/29 (38%) live-born children. 10/29 (34%) live-born children had a thoracic CT scan post-natally (**Figure 4**). One foetus had a post-mortem MRI (**Figure 5**).

Broncho-pulmonary branching: 6/10 (60%) children showed concordant patterns regarding the bronchial tree anatomy and the sub-type of isomerism diagnosed pre-natally and 4/10 (40%) children showed discordant patterns. Three children had post-natally confirmed situs inversus thoracalis, two of which were initially diagnosed with right isomerism and one of which was diagnosed with left isomerism based on the foetal situs view. One child was diagnosed with LAI, but had bronchial anatomy that is typical for RAI. The post-mortem MRI of the foetus showed a concordant pattern of broncho-pulmonary branching with the initial foetal definition of LAI.

Atrial appendage arrangement: 5/10 (50%) children showed a concordant pattern regarding the atrial appendage arrangement and the sub-type of isomerism diagnosed prenatally and 4/10 (40%) children showed discordant patterns. It was not possible to determine the atria on the post-mortem MRI.

Splenic status: In our LAI cohort, there were seven cases with asplenia, 13 cases with polysplenia, and six cases with a regular spleen. In three fetuses, a determination was not feasible. In the RAI cohort, there were 13 cases with asplenia, none with polysplenia, four with regular spleen locations, and one was not determinable.

TABLE 3 | Non-cardiac abnormalities among 46 fetuses with left atrial isomerism (LAI) (*n* = 29) and right atrial isomerism (RAI) (*n* = 17) from pre- and post-natal imaging studies and autopsy reports.

	Total number (%)	LAI number (%)	RAI number (%)
Situs anomalies			
Situs anomaly/ambiguus	37 (80)	25 (86)	12 (71)
Situs inversus	8 (17)	4 (14)	4 (24)
Partial situs inversus	1 (2)	0	1 (6)
Spleen			
Asplenia	17 (37)	7 (24)	12 (71)
Polysplenia	13 (28)	13 (45)	0
Regular spleen (right or left)	9 (19)	5 (17)	4 (24)
Small spleen	1 (2)	1 (3)	0
Central nervous system, face			
Craniofacial dysmorphism	6 (13)	5 (17)	1 (6)
Cleft (lip) palate	3 (6)	2 (7)	1 (6)
Ventriculomegaly	2 (4)	1 (3)	1 (6)
Ventricular asymmetry	2 (4)	1 (3)	1 (6)
Hydrocephalus	2 (4)	0	2 (12)
Cerebellar hypoplasia	1 (2)	0	1 (6)
Stenosis of the aqueduct	1 (2)	0	1 (6)
Delayed myelinisation	1 (2)	0	1 (6)
Dandy walker malformation	1 (2)	1 (3)	0
Rhombencephalosynapsis	1 (2)	0	1 (6)
Gastrointestinal tract			
Malrotation of the gut	12 (26)	9 (31)	3 (18)
Gallbladder aplasia	3 (6)	3 (10)	0
Duodenal atresia	2 (4)	1 (3)	1 (6)
Anal atresia	1 (2)	1 (3)	0
Omphalocele	1 (2)	1 (3)	0
Volvulus	1 (2)	1 (3)	0
Biliary atresia	1 (2)	1 (3)	0
Urinary tract			
Hydronephrosis	3 (6)	1 (3)	2 (11)
Duplex kidney	2 (4)	1 (3)	1 (6)
Urethral obstruction	1 (2)	1 (3)	0
Unilateral kidney agenesis	1 (2)	1 (3)	0
Bilateral kidney agenesis	1 (2)	1 (3)	0
Hypertrophy adrenal glands	1 (2)	0	1 (6)
Polycystic kidneys	1 (2)	1 (3)	0
Skeletal anomalies/others			
Scoliosis/skeletal abnormalities	3 (6)	2 (7)	1 (6)
Polydactyly/syndactyly	3 (6)	3 (10)	0
Uterine agenesis/aplasia	2 (1)	1 (3)	1 (6)

Clinical Outcomes in Left Atrial Isomerism

Of the 18 live-born children, three neonatal deaths occurred due to inoperable complex congenital heart disease, hydrops, and/or major extra-cardiac anomalies. Seven children (7/18, 39%)

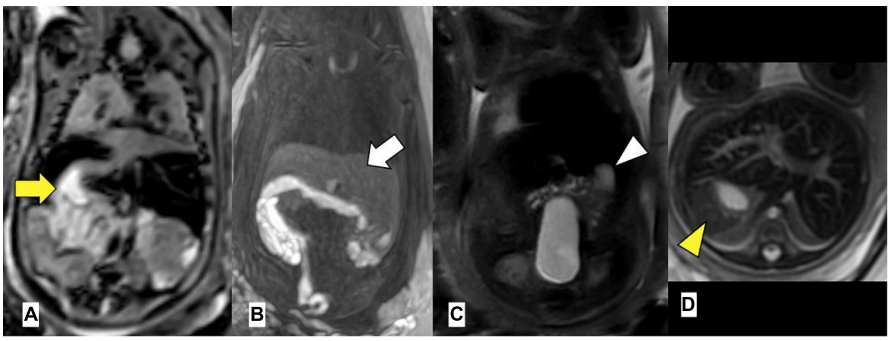

FIGURE 2 | Left atrial isomerism by foetal MRI. **(A)** Arrow yellow: right-sided stomach **(B)** arrow white: bilateral liver, **(C)** arrowhead white: left-sided gallbladder, **(D)** arrowhead yellow: left-sided spleen. Gestational age at MRI is 20 weeks + 0 day.

did not require cardiac surgery and are alive and well. Eight (8/18, 44%) children underwent cardiac surgery: primary bi-ventricular repair in 2/8 (25%), initial uni-ventricular palliation with conversion to bi-ventricular circulation in 2/8 (25%), and primary uni-ventricular palliation in 4/8 (50%). There were no survivors in the uni-ventricular palliation group. Reasons for death were extra-cardiac complications ($n = 3$) and septic multi-organ failure ($n = 1$) after a Glenn/Kawashima procedure with the incorporation of the hepatic veins. The bi-ventricular conversion was successful in two children with a late death at 14 years of age in one child. Three (17%) children who had surgery due to extra-cardiac anomalies underwent a Kasai procedure and liver transplantation ($n = 1$), duodenal resection ($n = 1$), or surgery for polydactyly ($n = 1$).

Clinical Outcomes in Right Atrial Isomerism

Of the 11 live-born children with RAI, comfort care was planned for two children due to inoperable heart disease and extra-cardiac anomalies. Nine children (9/11, 82%) had cardiac surgery. Nine children were initially planned for uni-ventricular repair: Blalock–Taussig (BT) shunt ($n = 9$), Glenn procedure, and subsequent total cavopulmonary connection (TCPC) palliation ($n = 5$). All the children with Fontan completion were alive and well at the time of data collection. Initial uni-ventricular repair with later conversion to bi-ventricular repair was planned in one child with AVSD, a double outlet right ventricle, transposition of the great arteries, pulmonary stenosis, and TAPVD. This child died in the post-operative period after conversion surgery at 7 months. Surgical intervention for extra-cardiac anomalies was performed in one child with duodenal atresia.

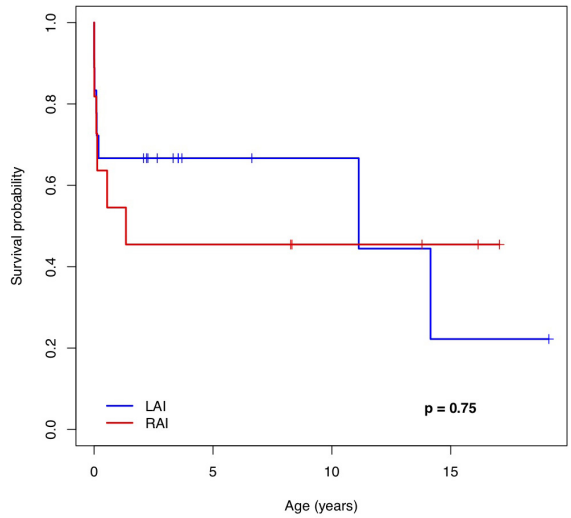

FIGURE 3 | The Kaplan–Meier survival curve of patients with a pre-natal diagnosis of left and right atrial isomerism. LAI, left atrial isomerism; RAI, right atrial isomerism.

DISCUSSION

Heterotaxy syndrome is defined as an abnormal arrangement of thoracic and abdominal organs often associated with a cardiac defect and major extra-cardiac malformations. In most cases, a multi-disciplinary approach is mandatory to provide good clinical care. The patients discussed in this article emphasise the complexity of managing patients with HS. The present cohort was evaluated with different types of imaging modalities, FE, obstetric US, foetal MRI, and post-natal echocardiography, US and CT scans. In addition, autopsy reports and pm MRI data were available. We have already published our summary on systematic phenotypic characterisation of fetuses with HS using the maximally available prenatal imaging methods (foetal MRI and US). In doing so, we were able to identify a series of extra-cardiac abnormalities, which can help to further specify the sub-type of HS (19). As this entity is rare, peri-natal and post-natal follow-up reports are particularly helpful for clinicians to provide accurate foetal counselling. Our study cohort was evaluated over a period of almost 21 years, which helped us understand the complexity of this entity even more. Even though this study is limited by the retrospective data collection and the small sample size in the outcome group, the present data is valuable for the current discussion on the nomenclature. In the following discussion, a step-wise approach is outlined

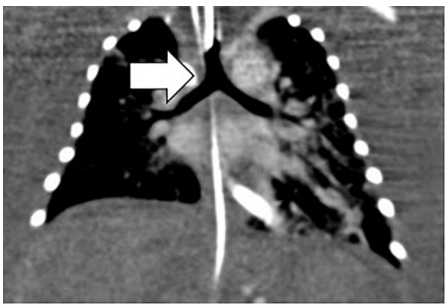

FIGURE 4 | Bronchial tree anatomy and the sub-type of isomerism by neonatal thoracic CT. Arrow white, left isomerism of tracheal bifurcation with bi-lobar lungs.

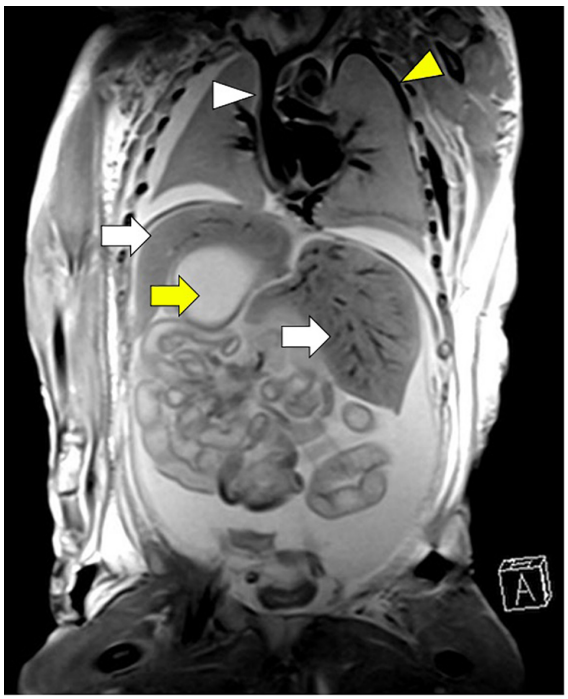

FIGURE 5 | Concordant pattern of broncho-pulmonary branching confirmed by post-mortem MRI in the left atrial isomerism cohort. Arrows: white, bilateral liver; yellow, right-sided stomach. Arrowheads: white, right atrium with insertion of vena cava superior, but without vena cava inferior, yellow, vena azygos supplying blood of the lower body half. Gestational age at MRI is 23 weeks + 4 days.

to provide information for prenatal counselling based on our findings and the current literature. Post-natal nomenclature, definition, and classification (4) remain an area of debate due to the complex nature of this diagnosis (12–14, 31, 32). It has not only been questioned if the terms isomerism and HS can be used as synonyms (3, 12–14, 32, 33), but also if it is appropriate to make a sub-type definition based on the currently used criteria (3, 13), as they might not always be consistent (13). The foetal definition of the sub-types is mainly based on the location of the aorta and IVC in the abdominal situs view and has been used relatively accurately (13, 34). Houyel et al. found different patterns (atrial pectinated muscles and status of the spleen) that were not always concordant with classical LAI and RAI in 44% of fetuses. However, the bronchial status was always concordant (14). In our cohort, 40% displayed a discordant pattern, including broncho-pulmonary branching and atrial appendage anatomy, which are in accordance with the scarce published literature on this particular topic (13, 14). To the best of our knowledge, this is the first study to investigate concordant and discordant patterns in live-born children after a foetal diagnosis of HS. The interpretation of our findings may certainly be biased and, therefore, limited by the fact that only 11 post-natal imaging studies were retrospectively available (10 CT scans, 1 pm MRI), as these were the only children for whom further imaging was necessary for surgical planning.

Nevertheless, we strongly agree with Yim et al. (13) and Houyel et al. (14) that the terms "isomerism" and "heterotaxy" cannot be used synonymously and that each anatomic feature should be described individually rather than categorically.

In utero diagnosis of HS is feasible, especially in 733 tertiary care centres (13, 20, 34–36). The rate of TOP (12/46, 26%) in our cohort is comparable to previously reported in a study by Akalin et al. (10), slightly higher than in a study by Escobar-Diaz et al. (20), but lower than the data reported in a study by Vigneswaran et al. (8). Several factors such as gestational age at diagnosis, presence of cardiac and extra-cardiac anomalies, and specific state law regulations might be responsible for the different TOP rates. There were no natural foetal deaths. In LAI, rhythm disturbances with a higher degree of AV block were present in 25%, resulting in a higher proportion of TOP or timely post-natal demise.

With respect to the foetal diagnosis of HS, suspicion commonly arises while examining the foetal heart. The cardiac findings are in accordance with previously published results (8–10, 37). RAI is generally associated with more complex congenital heart diseases with a poorer prognosis (22, 38).

Total anomalous pulmonary venous drainage (TAPVD) was more frequent in RAI than in LAI (53 vs. 7%), as were more complex anomalies with right outflow tract obstruction such as pulmonary stenosis or atresia (82%). Co-arctation was mainly seen in LAI (28%). Importantly, 20% of fetuses with LAI did not have any cardiac defect apart from interruption of the IVC and azygos continuity. In comparison, Gilljam et al. reported 13% (37) and Vigneswaran et al. (8) reported 9% in their cohort. An explanation might be that these fetuses presented with extra-cardiac anomalies and in turn, a detailed foetal echocardiogram was initiated. In conclusion, we would like to stress that a detailed foetal echocardiogram with situs evaluation should be included in the work-up for extra-cardiac anomalies in all the fetuses. Even if the intra-cardiac anomaly is normal, rhythm disorders can occur in this cohort and follow-up is warranted. Due to the presence of two anatomically left atria, the sinus node is missing in fetuses with LAI, thus resulting in rhythm disorders already present *in utero*. Foetal bradycardia was present in 24%

and four cases (4/7) developed hydrops, which is comparable to the 24% with bradycardia or AVB reported in a study by Escobar-Diaz et al. with a survival rate of 63% (39). 10% of our cohort needed pacemaker implantation post-natally, which is a lower rate than reported in a study by Baban et al. (1). All of them had sinus rhythm in the foetal period and developed overt rhythm disorders either post-natally or post-surgically. Extra-cardiac anomalies (apart from the situs and spleen) were found in 16/46 (35%) fetuses, which was less frequent than the 62.5% reported in a study by Escobar-Diaz et al. (20), but higher than the 15.8% reported in a study by Gottschalk et al. (40). Escobar-Diaz et al. found a rather high rate of gut-malrotation post-natally, as they run a general screening program for this anomaly at their institution (20). In our study, malrotation of the gut was suspected in foetal MRI (19) or found in autopsy. Overall, 39 mid-line-associated defects were present in 35% of the fetuses, which is in line with the 38% reported in a study by Ticho et al. (18). While additional imaging with foetal MR helps significantly, there is a relatively high percentage of autopsy cases in our study. Non-cardiac malformations were present in 10/14 (71%) TOP. Additional anomalies in post-natal (post-mortem) evaluation (autopsy or post-natal MRI) were found in 18% of these TOP fetuses. This is a common finding in foetal imaging due to the limited resolution in small fetuses.

All the live-born children with asplenia or polysplenia received prophylactic antibiotic treatment according to the guidelines and none had severe recurrent infections requiring hospitalisation. This is in accordance with a study by McGovern et al. where the absence of a spleen was not associated with poor outcomes (41). In contrast, Chiu et al. reported a higher rate of community-acquired severe bacterial infections due to lower memory B cell and immunoglobulin M (IgM) memory B-cell percentages. They note higher mortality compared to other cardiac patients, regardless of the presence of a spleen (42). Chromosomal disorders, such as aneuploidies, complex chromosomal rearrangements, and micro-deletions, have been described in HS, albeit very rarely (43). Our retrospective evaluation spans over 21 years and genetic testing strategies have changed tremendously during this time. The majority only underwent karyotyping and the results are not representative of the whole possible spectrum of chromosomal/genetic abnormalities. Ciliary dysfunction is increasingly recognised in HS. Of the three (3/29, 10%) live-born children tested for cilia dysfunction, one turned out to be pathologic. Nakhleh et al. reported a rather high prevalence (42%) in their cohort (44). A general screening program for ciliopathies in children with HS has only been established in some institutions.

The outcome, which has mostly been reported in relatively small cohorts, is associated with significant morbidity and mortality after the newborn period, both for LAI and RAI (16, 21, 22, 41, 45, 46). Banka et al. reported an overall mortality of 40% with a median follow-up of 1.2 years, 24% of which died of non-cardiac causes. In 36% of 106 children, the reason for death was unknown (16). In the neonatal period, death in our cohort was due to comfort care (n = 5). In the first 2 years of life, death was mainly attributable to complex cardiac procedures with extra-cardiac complications (n = 7) and after 10 years, it was the result of multi-organ failure after highly complex cardiac surgery (n = 2). Mortality is an extremely important topic and nearly always a major concern for parents during foetal counselling. Generally, the prognosis is reported to be worse in RAI than in LAI (9, 20, 22, 38). Long-term survival at 15 years of age was 46% in the RAI group vs. 22% in the LAI group, which is comparable to data published in a study by Vigneswaran et al. (8) and very recently in a study by Akalin et al. (10), but with quite a different pattern. A higher rate of late deaths in the LAI group was seen in children who required complex cardiac procedures. Early deaths did not complicate Fontan palliation and the long-term outcome was favourable for these children. A recent meta-analysis of 848 cases found higher early mortality in patients with HS and completed Fontan palliation compared to the overall Fontan population. Long-term survival, on the contrary, was reported to be acceptable and predictable in this study (47), in accordance with data published in a study by Baban et al. and Azakie et al. who reported reduced mortality rates and better long-term survival rates in patients with HS after Fontan procedure (1, 45). Banka et al. examined the outcome of patients born with HS between 1984 and 2014 (16). Patients were divided into four eras and the long-term outcome was assessed. The outcome remained poor with an overall mortality rate of 40% and did not improve over time. As expected, the greatest risk factors predicting poor outcomes were uni-ventricular circulation and TAPVD. Extra-cardiac morbidity was not reported (16). Therapeutic concepts for the complex cardiac disease have clearly evolved over time, but era-specific outcomes concerning survival in our cohort did not differ from each other. This might in part be due to the small sample size of each cohort.

Predictors for survival were difficult to assess. The sample size is small, which limited the power of the statistical analysis. However, again as expected, gestational weight at delivery turned out to be a statistically significant factor.

Limitations

This study has several limitations. It presents retrospective data from one tertiary centre comprising only 46 fetuses and 29 live-born children. Substantial data (e.g., for proper classification) are missing, as we included fetuses retrospectively rather than prospectively, making it difficult to follow a uniform protocol. This was especially true for our comparison of the discordant post-natal patterns with the pre-natal diagnosis, where the necessary additional imaging was only available in 11 children. Only fetuses with situs anomalies and cardiac defects pre-natally diagnosed as HS could be included. Therefore, cases with missed cardiac defects or fetuses with cardiac defects and not-detected bronchial isomerism were not enrolled. During the 21-year study period, pre-natal imaging, neonatal management, surgical procedures, and interventional cardiology significantly evolved, which may have influenced the outcome and weakened comparison. In addition, the neurological outcome, psychological development, and psychosocial status of

these children were not sufficiently available, even though these factors are now uniformly assessed in most paediatric cardiology centres. The data have been becoming increasingly available, providing important information for improving the quality of prenatal counselling.

CONCLUSION

HS is a rare and complex condition with significant morbidity and mortality related to severe cardiac and extra-cardiac manifestations. Accurate pre-natal diagnosis can help identify the fetuses at risk and ensure timely intervention in a multi-disciplinary setting. Further studies are warranted to shed light on the exact sub-type definition in fetuses with HS and the presence of discordant post-natal patterns. The sequential segmental approach of this multi-disciplinary disease is important.

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

The studies involving human participants were reviewed and approved by Ethical Committee of the Medical University of Vienna, Austria. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ES-M, IM-B, and BU designed the study. VJ, AW, GK, EK, BU, MS, and DZ contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. ES-M and IM-B wrote the manuscript with input from all authors. IS performed the statistical analysis. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.908505/full#supplementary-material

REFERENCES

1. Baban A, Cantarutti N, Adorisio R, Lombardi R, Calcagni G, Mortari EP, et al. Long-term survival and phenotypic spectrum in heterotaxy syndrome: a 25- year follow up experience. *Int J Cardiol.* (2018) 268:100–5. doi: 10.1016/j.ijcard.2018.02.050
2. Loomba R, Shah PH, Anderson RH. Fetal magnetic resonance imaging of malformations associated with heterotaxy. *Cureus.* (2015) 7:e269. doi: 10.7759/cureus.269
3. Sanders SP, Geva T. Classifying heterotaxy syndrome: time for a new approach. *Circ Cardiovasc Imaging.* (2018) 11:e007490. doi: 10.1161/CIRCIMAGING.118.007490
4. Jacobs JP, Anderson RH, Weinberg PM, Walters HL, Tchervenkov CI, Del Duca D, et al. The nomenclature, definition and classification of cardiac structures in the setting of heterotaxy. *Cardiol Young.* (2007) 17(Suppl. 2):1–28. doi: 10.1017/S1047951107001138
5. Phoon CK, Neill CA. Asplenia syndrome: insight into embryology through an analysis of cardiac and extracardiac anomalies. *Am J Cardiol.* (1994) 73:581–7. doi: 10.1016/0002-9149(94)90338-7
6. Anderson RH. Heterotaxy and isomerism of the atrial appendages. *Eur J Cardio Thorac Surg.* (2001) 40:532–4. doi: 10.1016/j.ejcts.2010.12.049
7. Carvalho JS, Allan LD, Chaoui R, Copel JA, DeVore GR, Hecher K, et al. ISUOG practice guidelines (updated): sonographic screening examination of the fetal heart. *Ultrasound Obstet Gynecol.* (2013) 41:348–59. doi: 10.1002/uog.12403
8. Vigneswaran TV, Jones CB, Zidere V, Charakida M, Miller OI, Simpson JM, et al. Effect of prenatal laterality disturbance and its accompanying anomalies on survival. *Am J Cardiol.* (2018) 122:663–71. doi: 10.1016/j.amjcard.2018.04.040
9. Lim JS, McCrindle BW, Smallhorn JF, Golding F, Caldarone CA, Taketazu M, et al. Clinical features, management, and outcome of children with fetal and postnatal diagnosis of isomerism syndromes. *Circulation.* (2005) 112:2454–61. doi: 10.1161/CIRCULATIONAHA.105.552364
10. Akalin M, Demirci O, Kumru P, Yücel IK. Heterotaxy syndrome: prenatal diagnosis, concomitant malformations and outcome. *Prenat Diagn.* (2022) 42:435–46. doi: 10.1002/pd.6110
11. Cohen MS. Clarifying anatomical complexity: diagnosing heterotaxy syndrome in the fetus. *Prog Pediatr Cardiol.* (2006) 22:61–70. doi: 10-1016/j.ppedcard.2006.01.006
12. Anderson RH, Spicer DE, Loomba R. Is an appreciation of isomerism the key to unlocking the mysteries of the cardiac findings in heterotaxy? *J Cardiovasc Dev Dis.* (2018) 5:11. doi: 10.3390/jcdd5010011
13. Yim D, Nagata H, Lam CZ, Grosse-Wortmann L, Seed M, Jaeggi E, et al. Disharmonious patterns of heterotaxy and isomerism: how often are the classic patterns breached? *Circ Cardiovasc Imaging.* (2018) 11:e006917. doi: 10.1161/CIRCIMAGING.117.006917
14. Houyel L, Bessieres B, Gonzales M, Grigorescu R, Talhi N, Lambert M, et al. Fetal heterotaxy: should we still categorize? *Arch Cardiovasc Dis Suppl.* (2021) 13:306. doi: 10.1016/j.acvdsp.2021.06.062
15. Loomba RS, Nijhawan K, Anderson R. Impact of era, type of isomerism, and ventricular morphology on survival in heterotaxy: implications for therapeutic management. *World J Pediatr Congenit Heart Surg.* (2016) 7:54–62. doi: 10.1177/2150135115601831
16. Banka P, Adar A, Schaetzle B, Sleeper LA, Emini S, Geva T. Changes in prognosis of heterotaxy syndrome over time. *Pediatrics.* (2020) 146:e20193345. doi: 10.1542/peds.2019-3345
17. Morales DL, Braud BE, Booth JH, Graves DE, Heinle JS, McKenzie. Heterotaxy patients with total anomalous pulmonary venous return: improving surgical results. *Ann Thorac Surg.* (2006) 82:1621–8. doi: 10.1016/j.athoracsur.2006.05.053
18. Ticho BS, Goldstein AM, Van Praagh R. Extracardiac anomalies in the heterotaxy syndromes with focus on anomalies of midline-associated structures. *Am J Cardiol.* (2000) 85:729–34. doi: 10.1016/s0002-9149(99)00849-8
19. Seidl-Mlczoch E, Kasprian G, Ba-Ssalamah A, Stuemplen M, Kitzmueller E, Muin DA, et al. Characterization of phenotypic spectrum of fetal heterotaxy syndrome by combining ultrasound and magnetix resonance imaging. *Ultrasound Obstet Gynecol.* (2021) 58:837–45. doi: 10.1002/uog.23705
20. Escobar-Diaz MC, Friedmann K, Salem Y, Marx GR, Kalish BT, Lafranchi T, et al. Perinatal and infant outcomes of prenatal diagnosis of heterotaxy syndrome (asplenia and polysplenia). *Am J Cardiol.* (2014) 114:612–7. doi: 10.1016/j.amjcard.2014.05.042

21. Eronen MP, Aittomäki KAU, Kajantie EO, Sairanen HI. Outcome of left atrial isomerism at a single instituation. *Pediatr Cardiol.* (2012) 33:596–600. doi: 10.1007/s00246-012-0184-0
22. Eronen MP, Aittomäki KAU, Kajantie EO, Sairanen HI, Pesonen EJ. The outcome of patients with right atrial isomerism is poor. *Pediatr Cardiol.* (2013) 34:302–7. doi: 10.1007/s00246-012-0445-y
23. Foerster SR, Gauvreau K, McElhinney DB, Geva T. Importance of totally anomalous pulmonary venous connection and postoperative pulmonary vein stenosis in outcomes of heterotaxy syndrome. *Pediatr Cardiol.* (2008) 29:536–44. doi: 10.1007/s00246-007-9128-5
24. Anagnostopoulos PV, Pearl JM, Octave C, Cohen M, Gruessner A, Wintering E, et al. Improved current era outcomes in patients with heterotaxy syndromes. *Eur J Cardiothorac Surg.* (2009) 35:871–7. doi: 10.1016/j.ejcts.2008.12.018
25. Chen W, Ma L, Cui H, Yang S, Xia Y, Zou M, et al. Early and middle term surgical outcomes in patients with heterotaxy syndrome. *Cardiology.* (2016) 133:141–6. doi: 10.1159/000440947
26. Salomon LJ, Alfirevic Z, Berghella V, Bilardo C, Hernandez-Andrade E, Johnsen SL, et al. Pracice guidelines for performance of the routine mid-trimester fetal ultrasound scan. *Ultrasound Obstet Gynecol.* (2011) 37:116–26. doi: 10.1002/uog.8831
27. Prayer D, Malinger G, Brugger PC, Cassady C, De Catte L, De Keersmaecker B, et al. ISUOG practice guidelines: performance of fetal magnetic resonance imaging. *Ultrasound Obstet Gynecol.* (2017) 49:671–80. doi: 10.1002/uog.17412
28. Loomba RS, Pelech AN, Shah PH, Anderson RH. Determining bronchial morphology for the purposes of segregating so-called heterotaxy. *Cardiol Young.* (2016) 26:725–37. doi: 10.1017/S1047951115001195
29. Uemura H, Ho SY, Devine WA, Kilpatrick LL, Anderson RH. Atrial appendages and venoatrial connections in hearts from patients with visceral heterotaxy. *Ann Thorac Surg.* (1995) 60:561–9. doi: 10.1016/0003-4975(95)00538-V
30. Anderson RH. Atrial structure in the presence of visceral heterotaxy. *Cardiol Young.* (2000) 10:299–849. doi: 10.1017/s1047951100009598
31. Jacobs JP, Pasquali SK, Morales DLS, Jacobs ML, Mavroudis C, Chai PJ, et al. Heterotaxy: lessons learned about patterns of practice and outcomes from the congenital heart surgery database of the society of thoracic surgeons. *World J Pediatr Congenit Heart Surg.* (2011) 2:278–86. doi: 10.1177/2150135110397670
32. Loomba RS, Hlavacek AM, Spicer DE, Anderson RH. Isomerism or heterotaxy: which term leads to better understanding? *Cardiol Young.* (2015) 25:1037–43. doi: 10.1017/S1047951115001122
33. Calder AL. Thoracic situs as an indicator of atrial appendage morphology: a postmortem study of 306 specimens with situs solitus in 250 and heterotaxy in 56 cases. *Pediatr Cardiol.* (2011) 32:875–84. doi: 10.1007/s00246-011-0003-z
34. Pepes S, Zidere V, Allan LD. Prenatal diagnosis of left atrial isomerism. *Heart.* (2009) 95:1974–7. doi: 10.1136/hrt.2009.165514
35. Berg C, Geipel A, Kohl T, Smrcek J, Germer U, Baschat AA, et al. Fetal echocardiographic evaluation of atrial morphology and the prediction of laterality in cases of heterotaxy syndromes. *Ultrasound Obstet Gynecol.* (2005) 26:538–45. doi: 10.1002/uog.1934
36. Taketazu M, Lougheed J, Yoo S-J, Lim JSL, Hornberger LK. Spectrum of cardiovascular disease, accuracy of diagnosis, and outcome in fetal heterotaxy syndrome. *Am J Cardiol.* (2006) 97:720–4. doi: 10.1016/j.amjcard.2005.09.119
37. Gilljam T, McCrindle BW, Smallhorn JF, Williams WG, Freedom RM. Outcomes of left atrial isomerism over a 28-year period at a single institution. *J Am Coll Cardiol.* (2000) 36:908–16. doi: 10.1016/s0735-1097(00)00812-3
38. Buca DIP, Khalil A, Rizzo G, Familiari A, Di Giovanni S, Liberati M, et al. Outcome of prenatally diagnosed fetal heterotaxy: systematic review and meta–analysis. *Ultrasound Obstet Gynecol.* (2018) 51:323–30. doi: 10.1002/uog.17546
39. Escobar-Diaz MC, Tworetzky W, Friedman K, Lafranchi T, Fynn-Thompson F, Alexander ME. Perinatal outcome in fetuses with heterotaxy syndrome and atrioventricular block or bradycardia. *Pediatr Cardiol.* (2014) 35:906–13. doi: 10.1007/s00246-014-0874-x
40. Gottschalk I, Stressig R, Ritgen J, Herberg U, Breuer J, Vorndamme A, et al. Extracardiac anomalies in prenatally diagnosed heterotaxy syndrome. *Ultrasound Obstet Gynecol.* (2016) 47:443–9. doi: 10.1002/uog.14871
41. McGovern E, Kelleher E, Potts JE, O'Brien JE, O'Brien J, Walsh K, et al. Predictors of poor outcome among children with heterotaxy syndrome: a retrospecitve review. *Open Heart.* (2016) 3:e000328. doi: 10.1136/openhrt-2015-000328
42. Chiu SN, Shao PL, Wang JK, Hsu HW, Lin MT, Chang LY, et al. Low immunoglobulin M memory B.cell percentag in patients with hterotaxy syndrome correlates with the risk of severe bacterial infection. *Pediatr Res.* (2016) 79:271–7. doi: 10.1038/pr.2015.221
43. Pierpont ME, Brueckner M, Chung WK, Garg V, Lacro RV, McGuire AL, et al. American Heart Association council on cardiovascular disease in the young; council on cardiovascular and stroke nursing; and council on genomic and precision medicine. genetic basis for congenital heart disease: revisited: a scientific statement from the American heart association. *Circulation.* (2018) 138:e653–711. doi: 10.1161/CIR.0000000000000606
44. Nakhleh N, Francis R, Giese RA, Tian X, Li Y, Zariwala MA, et al. High prevalence of respiratory ciliary dysfunction in congenital heart disease patients with heterotaxy. *Circulation.* (2012) 125:2232–42. doi: 10.1161/CIRCULATIONAHA.111.079780
45. Azakie T, Merklinger SL, McCrindle BW, Van Arsdell GS, Lee KJ, Benson LN, et al. Evolving strategies and improving outcomes of the modified Norwood procedure: a 10-year single-institution experience. *Ann Thorac Surg.* (2001) 72:1349–53. doi: 10.1016/s0003-4975(01)02795-3
46. Cohen MS, Anderson RH, Cohen MI, Atz AM, Fogel M, Gruber PJ, et al. Controversies, genetics, diagnostic assessment, and outcomes relating to the heterotaxy syndrome. *Cardiol Young.* (2007) 2:29–43. doi: 10.1017/S104795110700114X
47. Marathe SP, Cao JY, Celermajer D, Ayer J, Sholler GF, D' Udekem Y, et al. Outcomes of the fontan operation for patients with heterotaxy: a meta-analysis of 848 patients. *Ann Thorac Surg.* (2020) 110:307–15. doi: 10.1016/j.athoracsur.2019.11.02

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Microcephaly is associated with impaired educational development in children with congenital heart disease

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Objectives: This study aims to evaluate the school careers of patients with congenital heart disease (CHD) and microcephaly.

Methods: An exploratory online survey was conducted on patients from a previous study on somatic development in children with CHD in 2018 ($n = 2818$). A total of 750 patients participated in the online survey (26.6%). This publication focuses on 91 patients (12.1%) diagnosed with CHD and microcephaly who participated in the new online survey.

Results: Microcephaly was significantly associated with CHD severity ($p < 0.001$). Microcephalic patients suffered from psychiatric comorbidity two times as often (67.0%) as non-microcephalic patients (29.8%). In particular, the percentage of patients with developmental delay, intellectual debility, social disability, learning disorder, or language disorder was significantly increased in microcephalic CHD patients ($p < 0.001$). A total of 85.7% of microcephalic patients and 47.6% of non-microcephalic patients received early interventions to foster their development. The school enrollment of both groups was similar at approximately six years of age. However, 89.9% of non-microcephalic but only 51.6% of microcephalic patients were enrolled in a regular elementary school. Regarding secondary school, only half as many microcephalic patients (14.3%) went to grammar school, while the proportion of pupils at special schools was eight times higher. Supportive interventions, e.g., for specific learning disabilities, were used by 52.7% of microcephalic patients and 21.6% of non-microcephalic patients.

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Conclusion: Patients with CHD and microcephaly are at high risk for impaired educational development. Early identification should alert clinicians to provide targeted interventions to optimize the developmental potential.

KEYWORDS

microcephaly, congenital heart disease, education, school, supportive interventions, development

Introduction

Children with congenital heart disease (CHD) are at risk of impaired somatic growth, especially those with single ventricle physiology (1, 2). The cause of growth retardation is complex and multifactorial, with genetic and hemodynamic factors as essential determinants for the underlying CHD (3, 4).

Most studies analyzing somatic development focus on body weight and length but less often on the head circumference (2, 4, 5). However, head circumference is an important somatic parameter, as microcephaly may indicate impaired neurodevelopmental outcomes from early childhood until adolescence (6–9). Neurodevelopmental deficits may have a broad clinical manifestation and may also affect areas of memory and executive function, visual-spatial imagination, attention, and social skills (10) and therefore impair the child's school career.

To date, the association between microcephaly and education in children with CHD has not been analyzed. Hence, this study aimed to evaluate the scholastic development of CHD patients with microcephaly.

Patients and methods

Study design and setting

This is an exploratory cross-sectional follow-up study using an online survey to evaluate the school careers of patients with CHD. The ethics committee of the Charité—Universitätsmedizin Berlin, Germany, approved this study (no. EA2/190/19), which was conducted in 2020.

Study participants received an invitation to participate in the survey by email or postal letters, and if a response was missing, they were reminded once to participate. The survey could be completed by the patient, a parent, or a third party (legal guardian or caregiver). The corresponding addressee received a slightly different questionnaire. The survey consisted of a maximum of 74 questions, depending on the participant and the option of sequential questions. A total of 92% of the survey's questions were closed multiple-choice questions. Most questions offered the participant the option of adding their own answer if none of the possible answers adequately described their situation in a free-text box. The survey comprised questions about medical data such as further chronic diseases, psychiatric comorbidities (attention deficit disorder, developmental disability, intellectual debility, social disability, emotional disability, depression, anxiety disorder, learning disorder, and language disorder), genetic syndromes, and subjective health conditions. The focus was on questions about the school career: enrollment age, school form (primary and secondary), (early) supportive therapy (physiotherapy, speech therapy, occupational therapy, or psychotherapy), school year repetition, absenteeism from school, and participation in physical education. Furthermore, the educational achievement and qualifications of the parents were elicited. Medical data were supplemented by the database of the National Register for Congenital Heart Defects (NRCHD). The NRCHD is Germany's national repository for medical data on CHD patients. With ∼55,000 members, the NRCHD is Europe's largest register for CHD patients and can be regarded as a basis for representative studies (11).

Patient cohort

From 2006 to 2011, the Competence Network for Congenital Heart Defects (Berlin, Germany) conducted the "PAN-study" (Prävalenz angeborener Herzfehler bei Neugeborenen in Deutschland), which analyzed the prevalence of CHD prospectively in newborns in Germany (12). To determine the somatic development (height, length, and head circumference) of the PAN-cohort, the "PANKU-study" (Prävalenz angeborener Herzfehler bei Neugeborenen in Deutschland Kopfumfang) was carried out; a follow-up study analyzed somatic developmental data from the "Kinderuntersuchungsheft" ("child's medical records"), which records the examination results of the mandatory screening for children and adolescents (13). To assess the academic development of this particular cohort, we chose this cohort for the present study "PANKU-Education" (Prävalenz angeborener Herzfehler bei Neugeborenen in Deutschland: Kopfumfang—Education). Of the 2818 families that were contacted, 750 (26.6%) completed the survey.

Inclusion criteria

- Participation in the "PAN-study" and "PAN-KU-study"
- Availability of complete and up-to-date contact information at the time of the present study
- Complete answering the online-survey

Microcephaly

To analyze the prevalence of microcephaly in the presented study, head circumference data at the child's three-month checkup (corresponding to U4 screening between the 3rd and 4th month of life in the German health care system) were used. These data were converted into sex- and age-adjusted percentiles, taking into account the date of measurement, date of birth, sex, and gestational age at birth. The percentiles, according to Braegger et al., commonly used in Germany, served as the basis for the calculation (14). Microcephaly was defined as a head circumference $<3^{rd}$ percentile.

The german school system

In Germany, school attendance is compulsory until the age of 15 years and is free. Usually, children start elementary school at the age of 5–7 years, mainly, however, at the age of 6 years. If a child has special needs in their educational, developmental, and learning possibilities (e.g., due to a learning or mental/cognitive disability, a sensory and/or physical disability, or less frequently due to a long-term illness), they are introduced to a special school. After finishing primary education (4–6 years, depending on the federal state), there are several options for secondary schooling according to the student's abilities: the highest is the grammar school ("Gymnasium"), where pupils graduate after 8–9 years with a high school diploma, enabling them to study at university. Graduation from secondary school options (usually after 5–7 years) allows for starting an apprenticeship.

Statistical analyses

The cardiac diagnoses were arranged in accordance with the classification of the International Pediatric and Congenital Cardiac Code (IPCCC) (15). Following Warnes et al., the CHD diagnoses were assigned to four groups: simple CHD, moderate CHD, complex CHD, and other/non-classified CHD (16).

For the various research questions, different subgroups were defined. The influence of parental education level was analyzed using descriptive analysis due to limited data.

For this, the parental education level was classified as "high," "medium," and "low" according to the International Standard Classification of Education (ISCED) (17). Group differences were analyzed using the chi-square test for nominal variables of independent subsamples. The Mann-Whitney U test was used for ordinal scaled variables, and interval scaled variables were analyzed using the *t*-test. A *p*-value of <0.05 was considered statistically significant. SPSS (Statistics for Mac, Version 27.0, IBM Crop. Armonk, NY) was used for statistical analysis.

TABLE 1 Characteristics of all patients from our cohort.

	N		Mean Median	SD IQR
Total participants	750	100%		
Mean age			12.16	0.847
Sex				
Female	378	50.4%		
Male	372	49.6%		
Health status				
Subjective health status (1 very good- 6 bad)			*1*	*1*
Epilepsy	13	1.7%		
Optic support	262	34.9%		
Hearing support	22	2.9%		
Walking aid	11	1.5%		
Psychiatric comorbidity	259	34.5%		
Gestational age				
Preterm	115	15.8%		
Term	610	83.8%		
Post-term	3	0.4%		
Syndromic disorders	64	8.3%		
Alagille syndrome	1	1.6%		
DiGeorge syndrome	5	7.8%		
Goldenhar syndrome	2	3.1%		
Trisomy 18	1	1.6%		
Trisomy 21	38	59.4%		
Noonan syndrome	3	4.7%		
Williams syndrome	3	4.7%		
Others	11	17.2%		

Results

Description of the overall cohort

A total of 750/2818 study participants (26.6%) answered all survey questions and were included in the statistical analyses. The mean age of the overall study cohort was 12.16 years (confidence interval: 12.10–12.22), and 50.4% were females (Table 1). Subjective health status was excellent, but psychiatric comorbidity was reported in 34.5%. Most patients had simple CHD (51.3%), with ventricular septal defect (40.7%) and atrial septal defect (11.9%) being the most frequent ones (Table 2).

At the age of 3–4 months, the mean head circumference of CHD patients from our cohort (percentile 44.1 ± 33.3) equaled the age-dependent percentile; Figure 1 illustrates the head circumference percentiles. The mean percentile in female patients was 46.9 ± 33.3 and in male patients 41.2 ± 33.1. Patients with simple CHD had a head circumference approximating the 51.3 ± 33.8 percentile, moderate CHD 40.6 ± 33.1, and complex CHD 29.5 ± 33.2.

TABLE 2 CHD diagnoses of the patients in our cohort.

	N	
Ventricular septal defect	305	40.7%
Atrial septal defect	89	11.9%
Tetralogy of Fallot	48	6.4%
Univentricular heart	46	6.1%
Aortic valve disease	36	4.8%
Coarctation of the aorta	35	4.7%
Transposition of the great arteries (intact ventricular septum)	32	4.3%
Atrioventricular septal defect	29	3.9%
Pulmonary valve stenosis	28	3.7%
Patent ductus arteriosus	20	2.7%
Other	82	10.9%

Characterization of microcephalic CHD patients

In total, 91 out of 750 patients (12.1%) had a head circumference below the 3rd percentile and thus were classified as microcephalic (Tables 3, 4). This subgroup had a mean age of 12.2 ± 0.85 years; 48.4% were female, and 51.6% were male. Their subjective health was not as good as the non-microcephalic patients' but still very good (51.6% of microcephalic vs. 66.3% of non-microcephalic patients rated their health status as very good) (Table 3). The prevalence of epilepsy and the need for optic support, hearing support, or walking aid was higher among microcephalic patients. In contrast, gestational age was not significantly associated with microcephaly.

Syndromal diseases existed in 30.8% of the microcephalic patients (Table 3). Ventricular septal defect (31.9%), atrioventricular septal defect (13.2%), and univentricular heart (12.1%) were the most frequent CHDs in this subset (Table 4). Microcephaly was significantly associated with CHD severity (Figure 2). Simple CHD was seen in 55.9% of normocephalic patients, while moderate CHD was seen in 27.5% and complex CHD in 16.6%. In contrast, simple, moderate, and complex CHD was found in equal parts (31.1, 33.3, and 35.6%) in microcephalic patients.

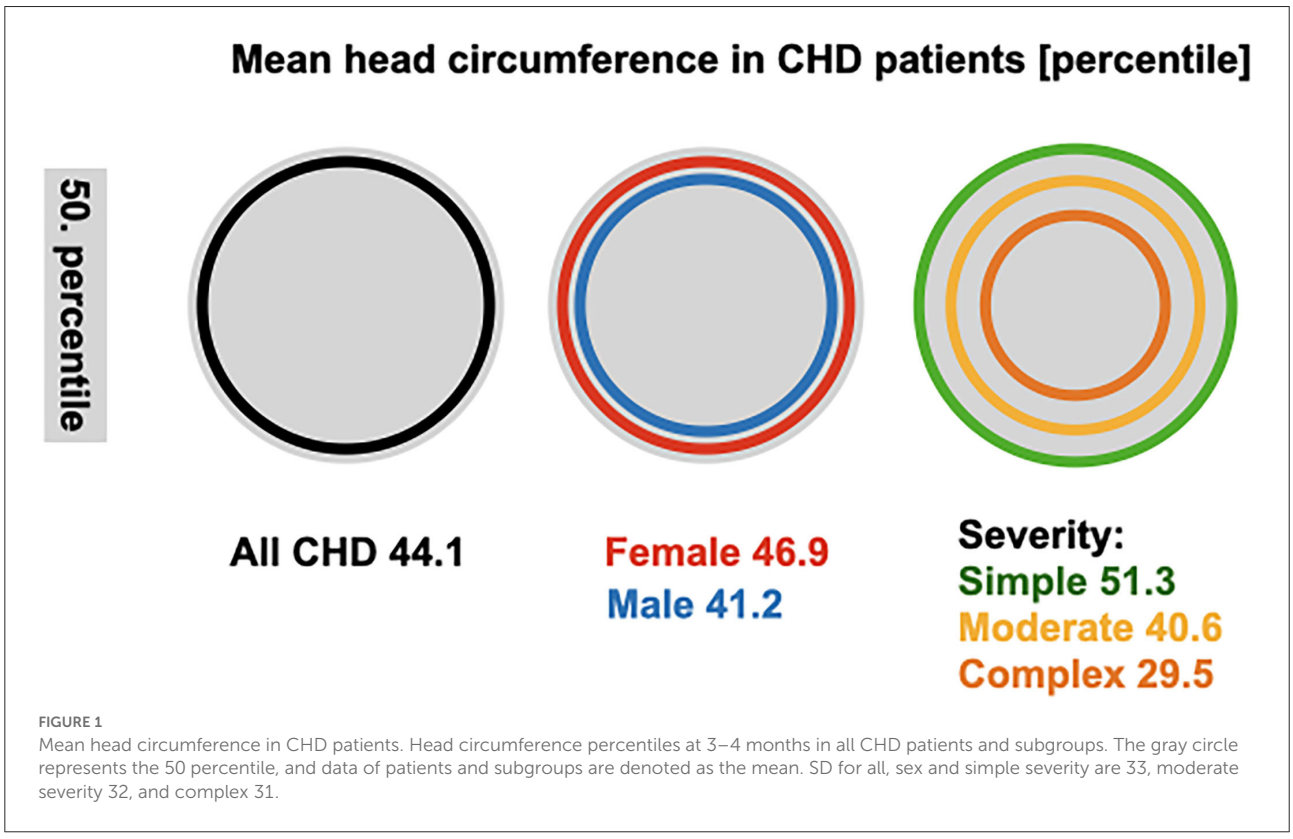

FIGURE 1
Mean head circumference in CHD patients. Head circumference percentiles at 3–4 months in all CHD patients and subgroups. The gray circle represents the 50 percentile, and data of patients and subgroups are denoted as the mean. SD for all, sex and simple severity are 33, moderate severity 32, and complex 31.

TABLE 3 Characteristics of microcephalic and non- microcephalic patients.

	Non-microcephalic patients				Microcephalic patients				*p*
	N		**Mean Median**	**SD IQR**	***N***		**Mean Median**	**SD IQR**	
Total participants	621	100%			91	100%			
Mean age			12.14	841			12.2	0.885	n.s.
Sex									
Female	317	51.0%			44	48.4%			n.s.
Male	304	49.0%			47	51.6%			n.s.
Health status									
Subjective health status (1 very good- 6 bad)			*1*	*1*			*1*	*1*	+
Epilepsy	6	1.0%			7	7.7%			*
Optic support	199	32.0%			44	48.4%			+
Hearing support	8	1.3%			11	12.1%			*
Walking aid	4	0.6%			7	7.7%			*
Psychiatric comorbidity	185	29.8%			61	67.0%			*
Gestational age									
Preterm	94	15.1%			16	17.6%			n.s.
Term	524	84.4%			75	82.4%			n.s.
Post-term	3	0.5%			0	0%			n.s.
Syndromic disorders	32	5.2%			28	30.8%			*
Alagille syndrome	1	3.1%			-	-			
DiGeorge syndrome	2	6.3%			2	7.1%			
Goldenhar syndrome	1	3.1%			1	3.6%			
Trisomy 18	–	–			1	3.6%			
Trisomy 21	18	56.3%			17	60.7%			
Noonan syndrome	–	–			1	3.6%			
Williams syndrome	2	6.3%			1	3.6%			
Others	8	25.0%			5	17.9%			

p * denotes significant difference compared to non-microcephalic p <0.001, + denotes $p < 0.05$, *n.s.* = not significant.
For ordinal scaled variables, median and IQR were given accordingly (printed in italics).

TABLE 4 CHD diagnoses of microcephalic patients.

	N	
Ventricular septal defect	29	31.9%
Atrial septal defect	7	7.7%
Tetralogy of Fallot	6	6.6%
Univentricular heart	11	12.1%
Aortic valve disease	2	2.2%
Coarctation of the aorta	4	4.4%
Transposition of the great arteries (intact ventricular septum)	7	7.7%
Atrioventricular septal defect	12	13.2%
Other	13	14.3%

A total of 29.8% of non-microcephalic patients suffered from psychiatric comorbidity, while in microcephalic patients, this proportion was more than two times as high (67.0%) (Table 3). In particular, the percentage of patients with developmental delay, intellectual debility, social disability, learning disorder, or language disorder was significantly increased in microcephalic CHD patients ($p < 0.001$; Figure 3).

Educational status of microcephalic CHD patients

The educational career and usage of support interventions of microcephalic patients compared to CHD patients without microcephaly are visualized in Figure 4. A total of 85.7% of the microcephalic patients but only 47.6% of non-microcephalic patients received early interventions to foster their development. The school enrollment of both groups was similar at approximately six years of age. 89.9% of non-microcephalic but only 51.6% of microcephalic patients were enrolled in a regular elementary school. About four years later, at the age

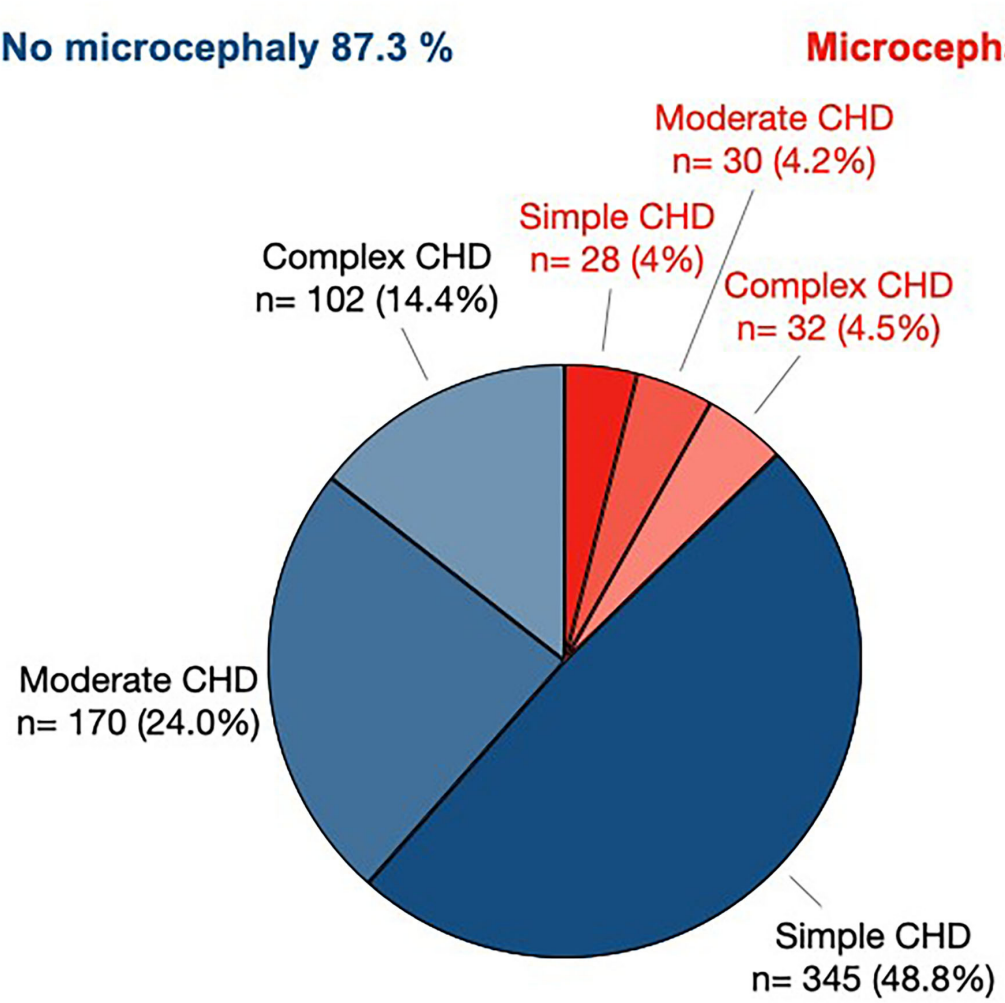

FIGURE 2
Prevalence of microcephaly in patients with simple, moderate, or complex CHD. The pie chart denotes the raw *n* of patients defined by CHD severity classification and head circumference. Only patients with known CHD severity scores and known head circumference are included (n = 707).

of 10, children from both groups transferred to a new school: 48.3% of the non-microcephalic patients went to grammar school, and 3.3% needed specialized schools. In contrast, only 14.3% of the microcephalic patients went to grammar school, while the proportion of pupils at special schools was eight times higher than in non-microcephalic patients. Supportive interventions, e.g., because of specific learning disabilities, were used by 52.7% of microcephalic patients and 21.6% of non-microcephalic patients.

Staying down a year was statistically insignificant between microcephalic and non-microcephalic patients (Table 5); school grades were similar in both groups, too. Absenteeism from school added to <1 month in most microcephalic patients (Table 5). In our cohort, parental educational level did not influence the attended school forms (primary and secondary school), the class repetition rate, or the utilization of (early) supportive measures.

Discussion

Our data demonstrate that microcephaly in early childhood is a crucial risk factor for impaired scholastic development in patients with CHD. These results expand the current state of research, as the educational career of microcephalic vs. non-microcephalic CHD patients has not been evaluated. This is noteworthy as education is a particularly important and objectively measurable characteristic of neurodevelopment. In our study, microcephalic participants had a high demand for early and specific interventions. They frequently attended

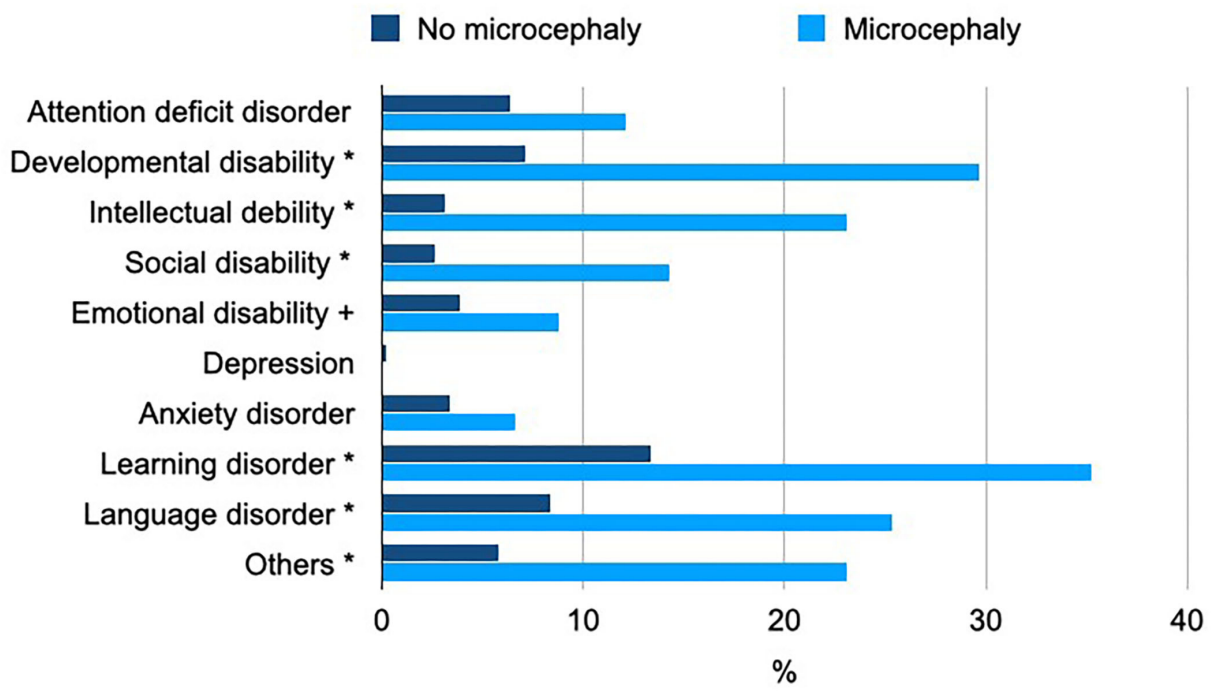

FIGURE 3
Psychiatric comorbidity in microcephalic CHD patients. The chart visualizes the percentage of patients with the most prevalent psychiatric disorders among microcephalic or non-microcephalic patients; * denotes a significant difference compared to non-microcephalic, $p < 0.001$, and + denotes $p < 0.05$.

special schools more frequently and compared to non-microcephalic CHD patients, their likelihood of attending a grammar school was halved. Approximately two-thirds of microcephalic patients were diagnosed with psychiatric disorders such as learning, emotional, or behavioral disorders.

Previous studies have shown that a small head circumference in CHD patients is related to neurodevelopmental outcomes in early childhood (6, 7, 18), preschool age (19), and adolescence (20). This is in line with our study results, as microcephalic CHD patients were confronted with multiple problems in their whole (pre-) scholastic development. The etiology of this phenomenon is complex and thought to be multifactorial.

First, mounting evidence suggests that prenatal factors play a crucial role. It has been proven that intrauterine brain growth is predominantly altered in children with complex CHD and may result in a smaller head circumference and brain volume at birth (21, 22). Hemodynamic factors are assumed as an explanatory variable and include umbilical vein oxygen saturation, altered blood flow, and reduced oxygen content in the ascending aorta (23). Moreover, animal and human studies suggest that prenatal maternal psychosocial stress may adversely affect the developing fetal brain (24, 25). However, for expectant mothers after the diagnosis of CHD in their child, this association has hardly been studied (26). A longitudinal study analyzing this would be even more important as a prenatal CHD diagnosis may be a traumatic situation for the expectant mother.

Second, postnatal growth is often impaired in CHD patients. This has mainly been attributed to disrupted normal feeding behavior in the neonatal and infant period (27). In CHD patients requiring early operative treatment, this problem often persists during the postoperative phase, as patients frequently require a nasogastric feeding tube (28, 29). Hypermetabolic state and malabsorption may be further pathophysiologic mechanisms, while genetic and environmental factors are thought to play a subordinate role (27, 30). These are important considerations when interpreting our study results because more than two-thirds of microcephalic CHD patients suffer from moderate or complex CHD.

Third, social environment in the meaning of parental education and supportive therapy may be a rationale as this is an important determinant in childhood development (31, 32). In our study cohort, almost all microcephalic patients received early supportive therapy, and specific interventions fostered more than half at school age. Supportive therapy may compensate for learning deficits (33) and contribute to the fact that a small proportion of microcephalic patients were able to attend grammar school. Interestingly, the parental educational level did not influence the child's scholastic development in the present analysis. This argues for the assumption that in

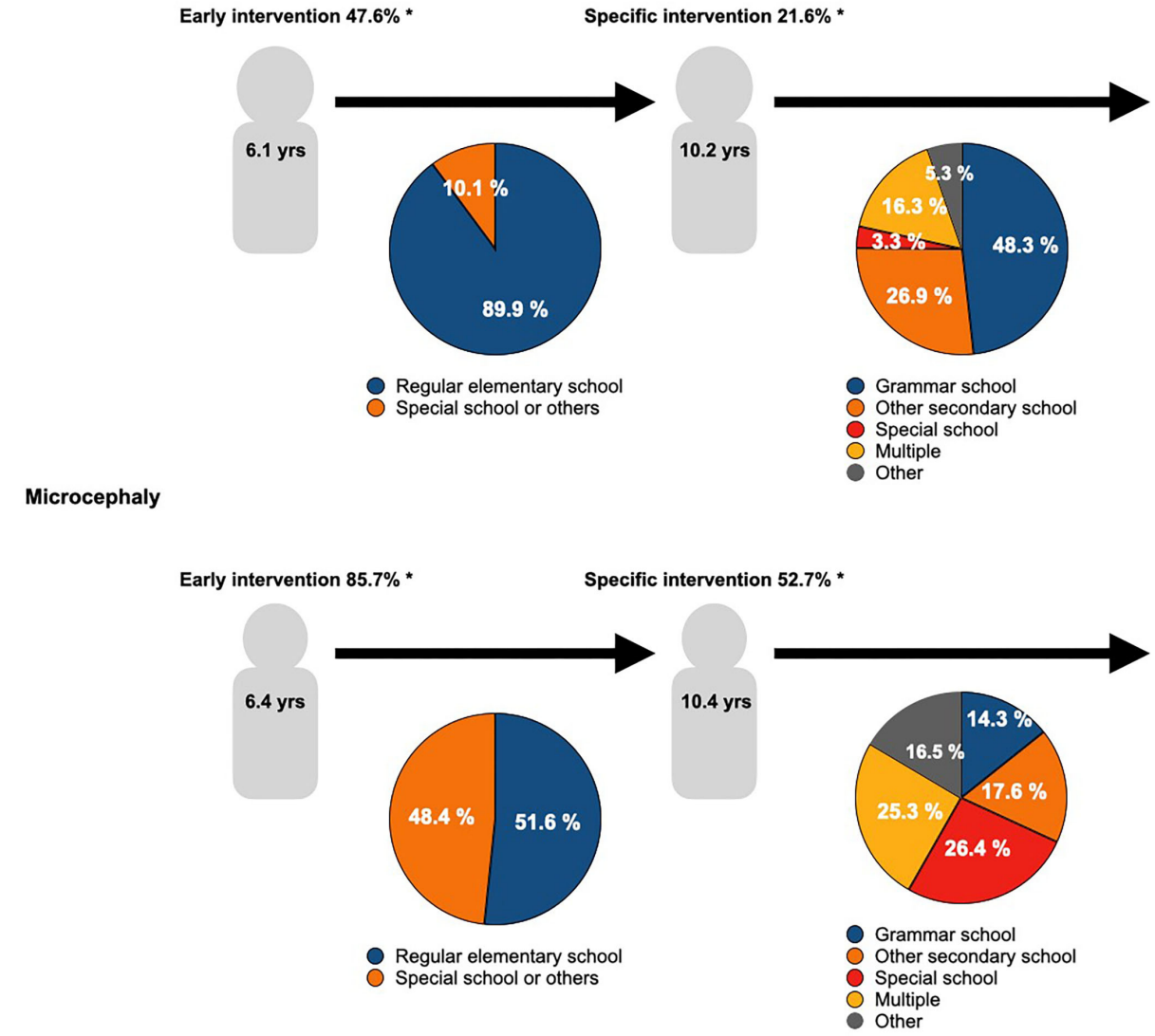

FIGURE 4
Educational development in CHD patients. The graph visualizes the school career of CHD patients with or without microcephaly. The median age of school enrollment and the first change of school are given in the figures. The distribution of different kinds of primary schools in the left pie chart is represented, and the pie chart on the right represents the different kinds of secondary schools. Further, the usage of early and/ or specific interventions to support the school careers is given. Differences in the kind of school are significant < 0.001; additionally * denotes a significant difference compared to non-microcephalic patients, $p < 0.001$, and + denotes $p < 0.05$.

this specific patient cohort, the neurodevelopmental outcome is predominantly associated with somatic factors. Preterm birth, a known risk factor for altered brain growth (34), did not significantly contribute to microcephaly in our study cohort as more than 80% of study participants were born at full term.

Another noteworthy result of the present analysis is the prevalence of psychiatric comorbidities: nearly one-third of non-microcephalic patients suffered from psychiatric comorbidity, but in microcephalic patients, this proportion was more than two times as high. Numerous studies have observed the clinical manifestation of developmental delay, intellectual debility, social disability, learning disorder, or language disorder (35, 36). Underlying pathophysiologic mechanisms are still under investigation. However, prenatal hemodynamic factors and a genetic link between heart and brain development are assumed to be important rationales (37).

TABLE 5 School career of the microcephalic patients.

	Microcephaly ($n = 91$)		No microcephaly ($n = 621$)		
	N		*N*		*p*
Stayed down?					
Yes	14	15.4 %	57	9.2 %	n.s.
No	77	84.6 %	564	90.8 %	
Participating in physical education?					
Yes	69	75.8 %	550	88.6 %	+
No	22	24.2 %	71	11.4 %	
Absenteeism from school					
<1 month	73	82 %	552	94 %	*
1 month−1 year	16	18 %	33	5.6 %	
>1 year	0	0 %	2	0.3 %	

The table informs about school attendance in microcephalic and non-microcephalic patients. The whole cohort comprises 750, but data on the head circumference are missing in 28 patients. Thus, the sum of microcephalic and non- microcephalic patients is 712. * denotes significant difference compared to non-microcephalic $p < 0.001$, + denotes $p < 0.05$, n.s. = insignificant data regarding missed school time was missing in $n = 2$.

Interestingly, the subjective health status of microcephalic patients was not as good as the non-microcephalic patients' but still very good. This has been reported before (38). A possible explanation could be that, as CHD patients were born with heart disease, they might have learned early in life how to develop a strong "sense of coherence" and select the right coping strategies (39).

Clinical implications for this study

It is important for CHD patients, affected families, and treating physicians to be aware of microcephaly as a risk factor for impaired scholastic development. Routine follow-up examinations should be established to identify developmental deficits. Unfortunately, underlying variables such as prenatal hemodynamic factors or the number and point of time of CHD operations are hardly modifiable. However, supportive therapy seems to be a promising compensation mechanism. Therefore, CHD patients and their families should be given low-threshold access to supportive interventions.

Limitations

Due to the data privacy policy of the NRCHD, a non-responder analysis could not be performed. Our results need to be interpreted in light of a potential selection bias. Highly educated and/or healthier CHD patients might be more inclined to participate in scientific studies than patients with lower educational levels and/or more health problems. However, a proportion of 48% of microcephalic patients attending a particular school speaks against this assumption. Our analysis of parental ISCED and child education supports this assumption that in microcephalic patients, somatic (co-) morbidities have a more significant influence than the parental level of education. However, parents with higher education might be overrepresented compared to the German general population. The response rate of 26.6% is in the middle range and may still be considered valid and quite representative (40). The results cannot be easily applied to other countries, as education and health care systems may differ. Due to the study setting (follow-up study of a patient cohort on the somatic development in children with CHD), we could not assess the highest educational/academic achievement as the mean age of our study cohort was ∼12 years of age. Seventy patients in the study were diagnosed with a syndromal disease; among these, 28 were microcephalic. Based on the heterogeneity of diagnoses and small subgroups, we could not correct our results for this or perform subgroup analyses. Our study does not answer whether microcephalic patients with or without CHD differ in their educational perspectives. Microcephaly appears to be a risk factor for impaired educational success in CHD patients.

Conclusion

Patients with CHD and microcephaly are at risk for impaired educational development. Head circumference measurement in infants and children with CHD should be integrated into the serial routine monitoring of somatic parameters in children with CHD. Microcephaly in early childhood should alert clinicians to provide targeted interventions to optimize the developmental potential. Further studies are necessary to evaluate the impact of these interventions and to determine the long-term follow-up of this specific patient cohort at risk.

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 the Charité—Universitätsmedizin Berlin, Germany (No. EA2/190/19). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

CP, H-AK, MP, FB, UB, PH, and KS: study concept/design. CP, PH, and KS: data interpretation. CP: drafting of the original manuscript. LS and AH: data analysis. AH: acquisition of data. LS: interpretation, visualization, and drafting of the original manuscript (results). PH, H-AK, MP, and KS: critical revisions of the manuscript. H-AK and MP: acquisition of data. FB and UB: critical revisions of the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest

Authors UB and PH were employed by the companies National Register for Congenital Heart Defects and Competence Network for Congenital Heart Defects.

The remaining 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.

The reviewer JL declared a shared affiliation with the author LS to the handling editor at the time of review.

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Supplementary material

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References

1. Daymont C, Neal A, Prosnitz A, Cohen MS. Growth in children with congenital heart disease. *Pediatrics.* (2013) 131:e236–42. doi: 10.1542/peds.2012-1157

2. Burch PT, Ravishankar C, Newburger JW, Lambert LM, Pemberton VL, Granger S, et al. Assessment of growth 6 years after the Norwood procedure. *J Pediatr.* (2017) 180:270–4. doi: 10.1016/j.jpeds.2016.09.048

3. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, et al. Neurodevelopmental outcomes after cardiac surgery in infancy. *Pediatrics.* (2015) 135:816–25. doi: 10.1542/peds.2014-3825

4. Vogt KN, Manlhiot C, Van Arsdell G, Russell JL, Mital S, McCrindle BW. Somatic growth in children with single ventricle physiology impact of physiologic state. *J Am Coll Cardiol.* (2007) 50:1876–83. doi: 10.1016/j.jacc.2007.07.050

5. Francois K, Bove T, Panzer J, De Groote K, Vandekerckhove K, De Wilde H, et al. Univentricular heart and Fontan staging: analysis of factors impacting on body growth. *Eur J Cardiothorac Surg.* (2012) 41:e139–45. doi: 10.1093/ejcts/ezs194

6. Limperopoulos C, Majnemer A, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkov C, et al. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. *J Pediatr.* (2002) 141:51–8. doi: 10.1067/mpd.2002.125227

7. Mussatto KA, Hoffmann R, Hoffman G, Tweddell JS, Bear L, Cao Y, et al. Risk factors for abnormal developmental trajectories in young children with congenital heart disease. *Circulation.* (2015) 132:755–61. doi: 10.1161/CIRCULATIONAHA.114.014521

8. Goldberg CS, Lu M, Sleeper LA, Mahle WT, Gaynor JW, Williams IA, et al. Factors associated with neurodevelopment for children with single ventricle lesions. *J Pediatr.* (2014) 165:490-6 e8. doi: 10.1016/j.jpeds.2014.05.019

9. Rotermann I, Logoteta J, Falta J, Wegner P, Jung O, Dutschke P, et al. Neurodevelopmental outcome in single-ventricle patients: is the Norwood procedure a risk factor? *Eur J Cardiothorac Surg.* (2017) 52:558–64. doi: 10.1093/ejcts/ezx119

10. Tabbutt S, Gaynor JW, Newburger JW. Neurodevelopmental outcomes after congenital heart surgery and strategies for improvement. *Curr Opin Cardiol.* (2012) 27:82–91. doi: 10.1097/HCO.0b013e328350197b

11. Helm PC, Koerten MA, Abdul-Khaliq H, Baumgartner H, Kececioglu D, Bauer UM. Representativeness of the German national register for congenital heart defects: a clinically oriented analysis. *Cardiol Young.* (2016) 26:921–6. doi: 10.1017/S1047951115001547

12. Lindinger A, Schwedler G, Hense HW. Prevalence of congenital heart defects in newborns in Germany: results of the first registration year of the PAN Study (July 2006 to June 2007). *Klin Padiatr.* (2010) 222:321–6. doi: 10.1055/s-0030-1254155

13. Poryo M, Paes LA, Pickardt T, Bauer UMM, Meyer S, Wagenpfeil S, et al. Somatic development in children with congenital heart defects. *J Pediatr.* (2018) 192:136-43 e4. doi: 10.1016/j.jpeds.2017.09.059

14. Braegger C JO, Konrad D, Molinari L. Neue Wachstumskurven für die Schweiz. *Paediatrica.* (2011) 22:9–11.

15. Franklin RC, Jacobs JP, Krogmann ON, Beland MJ, Aiello VD, Colan SD, et al. Nomenclature for congenital and pediatric cardiac disease: historical perspectives and the international pediatric and congenital cardiac code. *Cardiol Young.* (2008) 18:70–80. doi: 10.1017/S1047951108002795

16. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, et al. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol.* (2001) 37:1170–5. doi: 10.1016/S0735-1097(01)01272-4

17. Schneider S. The International Standard Classification of Education (ISCED-97): *An Evaluation of Content and Criterion Validity for 15 European Countries*. Mannheim: MZES. (2008).

18. Hangge PT, Cnota JF, Woo JG, Hinton AC, Divanovic AA, Manning PB, et al. Microcephaly is associated with early adverse neurologic outcomes in hypoplastic left heart syndrome. *Pediatr Res.* (2013) 74:61–7. doi: 10.1038/pr.2013.61

19. Majnemer A, Limperopoulos C, Shevell M, Rosenblatt B, Rohlicek C, Tchervenkov C. Long-term neuromotor outcome at school entry of infants with congenital heart defects requiring open-heart surgery. *J Pediatr.* (2006) 148:72–7. doi: 10.1016/j.jpeds.2005.08.036

20. Matos SM, Sarmento S, Moreira S, Pereira MM, Quintas J, Peixoto B, et al. Impact of fetal development on neurocognitive performance of adolescents with cyanotic and acyanotic congenital heart disease. *Congenit Heart Dis.* (2014) 9:373–81. doi: 10.1111/chd.12152

21. von Rhein M, Buchmann A, Hagmann C, Dave H, Bernet V, Scheer I, et al. Severe congenital heart defects are associated with global reduction of neonatal brain volumes. *J Pediatr.* (2015) 167:1259-63 e1. doi: 10.1016/j.jpeds.2015.07.006

22. Owen M, Shevell M, Donofrio M, Majnemer A, McCarter R, Vezina G, et al. Brain volume and neurobehavior in newborns with complex congenital heart defects. *J Pediatr.* (2014) 164:1121-7 e1. doi: 10.1016/j.jpeds.2013.11.033

23. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation.* (2015) 131:1313–23. doi: 10.1161/CIRCULATIONAHA.114.013051

24. Buss C, Davis EP, Shahbaba B, Pruessner JC, Head K, Sandman CA. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. *Proc Natl Acad Sci U S A.* (2012) 109:E1312–9. doi: 10.1073/pnas.1201295109

25. Entringer S, Buss C, Wadhwa PD. Prenatal stress, development, health and disease risk: a psychobiological perspective-2015 curt richter award paper. *Psychoneuroendocrinology.* (2015) 62:366–75. doi: 10.1016/j.psyneuen.2015.08.019

26. Wu Y, Andescavage N, Lopez C, Quistorff JL, Donofrio MT, du Plessis AJ, et al. Maternal mental distress and cortisol levels in pregnancies with congenital heart disease. *Cardiol Young.* 2021:1–5. doi: 10.1017/S1047951121003504

27. Schwalbe-Terilli CR, Hartman DH, Nagle ML, Gallagher PR, Ittenbach RF, Burnham NB, et al. Enteral feeding and caloric intake in neonates after cardiac surgery. *Am J Crit Care.* (2009) 18:52–7. doi: 10.4037/ajcc2009405

28. Mitchell IM, Logan RW, Pollock JC, Jamieson MP. Nutritional status of children with congenital heart disease. *Br Heart J.* (1995) 73:277–83. doi: 10.1136/hrt.73.3.277

29. Cameron JW, Rosenthal A, Olson AD. Malnutrition in hospitalized children with congenital heart disease. *Arch Pediatr Adolesc Med.* (1995) 149:1098–102. doi: 10.1001/archpedi.1995.02170230052007

30. Burnham N, Ittenbach RF, Stallings VA, Gerdes M, Zackai E, Bernbaum J, et al. Genetic factors are important determinants of impaired growth after infant cardiac surgery. *J Thorac Cardiovasc Surg.* (2010) 140:144–9. doi: 10.1016/j.jtcvs.2010.01.003

31. Cassedy A, Drotar D, Ittenbach R, Hottinger S, Wray J, Wernovsky G, et al. The impact of socio-economic status on health related quality of life for children and adolescents with heart disease. *Health Qual Life Outcomes.* (2013) 11:99. doi: 10.1186/1477-7525-11-99

32. McCusker CG, Doherty NN, Molloy B, Rooney N, Mulholland C, Sands A, et al. A randomized controlled trial of interventions to promote adjustment in children with congenital heart disease entering school and their families. *J Pediatr Psychol.* (2012) 37:1089–103. doi: 10.1093/jpepsy/8jss092

33. Pfitzer C, Buchdunger LA, Helm PC, Blickle MJ, Rosenthal LM, Ferentzi H, et al. Education of children with cyanotic congenital heart disease after neonatal cardiac surgery. *Ann Thorac Surg.* (2021) 112:1546–52. doi: 10.1016/j.athoracsur.2020.07.072

34. de Kieviet JF, Zoetebier L, van Elburg RM, Vermeulen RJ, Oosterlaan J. Brain development of very preterm and very low-birthweight children in childhood and adolescence: a meta-analysis. *Dev Med Child Neurol.* (2012) 54:313–23. doi: 10.1111/j.1469-8749.2011.04216.x

35. Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. *Pediatrics.* (2008) 121:e759–67. doi: 10.1542/peds.2007-1066

36. Bellinger DC, Watson CG, Rivkin MJ, Robertson RL, Roberts AE, Stopp C, et al. neuropsychological status and structural brain imaging in adolescents with single ventricle who underwent the Fontan procedure. *J Am Heart Assoc.* (2015) 4:1–16. doi: 10.1161/JAHA.115.002302

37. Homsy J, Zaidi S, Shen Y, Ware JS, Samocha KE, Karczewski KJ, et al. De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. *Science.* (2015) 350:1262–6. doi: 10.1126/science.aa8c9396

38. Amedro P, Dorka R, Moniotte S, Guillaumont S, Fraisse A, Kreitmann B, et al. Quality of life of children with congenital heart diseases: a multicenter controlled cross-sectional study. *Pediatr Cardiol.* (2015) 36:1588–601. doi: 10.1007/s00246-015-1201-x

39. Antonovsky A. The life cycle, mental health and the sense of coherence. *Isr J Psychiatry Relat Sci.* (1985) 22:273–80.

40. Taylor BV, Palmer A, Simpson S. Jr., Lucas R, Simmons RD, Mason D, et al. Assessing possible selection bias in a national voluntary MS longitudinal study in Australia. *Mult Scler.* (2013) 19:1627–31. doi: 10.1177/1352458513481511

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Myocardial extracellular volume is a non-invasive tissue marker of heart failure in patients with transposition of the great arteries and systemic right ventricle

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Background: Focal myocardial fibrosis in the systemic right ventricle (RV) is related to ventricular dysfunction and adverse outcome in patients with d-transposition of the great arteries (dTGA) post atrial redirection and those with congenitally corrected TGA (ccTGA). The role of diffuse fibrotic lesions in these conditions remains poorly understood. Our study aimed to investigate diffuse myocardial fibrosis by measuring extracellular volume (ECV) with cardiovascular magnetic resonance (CMR) and to explore correlations between ECV and clinical as well as functional markers of heart failure in patients with TGA and systemic RV.

Methods: We prospectively included dTGA and ccTGA patients aged ≥14 years and compared them to healthy controls. Standardized CMR included modified Look-Locker Inversion recovery T1 mapping to quantify diffuse myocardial fibrosis in the systemic RV and the subpulmonary left ventricle (LV). The centerline of RV and LV myocardium was marked with a line of interest tool to determine native and post-contrast T1 for quantification of ECV.

Results: In total, 13 patients (dTGA: $n = 8$, ccTGA: $n = 5$) with a median age of 30.3 years were enrolled. LV ECV was higher in patients than in controls [34% (30%–41%) vs. 26% (23%–27%), $p < 0.001$], with values increased above the upper limit of normal in 10/13 patients (77%). RV ECV tended to be higher in patients than in controls, albeit without statistical significance [29% (27%–32%) vs. 28% (26%–29%), $p = 0.316$]. Patients with elevated LV ECV had lower LV ejection fraction than those with normal ECV ($52 \pm 5\%$ vs. $65 \pm 4\%$, $p = 0.007$). Correlations with clinical parameters were not observed. LV ECV was significantly higher than RV ECV ($p = 0.016$) in the patient group.

Conclusions: In this study, LV ECV was significantly increased in TGA patients compared to controls, and was associated with LV dysfunction. Our data suggest that ECV may serve as a non-invasive tissue marker of heart failure

in TGA with systemic RV. Further research is necessary to evaluate the prognostic implications and the potential role of ECV in monitoring disease progression and guiding therapy, aiming to maintain LV function or train the LV for subaortic location in TGA patients from infancy to adulthood.

KEYWORDS

transposition of the great arteries, systemic right ventricle, cardiovascular magnetic resonance, extracellular volume, myocardial fibrosis, heart failure

Introduction

Given the advances in care for patients with congenital heart disease (CHD), the majority of children born with CHD reach adulthood (1, 2). However, increased mortality has been described in adult patients with CHD, particularly in the young, with heart failure as the leading cause of death (3). Heart failure signs and symptoms are seen in 22% of patients with d-loop transposition of the great arteries (dTGA) post atrial redirection, and in 32% of patients with congenitally corrected transposition of the great arteries (ccTGA) (4).

Myocardial fibrosis contributes to the development of heart failure in CHD (5, 6). Cardiovascular magnetic resonance (CMR) studies have identified focal myocardial fibrosis in the systemic right ventricle (RV) as assessed by late gadolinium enhancement (LGE) imaging to be associated with ventricular dysfunction and adverse outcome in dTGA post atrial redirection and in ccTGA (7–10). Data on diffuse myocardial fibrosis from CMR T1 mapping in TGA with a systemic RV are limited and somewhat controversial, pointing to an increased fibrotic burden in the systemic RV (11), the subpulmonary left ventricle (LV) (12), the interventricular septum (13), or both RV and LV (14).

With the present study, we aimed to determine biventricular extracellular volume (ECV) as a non-invasive measure of diffuse myocardial fibrosis by applying CMR T1 mapping and to evaluate the correlation of ECV with clinical and functional markers of heart failure in patients with TGA and systemic RV.

Materials and methods

Study population

We prospectively enrolled patients of ages ≥14 years with a diagnosis of dTGA post atrial redirection or ccTGA who were referred for clinically indicated CMR. Exclusion criteria were arrhythmias, cardiac decompensation, cardiomyopathies, chronic or acute infection up to four weeks prior to CMR, chronic systemic diseases, significant renal impairment, devices non-compatible with CMR, and claustrophobia. Patients further underwent blood sampling for hematocrit and N-terminal pro brain natriuretic peptide (NT-proBNP) immediately before CMR, and cardiopulmonary exercise testing (CPET).

Healthy subjects with normal 12-lead electrocardiogram (ECG), blood pressure, and renal function, and no history or symptoms of cardiovascular disease or contraindications for CMR were included as controls.

CMR protocol

All participants received standardized CMR at 1.5 T (Philips Healthcare, Best, The Netherlands). Blood samples for hematocrit and NT-proBNP were collected immediately before CMR. Cine images were acquired with a steady-state free precision sequence in short axis (SAX) and long axis planes as well as in axial orientation covering the entire ventricles. LGE imaging in SAX was conducted using a T1-weighted inversion-recovery three-dimensional spoiled gradient echo sequence 5 min after intravenous bolus application of gadolinium-DOTA (Dotarem®, Guerbet) at a dose of 0.1 mmol/kg. An individually adapted prepulse delay Look-Locker sequence was applied to determine inversion times for nulling myocardium.

For T1 mapping, an ECG-gated single-shot modified Look-Locker inversion-recovery (MOLLI) sequence was used (15) with sequence parameters as follows: MOLLI scheme 3b(3b)3b (3b)5b, slice thickness 8.0 mm, repetition time 2.4 ms, echo time 1.2 ms, flip angle 35°. Native and post-contrast T1 images were acquired in midventricular SAX and axial four-chamber orientation in breath-hold at end-expiration before and 15 min after contrast bolus application (**Figure 1**).

CMR analysis

A commercially available workstation (Philips Viewforum, Best, The Netherlands) was used to analyze LV and RV volumes [end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV)] and ejection fraction (EF) from cine image stacks in axial orientation. Volumetric parameters were indexed to body surface area (BSA). In TGA patients, the ventricle in the subpulmonary position was defined as the LV, and the ventricle in the subaortic position as the (systemic) RV.

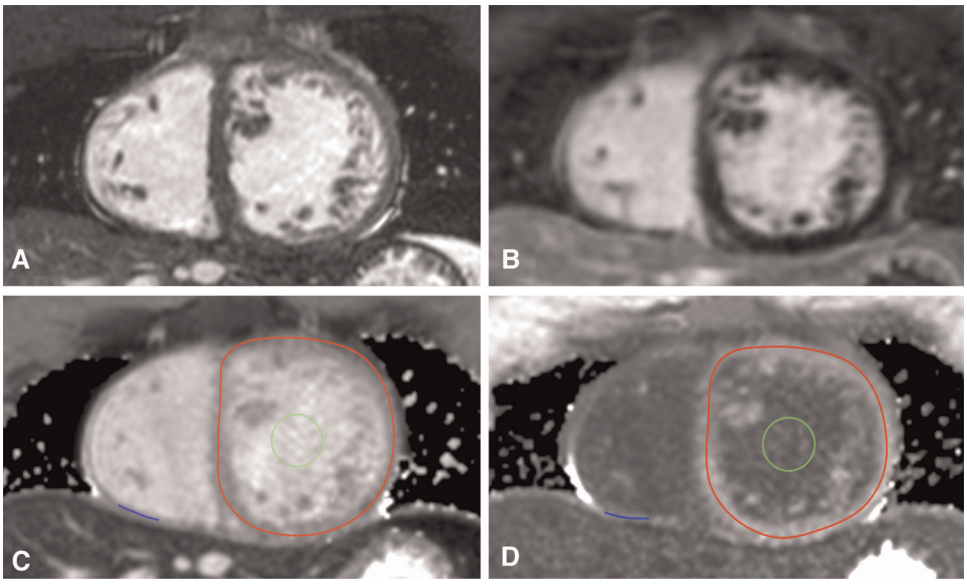

FIGURE 1
T1 mapping in congenitally corrected transposition of the great arteries. Corresponding cine (A) and late gadolinium enhancement images (B) as well as T1 maps in midventricular short axis before (C) and after contrast application (D) are shown. Lines of interest (LOIs) are drawn into the myocardium of the systemic right ventricle (red LOI) and the subpulmonary left ventricle (blue LOI). The blood pool is marked with a green region of interest.

T1 maps were generated with the open-source image reconstruction tool MRmap after manual correction for body motion (16), stored as DICOM files, and analyzed with OsiriX Lite. Native and post-contrast blood T1 values were gained from a region of interest placed in the blood pool of the systemic ventricle in subaortic location with exclusion of the papillary muscles and the trabeculae, respectively. For measurements of myocardial T1, a line of interest (LOI) was manually drawn in the center of the RV and LV myocardium as previously described (17). LOIs marked the myocardial circumference of the subaortic ventricle and the thickest part of the free, anterior or inferior wall of the subpulmonary ventricle on T1 maps in midventricular SAX (**Figure 1**). In the case of better delineation of myocardial walls, T1 maps in four-chamber-view were alternatively used. Native and post-contrast T1 values of myocardium and blood as well as hematocrit were then used to calculate RV ECV and LV ECV. ECV was considered to be elevated at values above the mean plus two standard deviations (SD) of the control ECV (18).

Follow-up

Medical records of TGA patients were reviewed for adverse events since the date of CMR, including supraventricular and ventricular arrhythmias, implantation of a pacemaker or implantable cardioverter defibrillator (ICD), heart failure-related hospitalization, heart transplantation (HTx), and cardiovascular death.

Statistical analysis

Statistical analyses were carried out with SPSS version 25.0 (IBM Corp., Armonk, NY, United States), considering p-values <0.05 to be statistically significant. Data between groups were compared with the Mann–Whitney U test, and within groups using Wilcoxon signed rank test with Bonferroni correction, respectively. For comparisons between categorical variables, Fisher's exact test was applied. Spearman's correlation coefficient was used to analyze associations between continuous variables. Results are presented as median (range), mean ± SD, or numbers (n) and percentages (%), as appropriate.

Results

Subject characteristics

In total, 13 patients with a systemic RV and a median age of 30.3 (25.2–37.9) years were enrolled. Of those, eight patients had dTGA post atrial redirection (Senning procedure: $n = 7$, Mustard procedure: $n = 1$), and five had ccTGA. A summary

TABLE 1 Patient characteristics.

	Patients total ($n = 13$)	dTGA Senning/Mustard ($n = 8$)	ccTGA ($n = 5$)	p-value
Gender (female/male)	9 (69)/4 (31)	5 (62.5)/3 (37.5)	4 (80)/1 (20)	1.000
Age at CMR (years)	30.3 (25.2–37.9)	32.2 (29.1–37.3)	25.0 (23.0–41.5)	0.524
BSA (kg/m²)	1.9 (1.9–2.0)	2.0 (1.7–2.2)	1.9 (1.9–2.0)	0.524
NYHA				
I	7 (54)	3 (37.5)	4 (80)	0.266
II	6 (46)	5 (62.5)	1 (20)	
III	0 (0)	0 (0)	0 (0)	
IV	0 (0)	0 (0)	0	
VO_2max (ml/min/kg)	22.3 (15.8–30.0) $n = 8$	20.4 (13.9–22.8) $n = 6$	25.6[a] $n = 2$	0.071
NT-proBNP (pg/ml)	236.3 (179.9–662.8)	247.4 (183.1–850.2)	198.8 (105.8–662.8)	0.622
Arrhythmias				
SVT	1 (8)	1 (14)	0 (0)	1.000
nsVT	2 (17) $n = 12$	2 (29) $n = 7$	0 (0)	0.470
Pacemaker	1 (8)	0 (0)	1 (80)	0.417
ICD	2 (17) $n = 12$	2 (29) $n = 7$	0 (0)	0.470
MCS	0 (0)	0 (0)	0 (0)	n.a.
HTx	1 (8)	0 (0)	1 (20)	0.417
Death	1 (8) $n = 12$	1 (14) $n = 7$	0 (0)	1.000
CMR findings				
LVEF (%)	55 (49–62)	50 (47–62)	56 (52–62)	0.435
LVEDV (mL/m²)	68 (52–90)	59 (47–67)	94 (77–105)	**0.006**
LVESV (mL/m²)	35 (24–39)	28 (21–35)	41 (32–45)	**0.045**
LVSV (mL/m²)	32 (30–51)	31 (27–32)	51 (42–63)	**0.011**
RVEF (%)	45 (34–55)	43 (31–56)	46 (39–54)	0.622
RVEDV (mL/m²)	113 (97–159)	106 (92–155)	128 (109–203)	0.284
RVESV (mL/m²)	67 (45–96)	63 (43–104)	70 (53–123)	0.435
RVSV (mL/m²)	53 (45–60)	47 (37–54)	60 (55–79)	**0.030**
Presence of LGE	9 (75)[b]	7 (100)	2 (40)	**0.045**

Values are median (range) or n (%). Statistically significant p-values are indicated in bold.

BSA, body surface area; ccTGA, congenitally corrected transposition of the great arteries; CMR, cardiovascular magnetic resonance; dTGA, d-loop transposition of the great arteries; HTx, heart transplantation; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; MCS, mechanical circulatory support; nsVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVSV, right ventricular stroke volume; SVT, supraventricular tachycardia; VO_2max, maximum oxygen consumption.

[a]Median value was given.

[b]LGE image quality was insufficient in one patient.

of patient characteristics is given in Table 1. Healthy controls ($n = 15$; female: $n = 7$) had a median age of 24.4 (23.8–29.0) years and were younger than the patient group ($p = 0.004$). Differences in gender distribution were not seen.

Cardiovascular magnetic resonance

Late gadolinium enhancement

Mild LGE was visible in 75% of the patients (dTGA post Senning: $n = 7$, ccTGA: $n = 2$), and was located at the insertion points ($n = 5$), the inferior ($n = 2$) or anterior RV wall ($n = 1$), and the septum ($n = 1$). Transmural LGE was not observed.

Extracellular volume

LV ECV was higher in patients than in controls [34% (30%–41%) vs. 26% (23%–27%), $p < 0.001$; Table 2]. Values were increased above the upper limit of normal (>31.5%) in 10/13 patients (77%). In two out of three dTGA patients with normal LV ECV, (sub-) pulmonary stenosis was present, and the remaining patient had ccTGA without stenosis. RV ECV tended to be higher in patients than in controls, yet without statistical significance [29% (27%–32%) vs. 28% (26%–29%), $p = 0.316$]. Elevated RV ECV (>29.8%) was detected in four patients (31%). LV ECV was significantly higher than RV ECV ($p = 0.016$) in the patient group. There were no differences in LV ECV and RV ECV between dTGA and ccTGA patients.

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TABLE 2 T1 mapping parameters in controls and patients.

	Controls ($n = 15$)	Patients ($n = 13$)	p-value
LV T1 native (ms)	989 (966–998)	1023 (978–1059)	0.072
LV ECV (%)	26 (23–27)	34 (30–41)	**<0.001**
RV T1 native (ms)	979 (953–1027)	1002 (978–1054)	0.235
RV ECV (%)	28 (26–29)	29 (27–32)	0.316

Values are median (range). Statistically significant p-values are indicated in bold. LV T1 native, left ventricular native T1; LV ECV, left ventricular extracellular volume; RV T1 native, right ventricular native T1; RV ECV, right ventricular extracellular volume.

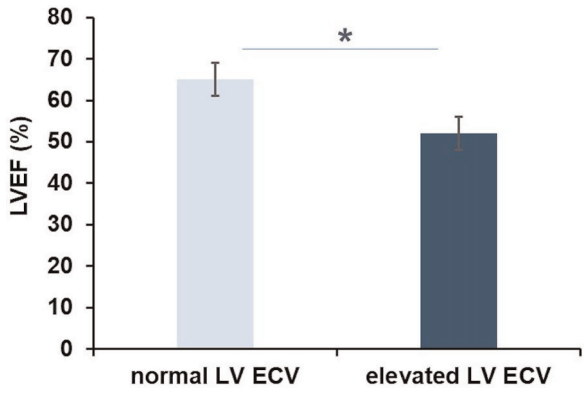

FIGURE 2
Extracellular volume and left ventricular function in transposition of the great arteries. Patients with elevated left ventricular extracellular volume (LV ECV) had significantly lower LV ejection fraction (LVEF) than patients with normal LV ECV (52 ± 5 vs. 65 ± 4%; *$p = 0.007$).

ECV and clinical data

LV ECV and RV ECV of patients did not correlate with clinical characteristics including age at CMR, BSA, systolic or diastolic blood pressure, NT-proBNP, maximum oxygen consumption from CPET, and gender distribution.

ECV and CMR measures

Patients with elevated LV ECV had significantly lower LVEF than those with values within the normal range (52 ± 5% vs. 65 ± 4%, $p = 0.007$; Figure 2). Both LVEF and RVEF were reduced in patients with elevated RV ECV as compared to those with normal values, but these differences were not statistically significant (51 ± 2% vs. 56 ± 3%, and 39 ± 5% vs. 46 ± 4%, $p = 0.371$, respectively). LV ECV and RV ECV did not differ between patients with and those without LGE ($p = 0.482$ and 0.145, respectively). Among patients with positive LGE in the systemic RV, 67% ($n = 6$) had elevated LV ECV ($p = 0.509$). There were no differences in the presence of LGE between those with elevated RV ECV and those without ($p = 0.509$).

Follow-up

Median follow-up time was 5.1 (2.5–8.2) years. One patient was lost to follow-up. Adverse events were observed in 6/12 patients (50%). Of those, four patients (67%) had elevated LV ECV, with additionally elevated RV ECV in two patients. Among those with dTGA post Senning and elevated LV ECV, one patient had isolated non-sustained ventricular tachycardia documented during Holter-ECG. The two patients with elevated LV ECV and RV ECV developed severe dysfunction of the systemic RV and underwent ICD implantation, in one followed by recurrent atrial and ventricular arrhythmias and progressing heart failure, hospitalization, and cardiovascular death 4.0 years after CMR. One patient with ccTGA and elevated LV ECV developed severe heart failure leading to hospitalization and HTx. In those with normal LV ECV, adverse events included hospitalization due to cardiac decompensation in one patient with dTGA post Senning, and complete heart block requiring pacemaker implantation in one patient with ccTGA.

Discussion

In our study, increased LV ECV in TGA patients as compared to controls indicates the presence of diffuse myocardial fibrosis in the subpulmonary LV in the setting of a systemic RV. LV ECV was elevated above the upper limit of normal in the majority of TGA patients and was associated with a reduction in LV function. LV ECV was higher than RV ECV in this cohort.

It has been shown that focal myocardial fibrosis visualized with LGE imaging in the systemic RV correlates with ventricular dysfunction, cardiac arrhythmias, exercise intolerance, and clinical deterioration in patients with dTGA post atrial redirection (7–10) and ccTGA (8). However, the ability of LGE to assess diffuse fibrotic lesions is restricted, and only a few studies have reported on CMR T1 mapping-derived measures of diffuse myocardial fibrosis in TGA (11–14). In the study by Plymen et al., septal ECV was significantly higher in 14 dTGA patients post Senning or Mustard procedure than in age- and gender-matched controls, and was positively related to NT-proBNP and negatively to the chronotropic index during CPET. ECV of the RV wall was not measured for technical reasons (13). Broberg et al. found significantly higher levels of diffuse myocardial fibrosis in association with NT-proBNP in the systemic RV of 53 patients with dTGA post atrial redirection or ccTGA. In that cohort, elevated RV ECV was associated with adverse clinical outcomes, suggesting a role of fibrosis in the development of

heart failure (11). Both studies did not report ECV of the subpulmonary LV (11, 13). We evaluated diffuse myocardial fibrosis in the systemic RV as well as in the subpulmonary LV and found significantly higher LV ECV in TGA patients as compared to controls. The majority of patients (77%) had elevated LV ECV and had significantly lower LVEF than those with normal ECV values. Given that conventional heart failure therapies generally fail to improve RV function significantly (19), we anticipate that our findings will stimulate further research on the impact of the LV on morbidity and mortality, and on its role as a potential therapeutic target. The assessment of diffuse myocardial fibrosis by ECV may be useful in selecting patients who may potentially benefit from pulmonary artery banding by improving RV function and tricuspid regurgitation, thus bridging to transplantation or delaying listing for transplantation (20), or by training the LV of ccTGA patients for double switch operation. Furthermore, in our patient group, LV ECV was significantly higher than RV ECV. This is in line with Shehu et al. and Cheung et al. describing greater LV ECV than RV ECV in 10 and 31 dTGA patients post Senning or Mustard, respectively (12, 14). We agree with Cheung et al. that the finding of a higher fibrotic burden in the subpulmonary LV than in the systemic RV is intriguing and that the cause is not immediately apparent. Chronic volume unloading of the eccentrically compressed LV in relation to septal shift and LV diastolic dysfunction, and postcapillary pulmonary hypertension have been discussed as potential contributors, yet the role of these factors in the development of LV fibrotic remodeling remains to be studied further (14).

Cheung et al. in addition to elevated LV ECV also detected higher RV ECV values in the TGA cohort, although with greater involvement of the subpulmonary LV (14). In our study, a trend toward higher RV ECV in patients than in controls was seen, albeit without statistical significance. We found RV ECV to be elevated in almost one-third of the patients (31%). Both RVEF and LVEF were lower than in those with normal RV ECV values, but again these differences were not statistically significant. Apart from technical-methodological differences, the younger age of our TGA cohort in comparison to the abovementioned work by Broberg et al. and Cheung et al. may be contributive to the discrepancies in RV ECV between the studies. Furthermore, we speculate that due to the relatively small sample size, our study may have been underpowered to achieve statistical significance with regard to the differences in RV ECV between patients and controls and the association with impaired biventricular function. Future long-term studies on larger cohorts are required to substantiate our speculations and explore the role of age in the development of diffuse myocardial fibrosis in TGA.

Interestingly, we saw both LV ECV and RV ECV to be elevated in the two dTGA patients requiring ICD implantation due to a severe decline in RV function during follow-up, followed by cardiovascular death in one patient. This points to the importance of interventricular interactions also on the extracellular matrix level, and in turn underlines the potential value of both systemic and subpulmonary myocardial ECV as non-invasive markers for prognosis, risk stratification, and monitoring of disease and therapy in TGA. Moreover, we suspect that the mild, but frequently present LGE in 75% of the TGA patients reflects fibrosis burden that may contribute to the RV dysfunction seen in our cohort. Among patients with positive LGE in the systemic RV, 67% had elevated LV ECV, again pointing to interactions between systemic and subpulmonary ventricles on the tissue level. However, our data in relation to LGE were not statistically significant, which may be explained by the limited number of patients included and the consequent lack of power. Therefore, further research to support our results and their prognostic implications is warranted. The importance of ventriculo-ventricular-interactions and the role of the subpulmonary LV not only as a contributor to morbidity and mortality but also as a potential therapeutic target in right-sided CHD has been well recognized (21). Further investigations need to address the use of ECV measurements for the management of disease and treatment with the goal of preserving LV function or training the LV for systemic pressure in subaortic position.

Limitations

Our study is limited by the small sample size. Due to the lack of clinical indication for regular CMR examinations with contrast enhancement, longitudinal ECV data were unfortunately not available. Future long-term studies on larger cohorts to confirm our findings are required, and may potentially elucidate further differences between groups and associations between ECV and markers of heart failure. Healthy controls were younger compared to the patient group. However, an age-related increase in ECV is seen in individuals significantly older than the patients included in our study (22) and, thus, should not affect comparability between the two groups. Despite the application of the previously described LOI tool, especially helpful for T1 measurements in thin structures (17), and particular care at placing the LOI in the center of the myocardium of the respective subpulmonary ventricle, partial voluming with blood or fat may have caused potential overestimation of ECV. Given the lack of clinical indication for biopsy, we did not perform histological validation of our results.

Conclusions

In this study, LV ECV was significantly higher in TGA patients than in controls and was associated with LV dysfunction. Our data suggest that ECV measurements may serve as an imaging marker of heart failure in the setting of TGA with a systemic RV. Further research is necessary to evaluate the prognostic implications and the potential role of ECV in non-invasively monitoring disease progression and guiding therapy, aiming to maintain LV function or train the LV for subaortic location in TGA patients from infancy to adulthood.

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 the Charité—Universitätsmedizin Berlin. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NA-W-M: conception and design of the study, acquisition, analysis and interpretation of data, and drafting the manuscript. TFdS: implementation of LOI tool. TK and FB: conception and design of the study. DM: conception and design of the study, interpretation of data. All authors contributed to manuscript revision, read, and approved the final manuscript.

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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

References

1. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. (2007) 115(2):163–72. doi: 10.1161/CIRCULATIONAHA.106.627224

2. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, et al. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol*. (2001) 37(5):1170–5. doi: 10.1016/s0735-1097(01)01272-4

3. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, et al. Mortality in adult congenital heart disease. *Eur Heart J*. (2010) 31 (10):1220–9. doi: 10.1093/eurheartj/ehq032

4. Budts W, Roos-Hesselink J, Radle-Hurst T, Eicken A, McDonagh TA, Lambrinou E, et al. Treatment of heart failure in adult congenital heart disease: a position paper of the working group of grown-up congenital heart disease and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J*. (2016) 37(18):1419–27. doi: 10.1093/eurheartj/ehv741

5. Broberg CS, Burchill LJ. Myocardial factor revisited: the importance of myocardial fibrosis in adults with congenital heart disease. *Int J Cardiol*. (2015) 189:204–10. doi: 10.1016/j.ijcard.2015.04.064

6. Krieger EV, Valente AM. Heart failure treatment in adults with congenital heart disease: where do we stand in 2014? *Heart (British Cardiac Society)*. (2014) 100(17):1329–34. doi: 10.1136/heartjnl-2014-305667

7. Babu-Narayan SV, Goktekin O, Moon JC, Broberg CS, Pantely GA, Pennell DJ, et al. Late gadolinium enhancement cardiovascular magnetic resonance of the systemic right ventricle in adults with previous atrial redirection surgery for transposition of the great arteries. *Circulation*. (2005) 111(16):2091–8. doi: 10.1161/01.CIR.0000162463.61626.3B

8. Giardini A, Lovato L, Donti A, Formigari R, Oppido G, Gargiulo G, et al. Relation between right ventricular structural alterations and markers of adverse clinical outcome in adults with systemic right ventricle and either congenital

complete (after Senning operation) or congenitally corrected transposition of the great arteries. *Am J Cardiol.* (2006) 98(9):1277–82. doi: 10.1016/j.amjcard.2006.05.062

9. Ladouceur M, Baron S, Nivet-Antoine V, Maruani G, Soulat G, Pereira H, et al. Role of myocardial collagen degradation and fibrosis in right ventricle dysfunction in transposition of the great arteries after atrial switch. *Int J Cardiol.* (2018) 258:76–82. doi: 10.1016/j.ijcard.2018.01.100

10. Rydman R, Gatzoulis MA, Ho SY, Ernst S, Swan L, Li W, et al. Systemic right ventricular fibrosis detected by cardiovascular magnetic resonance is associated with clinical outcome, mainly new-onset atrial arrhythmia, in patients after atrial redirection surgery for transposition of the great arteries. *Circ Cardiovasc Imaging.* (2015) 8(5):e002628. doi: 10.1161/CIRCIMAGING.114.002628

11. Broberg CS, Valente AM, Huang J, Burchill LJ, Holt J, Van Woerkom R, et al. Myocardial fibrosis and its relation to adverse outcome in transposition of the great arteries with a systemic right ventricle. *Int J Cardiol.* (2018) 271:60–5. doi: 10.1016/j.ijcard.2018.04.089

12. Shehu N, Meierhofer C, Messroghli D, Mkrtchyan N, Martinoff S, Ewert P, et al. Diffuse fibrosis is common in the left, but not in the right ventricle in patients with transposition of the great arteries late after atrial switch operation. *Int J Cardiovasc Imaging.* (2018) 34(8):1241–8. doi: 10.1007/s10554-018-1338-9

13. Plymen CM, Sado DM, Taylor AM, Bolger AP, Lambiase PD, Hughes M, et al. Diffuse myocardial fibrosis in the systemic right ventricle of patients late after Mustard or Senning surgery: an equilibrium contrast cardiovascular magnetic resonance study. *Eur Heart J Cardiovasc Imaging.* (2013) 14 (10):963–8. doi: 10.1093/ehjci/jet014

14. Cheung YF, Lam WWM, So EKF, Chow PC. Differential myocardial fibrosis of the systemic right ventricle and subpulmonary left ventricle after atrial switch operation for complete transposition of the great arteries. *Int J Cardiol Heart Vasc.* (2020) 30:100612. doi: 10.1016/j.ijcha.2020.100612

15. Messroghli DR, Greiser A, Frohlich M, Dietz R, Schulz-Menger J. Optimization and validation of a fully-integrated pulse sequence for modified look-locker inversion-recovery (MOLLI) T1 mapping of the heart. *J Magn Reson Imaging.* (2007) 26(4):1081–6. doi: 10.1002/jmri.21119

16. Messroghli DR, Rudolph A, Abdel-Aty H, Wassmuth R, Kuhne T, Dietz R, et al. An open-source software tool for the generation of relaxation time maps in magnetic resonance imaging. *BMC Med Imaging.* (2010) 10:16. doi: 10.1186/1471-2342-10-16

17. Al-Wakeel-Marquard N, Ferreira da Silva T, Jeuthe S, Rastin S, Muench F, O H-Ici D, et al. Measuring myocardial extracellular volume of the right ventricle in patients with congenital heart disease. *Sci Rep.* (2021) 11(1):2679. doi: 10.1038/s41598-021-81440-z

18. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the society for cardiovascular magnetic resonance (SCMR) endorsed by the European association for cardiovascular imaging (EACVI). *J Cardiovasc Magn Reson.* (2017) 19(1):75. doi: 10.1186/s12968-017-0389-8

19. Roche SL, Redington AN. Right ventricle: wrong targets? Another blow for pharmacotherapy in congenital heart diseases. *Circulation.* (2013) 127(3):314–6. doi: 10.1161/CIRCULATIONAHA.112.155887

20. Poirier NC, Yu JH, Brizard CP, Mee RB. Long-term results of left ventricular reconditioning and anatomic correction for systemic right ventricular dysfunction after atrial switch procedures. *J Thorac Cardiovasc Surg.* (2004) 127(4):975–81. doi: 10.1016/j.jtcvs.2003.10.024

21. Tretter JT, Redington AN. The forgotten ventricle? The left ventricle in right-sided congenital heart disease. *Circ Cardiovasc Imaging.* (2018) 11(3): e007410. doi: 10.1161/CIRCIMAGING.117.007410

22. Liu CY, Liu YC, Wu C, Armstrong A, Volpe GJ, van der Geest RJ, et al., Evaluation of age-related interstitial myocardial fibrosis with cardiac magnetic resonance contrast-enhanced T1 mapping: MESA (multi-ethnic study of atherosclerosis). *J Am Coll Cardiol.* (2013) 62(14):1280–7. doi: 10.1016/j.jacc.2013.05.078

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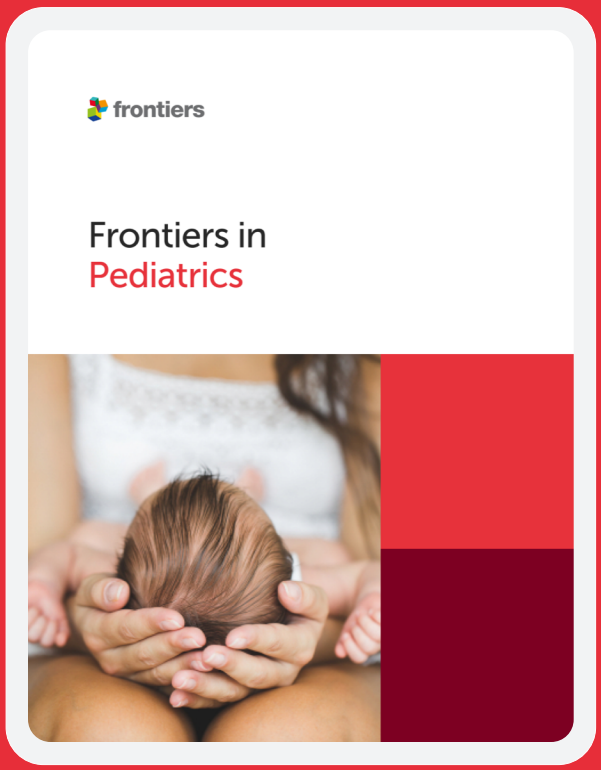

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