Cardiology in the Young

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Health-related quality of life in pre-school age children with single-ventricle CHD

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Abstract

Background: Little is known about health-related quality of life in young children undergoing staged palliation for single-ventricle CHD. The aim of this study was to assess the impact of CHD on daily life in pre-schoolers with single-ventricle CHD and to identify determinants of health-related quality of life. *Method:* Prospective two-centre cohort study assessing health-related quality of life using the Preschool Paediatric Cardiac Quality of Life Inventory in 46 children at a mean age of 38 months and 3 weeks. Children with genetic anomalies were excluded. Scores were compared with reference data of children with biventricular CHD. Multiple linear regression analysis was used to identify determinants of health-related quality of life. *Results:* Health-related quality of life in pre-schoolers with single-ventricle CHD was comparable to children with biventricular CHD. Preterm birth and perioperative variables were significant predictors of low health-related quality of life. Notably, pre-Fontan brain MRI findings and neurodevelopmental status were not associated with health-related quality of life. Overall, perioperative variables explained 24% of the variability of the total health-related quality of life score. *Interpretation:* Despite substantial health-related burden, pre-schoolers with single-ventricle CHD showed good health-related quality of life. Less-modifiable treatment-related risk factors and preterm birth had the highest impact on health-related quality of life. Long-term follow-up assessment of self-reported health-related quality of life is needed to identify patients with poorer health-related quality of life and to initiate supportive care.

Advances in surgical therapy and perioperative care have led to improved survival rates for children with single-ventricle CHD.[1] Reduction of long-term morbidity, improved health-related quality of life, and enhancement in psychosocial performance and neurodevelopmental outcome have become increasingly important in the care of this growing high-risk population.[2] Children with single-ventricle CHD are at risk for impaired health-related quality of life in adolescent years,[2–6] and into adulthood.[7] However, studies on health-related quality of life and its associated factors in pre-school age children are rare.[8,9,10]

Health-related quality of life was found to be comparable to a healthy reference population after stage I, with a decline for all dimensions after stage II, followed by improvement thereafter.[8] Others reported on poorer health-related quality of life for single-ventricle CHD patients as early as at the age of 3 years compared with healthy reference.[9] This seems to persist throughout school age and adolescents with mixed CHD.[6,11] Patients with single-ventricle CHD were found to be at greatest risk for poor perceived quality of life.[2,5]

Both, patient and medical factors, are known predictors for health-related quality of life. Despite complexity of the underlying CHD,[6,11] an underlying genetic defect and family income are negative predictors.[2,12,13] Other risk factors for poor health-related quality of life are predominantly treatment-related, such as longer circulatory arrest time, shorter time since last surgery or last hospitalisation, number of doctor visits, and tube feeding.[5,8,12]

The aim of this study was to examine the impact of patient-related and surgical variables on health-related quality of life at a time when disease burden is high due to mandatory surgical procedures.[1] We hypothesised that children with complex CHD undergoing staged

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cardiac surgery in early life would have lower health-related quality of life compared to patients with less severe CHD.

Materials and methods

Setting and study population

This study was part of a two-centre study of the University Paediatric Heart Centre Giessen, Germany – Centre A – and the University Children's Hospital Zurich, Switzerland – Centre B – among preschool-aged patients undergoing Fontan procedure for single-ventricle CHD.[14] The study protocol conforms to the ethical guidelines as reflected in approval by both local ethics committee. Written informed consent was provided by parents or caregivers at study entry.

Using a longitudinal design, the original study population of children with single-ventricle CHD without genetic comorbidities enrolled between August 2012 and July 2015 – details were published previously[14] – was followed for health-related quality of life assessment until the age of 3–4 years. From the original cohort, two patients were excluded: one moved away and another refused from participation. The follow-up rate was 97.9%, and the participation rate was 95.8%. Demographics, cardiac diagnosis, and surgical treatment variables of the excluded children did not differ from the included children, the data are not shown.

Demographic measures and clinical data

Demographics were derived from patient charts. Growth measures were taken at birth and transformed to World Health Organisation growth standard deviation scores.[15] Small for gestational age was defined as weight or length lower than the 10th percentile of reference data. Family status, defined as married/living together, or divorced, and the socioeconomic status were assessed as proposed by Largo et al.[16] Socioeconomic status was determined based on maternal education and paternal occupation, each scored from one to six, resulting in a score ranging from two to 12, with higher scores indicating higher socioeconomic status. Perioperative variables, that is cumulative length of hospital stay, cumulative length of ICU stay, cumulative duration of mechanical ventilation until stage II, number of cardiac medication at admission for stage I, II, and III, and the occurrence of complications – such as re-operations, catheter re-interventions, need for extra-corporal membrane oxygenation, or re-animation – were derived from patient charts and entered into a pre-defined database as described earlier.[14]

Surgical procedures

Standard of care was a three-staged procedure. Palliation at stage I was either a classical Norwood procedure or a shunt palliation, including modified Blalock–Taussig shunt, systemic ventricular to pulmonary artery shunt, pulmonary artery banding, followed by bidirectional cavopulmonary anastomosis, also known as Glenn procedure, at stage II. Other children were followed by the hybrid approach, undergoing catheter-guided stenting of patent arterial duct and surgical bilateral pulmonary banding as stage I, followed by a comprehensive stage II procedure including removal of pulmonary artery bandings and the patent arterial duct stent, aortic arch reconstruction, and bidirectional cavopulmonary anastomosis. Two patients did not undergo the Fontan procedure/stage III (complete separation of passive pulmonary blood flow) at the time of health-related quality of life assessment: one patient was heart transplanted after comprehensive stage II, and one patient was still awaiting the stage III operation.

Neurodevelopmental testing and brain MRI

Patients underwent neurodevelopmental assessment and brain MRI scan at a mean age of 26 months and 1 week (SD 14 weeks) with the third version of the Bayley Scales of Infant and Toddler Development, Bayley-III,[17] and a neurological examination by trained paediatric neurologists or developmental paediatricians. Severe developmental delay was indicated by Bayley-III scores below −2 SD, and mild/moderate developmental delay was defined as scores below −1 SD relative to the normative mean. The neurological examination focussed on motor functioning, graded as normal, reflex or tone abnormality, reflex and tone abnormality, or cerebral paresis, and on abnormalities in sight and hearing, with the overall result summarised in a single score.[18] Details on brain MRI and neurodevelopmental outcome were published earlier.[14,19]

Health-related quality of life

Health-related quality of life was assessed with the German version of the Pre-school Paediatric Cardiac Quality of Life Inventory by parental report.[20] All families were comfortable completing the questionnaire in German. The Paediatric Cardiac Quality of Life Inventory is a 51-item, five-scale generic instrument measuring the frequency of disease-related problems and severity of negative emotions about these by proxy report. The total score is calculated as the average score of the five scales. The physical scale assesses impact of the underlying CHD on physical capacity and functioning, for example, quality and quantity of physical activity, restlessness, and physical appearance, sweating, weight/eating problems, and frequency of pain experience. Disease impact on emotional wellbeing and behaviour is measured by the emotional scale, including anxiety, self-confidence, self-regulation, and reactions towards unfamiliar environment and medical interventions. The social scale assesses integration in the society and asks for the amount of peer contact, the amount of help needed, and the reaction of unrelated persons towards the child. The therapeutic scale assesses treatment burden, for example, implements needed, side effects of medication, how the child handles pain, and the frequency of medical visits. The functional scale estimates impact on everyday life, such as problem-solving approaches, restriction arising from the underlying CHD, apparent developmental delay, sleeping, recognition of performance limits, and the understanding of the heart disease. Higher scores relate to higher health-related quality of life in all scales. We used the computerised analysis tool, calculating transformed values of the raw data, ranging from 0 to 100. Of the reference group,[20] scores from 26 children with biventricular CHD, of which 16 were males, were in the target age range between 3 and 4 years, with mean age of 41 months 3 weeks, SD 13 weeks, and eligible for comparison.

Statistical analysis

Data were analysed with IBM SPSS Statistics for Macintosh, version 24.0, IBM Corp., Armonk, NY, United States of America. Descriptive statistics are presented as mean with SD or median with interquartile range for the respective dispersion of the data.

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Table 1. Patient characteristics (n = 46).

Centre A / Centre B	25 (54) / 21 (46)
Male sex	31 (67)
Race/ethnicity, Caucasian	46 (100)
Gestation age at birth (weeks)	39 2/7, SD 10 days
Pre-term infant	2 (4)
Small for gestational age	13 (28)
Head circumference at birth (SDS)	−0.34, SD 0.98
Prenatal diagnosis	25 (54)
Socioeconomic status (total score)	7 (6, 9)
Family status, divorced/separation	2 (4)
Bayley-III scales <85 points at 26 months, any	11 (24)
Neuroscore, pathologic at 26 months	16 (35)
Cardiac diagnosis	
Hypoplastic left-heart syndrome	26 (57)
Non-hypoplastic left-heart syndrome with left-ventricular dominance	9 (20)
Pulmonary atresia with ventricular septum defect	2 (4)
Pulmonary atresia with intact ventricular septum	1 (2)
Tricuspid valve atresia	3 (7)
Double inlet left-ventricle with transposition of the great arteries	1 (2)
Levo-transposition of the great arteries with hypoplastic left ventricle	1 (2)
Imbalanced atrioventricular septal defect	1 (2)
Non-hypoplastic left-heart syndrome with right-ventricular dominance	11 (24)
Borderline left ventricle/shone complex	4 (9)
Double outlet right ventricle with transposition of the great arteries	2 (4)
Imbalanced atrioventricular septal defect	5 (11)
Surgical approach stage I*	42 (91)
Age, days	9, SD 11
Hybrid approach stage I	25 (54)
Norwood I	6 (13)
Shunt operation without cardiopulmonary bypass operation	11 (24)
Neonatal cardiopulmonary bypass operation	9 (20)
Surgical approach stage II	46 (100)
Age, months	4.75, SD 1.43
Comprehensive stage II	26 (57)
Glenn, bidirectional	20 (43)
Surgical approach stage III**	44 (96)
Age, months	32.21, SD 6.42
s/p re-animation or extra-corporal membrane oxygenation	8 (17)
Need for re-operation	24 (52)
Need for re-intervention	23 (50)
Surgery severity score (0–9)	5 (3, 6)

Data are presented as n (%), mean ± SD or median (interquartile range), SDS, standard deviation score.
*n = 42, Four children (9%) with balanced haemodynamic state because of pulmonary artery stenosis did not undergo stage I procedure and were later palliated with bidirectional cavopulmonary anastomosis, known as Glenn procedure, at stage II
**n = 44, one did not undergo stage III because of balanced haemodynamics; one patient received heart transplantation

Normality of data was tested with the Shapiro–Wilk test. Internal consistency of various measures was tested with the Cronbach's α. The Welch's t-test was applied to compare Preschool Paediatric Cardiac Quality of Life Inventory scores of our patients with the reference data of 26 patients with biventricular CHD. Between-groups comparisons were performed with χ^2 tests in case of binary variables. To correct for multiple testing, a Bonferroni correction for group comparison was applied. Linear regression analysis was used to test for statistical relevance of association with health-related quality of life. The natural logarithm was calculated for non-normally distributed data. Collinearity among factors entered in the regression analysis was identified with Pearson's or Spearman's correlation for the respective dispersion of the data. Owing to the exploratory nature of the correlational analyses among candidate factors for the regression analyses, we did not adjust for multiple testing. In the first step, univariate linear regression for each factor was assessed. Variables with p-value <0.1 in the univariate analysis were included in the second step in a multi-variate linear regression model for each Preschool Paediatric Cardiac Quality of Life Inventory dimension. A maximum of four variables were allowed in each regression model as given by the sample size. A surgery severity score reflecting the broad spectrum of medical variables was thus calculated as sum of median split-half of each medical factors, such as cumulative length of hospital stay, cumulative length of ICU stay, mechanical ventilation, number of cardiac medications at stages I, II, and III, status post re-animation or need for extra-corporal membrane oxygenation, number of re-operations, and re-interventions, encoding the lower as zero and the higher as one. The score ranged from zero to nine, with higher scores indicating greater complexity. A two-sided significance level of $p < 0.05$ was applied.

Results

Patient characteristics

Detailed patients' characteristics, cardiac diagnosis, and surgical procedures are presented in Table 1. Mean age at follow-up of the 46 patients included was 38 months and 3 weeks (SD 14 weeks), with a median time after the patient's last operation of 10 months and 3 weeks; interquartile range 6.67, 29.24 months. Demographic characteristics did not differ among the two centres, data not shown.

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Neurodevelopmental outcome and brain MRI findings

Mean Bayley-III cognitive composite score was 97, SD 12, ranging from 65 to 120. Severe and mild/moderate developmental delay was present in 4% (n = 2) and 7% (n = 3), respectively. All Bayley scales were intercorrelated: cognitive composite score with language composite score $r = 0.69$, $p < 0.001$; cognitive composite score with motor composite score $r = 0.75$, $p < 0.001$; language composite score with motor composite score $r = 0.66$, $p < 0.001$. Neurological examination revealed mild abnormalities such as reflex abnormalities or muscular hypotonia in 16 patients (35%). None of the patients were subject to major neurological handicap, that is cerebral palsy, deafness, or blindness.

From 45 patients undergoing a brain MRI scan, 17 patients (38%) had at least one abnormality, including ventriculomegaly or atrophy (n = 10), status post infarction (n = 9), white matter injury (n = 5), suspected hypoxic brain injury (n = 2), with multiple findings in eight patients (18%). Brain MRI scan was not feasible in one patient due to an MRI-incompatible pacemaker.

Health-related quality of life and associated factors

Overall, health-related quality of life of our population was favourable (Table 2). Health-related quality of life of our single-ventricle CHD cohort was comparable to the reference data of patients with biventricular CHD. All differences were not significant both with Bonferroni correction and without.

All Preschool Paediatric Cardiac Quality of Life Inventory subscales showed acceptable to excellent internal consistency reflected by following Cronbach's α values: total score: 0.94; physical: 0.85; emotional: 0.70; social: 0.85; therapy: 0.73; functional: 0.67 and were eligible for the risk factor analyses.[21] Given the high collinearity among Bayley-III scales, only the cognitive composite score was included for the regression analysis. Furthermore, the Apgar at 5 minutes showed high collinearity with the risk factor preterm birth ($r = 0.50$, $p < 0.001$). The latter was included in the subsequent analysis. Results of the regressions analysis are given in Table 3. Perioperative variables were important determinants for all Preschool Paediatric Cardiac Quality of Life Inventory dimensions at 3–4 years of age in the univariate analysis (Supplementary Table S4). Interestingly, the emotional score was associated with head circumference at birth, but not with any perioperative candidate variables. The total score was associated with length of ICU stay, mechanical ventilation, and number of cardiac medication after stage II and stage III. The same variables were significant determinants for the physical score, which was additionally associated with cumulative length of hospital stay. Lower social, therapy and functional health-related quality of life were all associated with longer ICU stay, and greater number of cardiac medication after stage II and stage III, whereas a status of pre-term birth also predicted poor therapeutic health-related quality of life.

To adjust for the small sample size in the multi-variate model, the surgery severity score reflecting overall medical case complexity was entered. The score showed acceptable internal consistency (Cronbach's α: 0.67). Multi-variate linear regression identified the surgery severity score as the only independent associated factor for the total health-related quality of life score, the physical score, and the social score (Table 3). Preterm birth and a higher surgery severity score were independently associated with lower scores in the therapy dimension. Preterm birth was the only remaining factor in the multi-variable analysis for the functional dimension, although there was no collinearity between preterm birth and the surgical severity score.

Health-related quality of life scores were neither associated with CHD-related pathological brain MRI findings, pathological neuroscore, nor with mild/moderate neurodevelopmental delay. Health-related quality of life was independent of socioeconomic status, family status, prenatal diagnose, small for gestational age or surgical approach (all $p > 0.05$).

Table 2. Comparison of health-related quality of life between the sample and the reference cohort

		Single-ventricle CHD	Biventricular CHD[20]	
		Mean (SD)	Mean (SD)	
	Range	n = 46	n = 26	p-value
Male gender, n (%)		31 (67%)	16 (62%)	0.618
Total	51–255	196.83 (21.50)	203.95 (36.40)	0.370
Physical	16–80	62.17 (8.25)	63.33 (14.74)	0.715
Emotional	11–55	40.52 (5.52)	14.74 (7.53)	0.614
Social	9–45	37.89 (5.07)	37.73 (6.19)	0.910
Therapy	6–30	23.98 (3.26)	24.04 (3.73)	0.944
Functional	9–45	31.63 (6.19)	31.64 (7.40)	0.995

Group differences were tested with the Welch's t-test for continuous variables and with the χ^2 test for binary variables.

Discussion

In this study, overall health-related quality of life in young children with single-ventricle CHD was found to be favourable. In contrast to our hypothesis and findings of other studies, health-related quality of life was comparable to children with biventricular forms of CHD.[2,5]

Despite overall good health-related quality of life in children with mixed CHD at pre-school age,[6,11,12] children with single-ventricle CHD seem to be at greatest risk for less favourable health-related quality of life.[2,4–6] Goldberg et al reported on lower quality of life accompanied by poor functional status in single-ventricle CHD in comparison to healthy controls at 3 years of age.[9] An important difference to this particular study despite the comparison to healthy children, is the exclusion of children with genetic syndromes in our study, which are known to be at greatest risk for impaired quality of life and the comparison to healthy children.[12]

We identified treatment-related variables as important determinants of health-related quality of life, reflected in the association of the surgery severity score with the Preschool Paediatric Cardiac Quality of Life total score. This finding is in line with the studies investigating health-related quality of life reports of school-aged children and adolescents with mixed CHD, where the number of doctor visits and cumulative hospital stay were identified as significant associated factors of health-related quality of life,[5,13] whereas initial surgical risk score had no impact on outcome in adolescence.[5] These findings suggest that variability in complexity of the treatment courses influence prospective health-related quality of life, rather than the nature of the cardiac diagnose in a subgroup of single-ventricle CHD.

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Table 3. Associated variables for lower health-related quality of life

	Total score		Physical score		Emotional score		Social score		Therapy score		Functional score	
	Univariate	Multivariate adj R^2=0.24	Univariate	Multivariate adj R^2=0.28	Univariate	Multivariate adj R^2=0.06	Univariate	Multivariate adj R^2=0.18	Univariate	Multivariate adj R^2=0.22	Univariate	Multivariate adj R^2=0.15
	ß, SE (R^2)	ß, SE	ß, SE (R^2)	ß, SE	ß, SE (R^2)	ß, SE	ß, SE (R^2)	ß, SE	ß, SE (R^2)	ß (SE)	ß, SE (R^2)	ß, SE
Male sex	2.02, 6.83 (0.002)		−5.93, 5.96 (0.02)		−3.16, 4.01 (0.01)		0.93, 1.61 (0.008)		0.66, 1.03 (0.009)		1.83, 1.95 (0.02)	
Pre-term infant	−28.57, 15.12 (0.08)		13.16, 11.17 (0.03)		10.24, 6.98 (0.05)		−5.11, 3.62 (0.04)		**−5.21, 2.25 (0.11)***	**−5.48, 2.08***	−8.50, 4.34 (0.08)	**−28.86, 4.14***
Head circumference at birth	**−5.59, 3.21 (0.06)**	**−1.63, 3.07**	**−1.99, 1.24 (0.06)**	**−0.75, 1.16**	**−1.68, 0.81 (0.09)***	**−1.27, 0.90**	−0.89, 0.77 (0.03)		−0.17, 0.50 (0.002)		−0.73, 0.95 (0.01)	
Bayley-III CCS	0.31, 0.27 (0.03)		0.03, 0.10 (0.002)		0.06, 0.07 (0.02)		0.06, 0.06 (0.02)		0.07, 0.04 (0.06)		0.03, 0.08 (0.003)	
Pathologic neuroscore	3.95, 6.71 (0.008)		0.08, 2.58 (0)		1.57, 1.71 (0.02)		−0.17, 1.59 (0)		0.73, 1.01 (0.01)		0.78, 1.94 (0.004)	
CHD-related finding in brain MRI‡	−5.27, 6.55 (0.008)		−2.23, 2.39 (0.02)		0.51, 1.72 (0.02)		−0.99, 1.59 (0.009)		−1.04, 1.01 (0.024)		−3.22, 1.88 (0.04)	
Prenatal diagnose	−4.53, 6.40 (0.01)		−0.21, 2.47 (0)		−0.91, 1.65 (0)		−1.43, 1.50 (0.02)		−1.004, .096 (0.02)		−0.42, 1.85 (0.001)	
Socioeconomic status	4.19, 8.22 (0.006)		1.01, 3.16 (0.002)		−0.58, 2.12 (0.002)		0.62, 1.94 (0.002)		1.25, 1.24 (0.02)		1.91, 2.36 (0.02)	
Family status, married	3.32, 12.97 (0.001)		4.36, 5.99 (0.01)		−1.02, 4.03 (0.001)		1.98, 3.69 (0.006)		−1.07, 2.38 (0.005)		−2.48, 4.51 (0.007)	
Hypoplastic left-heart syndrome	**−9.77, 6.30 (0.05)**	**1.52, 6.31**	**−4.20, 2.40 (0.07)**	**2.98, 3.19**	−2.00, 1.6 (0.03)		**−2.85, 1.46 (0.08)**	**0.95, 1.55**	−0.39, 0.98 (0.004)		−1.45, 1.85 (0.01)	
Hybrid procedure stage I	−8.61, 6.28 (0.04)		**−4.44, 2.37 (0.07)**	**−3.89, 2.93**	−2.00, 1.61 (0.03)		−1.17, 1.5 (0.01)		0.82, 0.96 (0.02)		**−3.09, 1.79 (0.06)**	**−2.2, 1.75**
Time since last operation	−0.35, 0.26 (0.04)		−0.10, 0.10 (0.02)		−0.10, 0.07 (0.05)		−0.08, 0.06 (0.03)		−0.03, 0.04 (0.02)		0.03, 0.08 (0.003)	
Surgery severity score	**−5.14, 1.21 (0.29)*** **	**−5.04, 1.46****	**−2.04, 0.46 (0.31)‡**	**−2.09, 0.55****	**−0.68, 0.36 (0.08)**	**−0.49, 0.39**	**−1.01, 0.30 (0.18)*** **	**−0.91, 0.34****	**−0.53, 0.20 (0.13)****	**−0.55, 0.19****	**−0.82, 0.40 (0.09)***	**−0.72, 0.39**

Bold indicates the variables entered in the multi-variate model. The surgery severity score reflects a summary of following surgical variables: cumulative length of hospital stay, cumulative length of ICU stay, mechanical ventilation, number of cardiac medications at stages I, II, and III, status post re-animation or need for extra-corporal membrane oxygenation, number of re-operations and re-interventions

ß unstandardised beta, SE, standard error, R^2, adjusted coefficient of determination. Bold numbers represent significant associations. Of following non-normally distributed variables, the natural logarithm was used: socioeconomic status, total hospital stay, total ICU stay, cumulative time of mechanical ventilation, number of cardiac medication, number of re-operations and re-interventions. ECMO, extra-corporal membrane oxygenation

*p<0.05, **p<0.01, ***p<0.001, n=46

‡n=45 (MRI scan not feasible in one patient with MR-incompatible pacemaker)

#n=44 (one patient had heart transplantation, one patient awaiting stage III)

Pre-term birth was associated with lower treatment and functional dimension of quality of life. Despite being at risk for a complicated course, greater parenting stress in families of pre-term infants was previously shown.[22] These families are challenged with numerous medical and developmental needs in addition to the palliation of the underlying CHD. These additional stressors may influence parental report, as elevated state of anxiety was shown to alter perception of a child's health-related quality of life.[23] Interestingly, socioeconomic status and family status, as a surrogate for social integrity, were not associated with health-related quality of life in our cohort. The relatively high socioeconomic status, with only 20% parents with low socioeconomic status, and few number of divorced couples (4%) in our sample might explain this finding.

Neurocognitive functioning at 26 months did not predict health-related quality of life at 3–4 years of age. This is in contrast to the studies in older CHD patients showing deterioration of health-related quality of life at school-age and adolescence.[1,5,7,24] The rather minor neurodevelopmental impairments found in our young population and the disability paradox might account for this finding to some extent.[25] However, minor functional disabilities may not be relevant until school-aged children grow into a more and more demanding environment, when executive functions, demanding communication skills, visuo-constructive functions, and fine motor skills become more important for academic achievement and peer interaction.[11]

The results of this study have several implications for future research and clinical management. Treatment-related variables were associated with health-related quality of life. Thus, it is essential to provide comprehensive care during the vulnerable clinical phase with high treatment burden, and to identify patients with special needs. Standardised long-term follow-up assessments are warranted exploring the patients' self-reported health-related quality of life of clinical significance and to plan for interventions if needed. These follow-up visits can ideally be combined with routine cardiac examinations at the same centre to minimise time and effort for the accompanying parents. Future research evaluating family emotions towards cardiac diagnosis and treatment will allow further insight in this underlying comorbidity in children with single-ventricle CHD.

The strengths of our study are the prospective study design and the homogeneous sample regarding cardiac diagnosis and age at assessment. However, this study is subject to several limitations. One limitation arises from the small sample size, limiting the statistical power of the study. From the original reference data,[20] 26 cases with biventricular CHD aged 3–4 years at parental report were eligible for the analysis. The different group size is a limitation to the statistical analysis. The reference data were tested somewhat earlier, and improved patient care might have biased some of the results. Our multi-variate models explained 6–28% of variance in health-related quality of life. Additional factors that may also influence health-related quality of life such as financial problems or the parents' well-being were not evaluated in this study. Although the patients' demographic characteristics did not differ between the two study centres, some disparity in living condition among the two countries cannot be excluded. Another limitation arises from lacking details on parental stress, for example depression and anxiety levels. Parents stress levels have been shown to remain moderate to high in CHD patients hospitalised at the cardiac ICU after cardiac surgery regardless of the illness severity,[26] and may alter their perception of the child's health-related quality of life. Future research is warranted to further explore impact of these variables on the parents' rating. The surgical complexity score used in the analysis was developed to identify patients with highest disease burden in this sample with complex CHD. The score did show statistical reliability, however, its application in other population warrants further investigations.

Conclusions

The complex treatment-related and the psychosocial environment in children with single-ventricle CHD and evaluation by parental report make it difficult to draw conclusions on health-related quality of life. However, our finding of comparable health-related quality of life in early childhood in single-ventricle CHD without genetic abnormalities compared to biventricular CHD is encouraging. Treatment-related variables and preterm birth are important determinants of health-related quality of life at 3–4 years of age. It is important to recognise social concerns and provide comprehensive support to the children and their families during the time of high disease burden. To better understand the evolution of health-related quality of life and its associated factors, a follow-up assessment at school age is planned.

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Conflicts of Interest. None.

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