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Motor outcome, executive functioning, and health-related quality of life of children, adolescents, and young adults after ventricular assist device and heart transplantation

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Abstract

Objective: The aim of the current study is to measure long-term executive function, motor outcome, and QoL in children, adolescents, and young adults after VAD and Htx.

Methods: Patients were examined during routine follow-up. Investigation tools were used as follows: Examination for MND of motor outcomes, Epitrack® for attention and executive functioning, and Kidscreen-52 and EQ-5D-5L questionnaires for QoL. Additional data were retrospectively obtained by an analysis of patient medical records.

Results: Out of 145 heart transplant recipients at the department of pediatric cardiology of the University Hospital Munich, 39 were implanted with a VAD between 1992 and 2016. Seventeen (43.6%) patients died before or after Htx; 22 (56.4%) patients were included in our study. Mean age at transplant was 9.52 years (range: 0.58-24.39 years, median 9), and the mean follow-up time after Htx was 6.18 years (range: 0.05-14.60 years, median 5.82). MND examination could be performed in 13 patients (normal MND: n = 11, simple MND: n = 1, complex MND: n = 1). Executive functioning was tested in 15 patients. Two (13.3%) patients had good results, six (40%) average results, three (20%) borderline results, and four (26.7%) impaired results. QoL (Kidscreen n = 7, EQ-5D-5L n = 8) was similar to a healthy German population.

Conclusion: Motor outcome, executive functioning and QoL in survivors of VAD bridging therapy and Htx can be good, though underlying diseases and therapies are associated with a high risk of cerebral ischemic or hemorrhagic complications.

Abbreviations: B-BVAD, Berlin Heart® biventricular VAD; B-LVAD, Berlin Heart® left heart VAD; BTR, bridge to recovery; BTT, bridge to transplantation; BWGS, Bland-White-Garland syndrome; DCM, dilated cardiomyopathy; GMFCS, Gross Motor Function Classification System; HLHS, hypoplastic left heart syndrome; H-LVAD, HeartWare left heart VAD; HRQoL, health-related quality of life; HTx, heart transplantation; ISHLT, International Society for Heart and Lung Transplantation; MACS, Manual Ability Classification System; M-BVAD, Medos® biventricular VAD; M-LVAD, Medos® left heart VAD; MND, minor neurological dysfunction; NCCM, non-compaction cardiomyopathy; QoL, quality of life; RCM, restrictive cardiomyopathy; VAD, Ventricular assist device; VAS, visual analogue scale.

Gerstl and Dalla-Pozza contributed equally.

KEYWORDS
cognitive outcome, executive functioning, health-related quality of life, motoric outcome, neurological outcome, Pediatric heart transplantation, ventricular assist device

1 | INTRODUCTION

The first human heart transplant was performed at the Groote Schuur Hospital in Cape Town on December 3, 1967.[1] Since then, this therapy has gained importance for the treatment of end-stage heart failure, both in adult and in pediatric patients.[2,3] Increasing survival rates, associated with tailored immunosuppression, are considered to be responsible for this trend.[4,5] Nowadays, HTx is an established treatment option for terminal heart failure in children.[6,7] In 2014, about 11 000 pediatric Htxs worldwide were registered by the ISHLT.[7]

However, long waiting times for a suitable pediatric donor organ underline the importance of optimizing therapy for patients on the wait list. Thus, mechanical circulatory support is of increasing use.[4,7]

VAD are able to bridge time until transplantation (BTT), or in some cases, until recovery (BTR). According to the ISHLT, nearly 30% of pediatric patients treated for terminal heart failure between 2009 and 2015 needed an assist device as bridge to transplantation.[5]

Despite satisfactory initial results of this therapy, long-term consequences should be assessed.[8,9] Assist device implantations, as well as cardiac transplantations and prolonged waiting times, can have a severe impact on the psychological and physiological development, leading to a limited integration of young adults into their educational, professional, and social environments.[9-13] Risk factors for neurological and cognitive impairment around this therapy concept can be classified as preoperative (such as cerebral hypoperfusion due to congestive heart failure), intra-operative (eg, due to extracorporeal circulation and analgesic drugs), and postoperative (eg, cerebral hypoperfusion and immunosuppressive drugs).[14-18] Further, VAD therapy poses additional risks due to the device implantation, required anticoagulation, and increased risk for thrombosis, but also potential benefits for the preservation of intellectual function.[13,19-21]

Therefore, the aim of this study is to investigate motor outcomes and executive functioning, as well as the HRQoL in children, adolescents, and young adults after VAD and Htx.

2 | PATIENTS AND METHODS

All pediatric patients who received an assist device (BTT or BTR) at the LMU Munich, University Hospital between 1992 and 2016 were included and their medical records were reviewed.

To assess the motor and executive functioning outcomes, as well as the HRQoL, a protocol, including the specific tests outlined below, was developed.

This study was approved by the local institutional ethics committee and was executed according to the Declaration of Helsinki (1997) and subsequent revisions. Informed consent was obtained from all individual participants included in the study. Our patients were examined in the setting of our outpatient clinic during a routine follow-up. Intraobservational and interobservational variability was assessed by comparing results. Reliability was reported and is supported by previous studies.[22-28]

2.1 | Assessment of MND

To assess motor function we utilized testing for MND. It is based on the Touwen Infant Neurological Examination, originally developed to monitor development in children.[29] This standardized neurodevelopmental examination is mainly part of clinical practice, but it is also used in study protocols, particularly in neonatology, to investigate and follow up on the development of preterm infants and newborns at risk.[30]

The examination for MND includes standard items such as reflexes, cranial nerve health motor and sensory functioning, body tone, and coordination. It contains eight domains of appreciation: posture and muscle tone, reflexes, choreiform dyskinesia, coordination, fine manipulative ability, associated movements, sensory deficits, and cranial nerve function. It includes for these items an age-specific appreciation of the child's performance during examination with special attention given to involuntary and associated movements. Each domain is assessed by several different tests and can be appreciated separately, according to the child's performance. Subsequently, a distinction can be made between a normal finding, and a simple or a complex MND, based on the number of dysfunctional domains.

The accuracy and validity of this method were reported in previous studies, showing a good to excellent test-retest reliability.[25,30,31]

There are two different forms of MND: simple and complex MND. This classification is based on the number of dysfunctions present (before the onset of puberty) or on the type of dysfunction (after the onset of puberty). A simple MND is considered to be in the range of a “normal” neurological performance and is also described as “minor neurological difference”. In contrast, the presence of a complex MND reflects a neurological dysfunction and, regarding developmental aspects, is strongly related to learning and behavioral disorders.

We used the MND examination forms to assess patients aged 6 years and older to detect even slight neurological deviations. All patients or the parents of underage children signed an informed

consent form for video documentation, in order to validate the results by a pediatric neurologist (LG).

2.2 | Epitrack®

To assess the executive functioning of our patients, the Epitrack® test was used. This is a cognitive test instrument originally developed as a 15-minute screening tool for the detection and tracking of cognitive side effects of both antiepileptic drugs and seizures in patients with epilepsy.[32] The EpiTrack® test comprises six subtests; these are borrowed from other well-established tests: The German "Kurztest für cerebrale Insuffizienz" (subtest 1); the Trail Making Test (subtests 2 and 3); the Chapuis maze test (subtest 4); the German "Leistungsprüfsystem" (subtest 5); and the German Wechsler adult intelligence scale—revised).[26] The 6 subtests are (examined function): (a) interference (response inhibition), (b) connecting numbers (visual planning and psychomotor speed), (c) connecting numbers and circles (2 + mental flexibility and working memory), (d) maze test (visuomotor anticipation), (e) word fluency (access to the lexicon using a phonematic algorithm), and (f) inverted digit span (working memory).[33] The EpiTrack® test allows for the quick and simple screening of attention and executive functioning, including working memory.[26,32] The reliability of the Epitrack® test has been reported in previous studies, examining 277 (Epitrack® junior) and 689 (Epitrack® adult) patients in total. Some of these patients were retested after a few months, achieving a retest reliability of $r = 0.78$ and $r = 0.90$.[22,26,27] This test has been described in previous studies as a valid and reliable screening tool for the assessment of executive functioning.[26]

The Epitrack® test is available in two different versions: a junior (for children from 6 to 18 years of age) and an adult version. Total scores in the junior version range from 6 to 56 points and are classified into four categories: good (≥36 points), average (31-35 points), borderline (29-30 points), and impaired (≤28 points). The adult version is scored within 9-49 points, as good (≥39 points), average (32-38 points), borderline (29-31 points), and impaired (≤28 points).

As the Epitrack® test is time-efficient, shown to be a sensitive instrument for detecting problems with attention and executive functions, and has also been used in research fields beside epilepsy and schizophrenia, we decided to include the Epitrack® test in our study.[33-35]

2.3 | Assessment of quality of life

The QoL of children, adolescents, and young adults was assessed with the self- and proxy version of the Kidscreen-52 questionnaire (≤18 years). It was completed by the patient (minimum age: 8 years) and their parents (for patients of all ages). The EQ-5D-5L was also used, completed by the patients themselves if patients were adults at the time of follow-up.

2.3.1 | The Kidscreen-52 Questionnaire

The Kidscreen-52 was developed by the Kidscreen Group Europe as a generic and cross-cultural instrument, which is available in 32 languages (including German).[23,36,37] It consists of 10 dimensions: (a) physical well-being, (b) psychological well-being, (c) moods and emotions, (d) self-perception, (e) autonomy, (f) parent relations and home life, (g) financial resources, (h) social support and peers, (i) school environment, and (j) social acceptance and bullying. Each scale consists of 3-10 items (52 items in total). For comparisons of results, there is a representative Kidscreen population of 22 827 children and adolescents (8-18 years) available.[37] The reliability and validity of the Kidscreen questionnaire have been reported in previous studies.[23,37]

2.3.2 | EQ-5D-5L

The EQ-5D-5L was developed by the EuroQoL Group as a standardized, generic measure of health status.[38] It consists of a descriptive system and a VAS. The descriptive system comprises five dimensions: (a) mobility, (b) self-care, (c) usual activities, (d) pain/discomfort, and (e) anxiety/depression, each associated with 5 ordinal levels: no/slight/moderate/severe or extreme problems.

The VAS is a vertical line numbered 0-100 with end-points labeled as "the best health you can imagine" (100) and "the worst health you can imagine" (0). The person is asked to mark an X on the scale to indicate how his/her health is on the day of assessment. Calculated index values are compared to an average German population, with index values ranging from 0.205 to 1.00 (1.00 indicating full health). The reliability and validity of the EQ5D-5L questionnaire were reported in previous studies.[39-42] It also has been assessed via the examination of patients with several different diseases in numerous countries and is used in the INTERMACS report, which describes the QoL of patients treated with assist devices.[43-47]

2.4 | Statistical analysis

Statistical analysis of the data was performed with IBM SPSS Statistic software (version 24. IBM Corporation) and Microsoft Excel (version 12.1.0 for Mac). Analysis of the Kidscreen data was performed according to the instruction on the Kidscreen Manual.[48] The EQ-5D-5L index values were calculated with the EQ-5D-5L Crosswalk Index Value Calculator, which can be downloaded from the EuroQoL website (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/).[49] Descriptive analysis was carried out for the entire cohort with continuous variables reported as percentage, mean, median, range, and standard deviation. *P*-values were calculated using the nonparametric Wilcoxon signed-rank test.

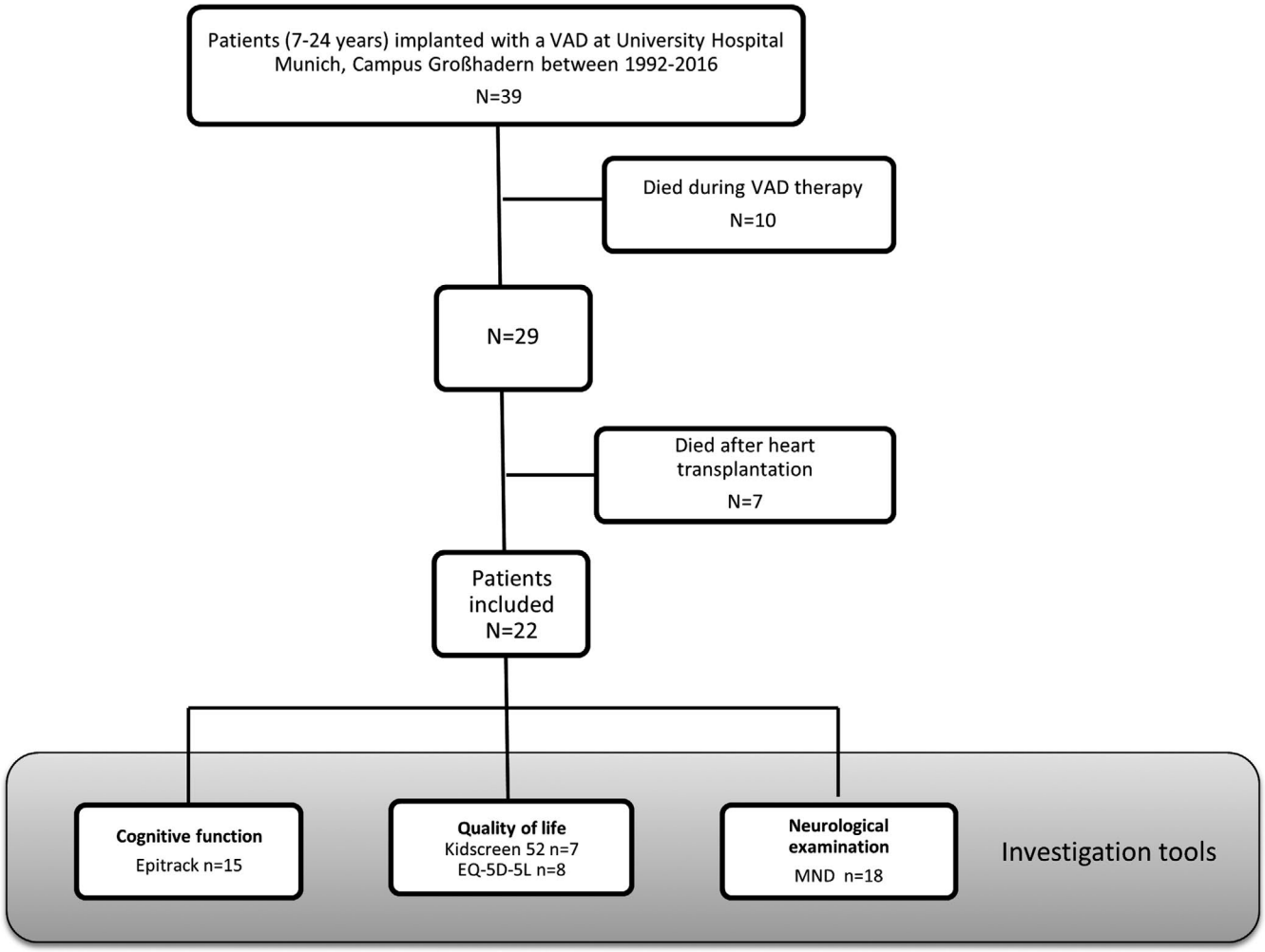

FIGURE 1 Description of inclusion process

3 | RESULTS

3.1 | Patients' characteristic and clinical data

Out of a total of 145 pediatric heart transplant patients, 39 patients (20 males/19 females), ages ranging from 7.34 to 24.31 years old (mean 8.86, median 8.51), were implanted with a VAD at the department of pediatric cardiology of the Großhadern campus of the LMU hospital in Munich between 1992 and 2016 (Figure 1). Out of these 39 patients, 28 received the assist device as a bridge to transplantation, 1 patient as a BTR, while 10 patients died during the VAD therapy.

Most patients were bridged using a pulsatile flow device (Berlin Heart Excor®: n = 23, Medos VAD: n = 8, and Novacor-LVAD: n = 2). Continuous flow devices were used in 5 patients (HeartWare VAD: n = 4 and Jarvik 2000: n = 1). One patient became an ECMO implanted as a bridge to transplantation, without using a further assist device.

On average, patients spent 74.26 days with a VAD (median 29 days [1-484 days]). Eleven patients required ECMO therapy before or after their VAD therapy.

Seven patients died following Htx. The leading cause of death is specified in Table 1. The 1-year post-transplantation survival percentage of the sample was 92.86%, 85.71% after 5 years, and 78.57% after 10 years. Demographics of the 22 included patients are shown in Table 2 and Figure 1.

3.2 | Neurological examination using the assessment for MND

The MND assessment is considered to be an excellent tool for detecting and classifying neurological dysfunction in seemingly healthy patients.[50] Some of the patients had known neurological diseases. For this reason, two patients with a known unilateral motoric deficit were classified using more common motor tests. Specifically, the GMFCS (http://www.klinikum.uni-muenchen.de/mashup/blaetterkatalog_ispz_gmfcs/blaetterkatalog/pdf/complete.pdf) and Manual Ability classification system-MACS (http://www.macs.nu) were employed. Both patients were classified as GMFCS 1 and MACS 2. Etiology of the unilateral motor deficits is a presumed complication of the period of time after VAD

TABLE 1 Study population (retrospective data)

Patient	Sex	Age at VAD implantation (y)	VAD time (d)	ECMO time (d)	Time spent on the waitlist (d) until heart transplantation[a]	Underlying disease prior to heart failure	Assist device type	Death cause
1	F	7	0	1	47	GR	ECMO	CAV
2	M	1	26	0	33	NCCM	B-LVAD	PTLD
3	F	12	189	0	177	MC	B-BVAD	P
4	F	1	115	6	187	DCM	B-LVAD	S
5	M	18	2	0	35	MC	Novacor-LVAD	GR
6	M	16	2	0	2	MC	Novacor-LVAD	GF
7	M	0	44	0	NT	DCM	N/A	N/A
8	F	3	21	0	NT	HLHS	M-BVAD	S
9	M	15	14	0	17	DCM	M-LVAD	GR
10	F	3	16	0	NT	DCM	M-LVAD	ICH
11	M	1	38	13	NT	DCM	M-BVAD	ICH
12	M	2	58	0	NT	MC	B-BVAD	ICH
13	F	1	18	0	NT	DCM	B-LVAD	ICH
14	M	15	46	0	NT	MC	Jarvik 2000	RVHF
15	M	16	8	0	NT	MC	B-BVAD	HS
16	F	14	37	1	NT	MC	B-BVAD	ICH
17	F	17	61	7	NT	MFB	H-LVAD	ICH

Abbreviations: CAV, cardiac allograft vasculopathy; GF, graft failure; GR, graft rejection; HS, hemorrhagic shock; ICH, intracerebral hemorrhage; MC, myocarditis; MFB, myocardfibrosis; N/A, not known; NT, patient died before transplantation during VAD time; P, pneumonia; PTLD, post-transplant lymphoproliferative disorder; RVHF, right ventricular heart failure; S, sepsis.

[a]Interruptions due to the status "not transplantable" were not taken into account.

TABLE 2 Study population (examined patients)

Patient	Sex	Age at VAD implantation (y)	VAD time (d)	ECMO time (d)	Time spent on the waitlist (d)[a]	Age at examination (y)	Underlying disease prior to heart failure	Assist device type	MND normal = 0 Simple MND = 1 Complex MND = 3 Other	Epitrack® J = Junior A = adult Total score (1 = good, 2 = average, 3 = borderline, 4 = impaired)	Kidscreen = K EQ-5D-5L = E (VAS 0-100)
1	M	7	27	0	54	17	DCM	M-BVAD	GMFCS1, MACS2	J 28 (4)	K
2	F	25	29	0	28	34	Myocarditis	B-BVAD	0	A 39 (1)	E (50)
3	F	11	460	0	408	20	DCM	B-BVAD	0	A 29 (3)	E (80)
4	F	4	14	0	35	13	DCM	M-LVAD	0	J 31 (2)	K
5	M	21	57	2	58	28	Graft rejection[b]	B-BVAD	0	A 35 (2)	E (90)
6	M	17	6	0	10	24	DCM	B-BVAD	pd	A 10 (4)	E (80)
7	F	1	365	7	386	7	NCCM	B-LVAD	ne	ne	K
8	F	8 mo	34	16	78	6	BWGS	B-LVAD	GMFCS1, MACS2	ne	K
9	F	9 mo	85	0	137	6	Myocarditis	B-LVAD	pd	ne	K
10	M	9	20	3	11	12	DCM	H-LVAD	0	J 36 (1)	K
11	M	15	23	0	47	17	DCM	B-BVAD	1	J 27 (4)	K
12	F	10	1	2	475	13	RCM	B-LVAD	0	J 31 (2)	K
13	F	1	115	0	156	3	DCM	B-LVAD	ne	ne	K
14	M	18	265	0	254	19	Myocarditis	H-LVAD	0	A 28 (4)	E (80)
15	M	3	13	0	16	3	Kawasaki syndrome	B-LVAD	ne	ne	K
16	M	4 mo	80	0	73	1	DCM	B-LVAD	ne	ne	K
17	M	9	6	0	8	23	DCM	M-LVAD	0	A 38 (2)	E (80)
18	F	4	16	1	13	17	Myocarditis	M-BVAD	0	J 29 (3)	K
19	M	17	29	0	34	30	DCM	M-BVAD	0	A 31 (3)	E (95)
20	M	17	79	3	132	24	Myocarditis	B-BVAD	0	A 32 (2)	E (80)
21[c]	F	1	484	0	496	2	DCM	B-LVAD	ne	ne	K
22	F	15	7	0	26	15	NCCM	H-LVAD	2	J 32 (2)	K

Abbreviations: ne, not examined; pd, psychomotor deficit.

[a]Interruptions due to the status "not transplantable" were not taken into account.

[b]Original diagnosis at first Htx in case of rejection and reTx: patient number 5: dilated cardiomyopathy.

[c]This patient had her VAD explanted after 484 d as a bridge to recovery,.

TABLE 3 Epitrack® results of n = 15 patients

	n = 15	Mean	Median	Min	Max	SD
Total score						
Epitrack® Jr n = 7		30.57	31	27	36	2.99
Epitrack® adult n = 8		30.25	31.5	10	39	9.099
Classification in						
Good	2 (9.1%)					
Epitrack® Junior	1					
Epitrack® adult	1					
Average	6 (27.3%)					
Epitrack® Junior	3					
Epitrack® adult	3					
Borderline	3 (13.6%)					
Epitrack® Junior	1					
Epitrack® adult	2					
Impaired	4 (18.2%)					
Epitrack® Junior	2					
Epitrack® adult	2					

implantation. Two patients could not be examined due to a psychomotor deficit and difficulties of comprehension. It was too difficult to perform the standardized neurological examination in one patient because of excessive shyness and in four toddlers (aged 1-3 years) during routine appointments; however, besides a speech delay in one patient, there were no neurological deficits documented in their medical records.

The MND assessment was performed on a total of 13 patients, ≥6 years, without apparent neurological deficit, in order to detect even slight neurological impairment. Eleven patients had normal examination results, 1 patient showed a simple MND, and 1 patient presented with a complex MND.

3.3 | Epitrack®

The Epitrack® test was completed by 15 patients. Three patients could not complete the questionnaire due to task comprehension difficulties (n = 2) and excessive shyness (n = 1). Four patients were under 6 years old at the time of the test.

The average result of the Epitrack® Junior test, completed by 7 patients, was 30.57 (min 27, max 36), while the average Epitrack® Adult test result was 30.25 (min 10, max 39), completed by 8 patients. A majority of patients scored an "average" result (n = 6), followed in frequency by the results "Impaired" (n = 4), "borderline" (n = 3), and "good" (n = 2). The results of the Epitrack® test are presented in Table 3.

3.4 | Quality of life

3.4.1 | Kidscreen-52

A total of 7 children and 11 parents completed the self- and proxy version of the Kidscreen-52 Questionnaire. Children estimated their HRQoL similar to the age-matched German reference population, without significant difference (Table 4). In the proxy version (parents estimating QoL of their children), the score in the autonomy scale was significantly lower compared to the German reference sample. The difference in the responses to the financial resources scale between self- and proxy versions of the questionnaire did not reach significance. Parents rated all other scales similar to the German reference population, meaning that they do not perceive their child to suffer from any disadvantages in daily life, compared to healthy children (see Table 5). The comparison of the HRQoL scores given by patients themselves (n = 7) to scores given by parents (n = 7) is presented in Figure 2 and Table 6. Parents estimated social acceptance and bullying to be a significantly larger burden than their children, while children scored their financial resources significantly higher.

TABLE 4 Differences between patients (n = 7) and German reference sample assessed by the nonparametric Wilcoxon signed-rank test

Kidscreen dimensions	*P*-value
Physical well-being	.9063
Psychological well-being	.8125
Moods and emotions	.5469
Self-perception	.9219
Autonomy	.7969
Parent relation and home life	.3750
Financial resources	.6719
Social support and peers	.5313
School environment	.3594
Social acceptance and bullying	.1875

TABLE 5 Differences between child´s quality of life scored by the parents (n = 11) and German reference sample assessed by the nonparametric Wilcoxon signed-rank test

Kidscreen dimensions	*P*-value
Physical well-being	.6201
Psychological well-being	.3086
Moods and emotions	.4014
Self-perception	.4375
Autonomy	.0225*
Parent relation and home life	.2246
Financial resources	.0576
Social support and peers	.5146
School environment	.3730
Social acceptance and bullying	.2285

*$P < .05$ are considered to be significant.

3.4.2 | EQ-5D-5L

Eight adult patients (≥18 years) completed the EQ-5D-5L questionnaire. Answers to the descriptive part of the EQ-5D-5L questionnaire are provided in Table 7. Calculated index values in comparison with a German reference population are shown in Table 8. Both the index values and the results of the VAS were similar to the German reference population, indicative reflecting a high QoL.

4 | DISCUSSION

After over 50 years of pediatric Htx, this therapy option has become well established.[51] The VAD treatment has also grown in importance over the years, in both the pediatric and adult fields, and now represents an often used bridge-to-transplant or bridge-to-recovery option.[52] It is therefore critical to assess possible complications and long-term outcome of these therapies.

Possible side effects of Htx and of assist device therapy are neurological events.[52] The implantation of an assist device or a Htx requires the use of a cardiopulmonary bypass, with known potential risks for embolic stroke.[15,18] Further, during assist device therapy, a strict anticoagulation protocol must be carried out. This leads to an increased risk for anticoagulation drug-associated complications. These can manifest as acute bleeding, stroke, and further neurological dysfunction. Besides acute events, it is also conceivable that these therapies may affect long-term motor and executive functioning.

HRQoL is an important outcome indicator for children with neurological disabilities and might be influenced, among others, by motor functioning and psychosocial domains like cognition, behavior, and education.[53,54]

In children with VAD and Htx, outcome studies often focus on technical details, survival, and medication.[55-58] Therefore, we aimed to examine motor outcomes, executive functioning, and HRQoL, as these outcome parameters are linked one to another and might reflect the participation of VAD and Htx survivors in daily life.

We examined 22 patients that received an assist device and a heart transplant at the department of pediatric cardiology at the university hospital of the Ludwig-Maximilians-University Munich, campus Großhadern, between 1992 and 2016.

With respect to motor neurological deficits, 4 patients were already diagnosed with unilateral motor deficits (presumed complication during time with VAD: n = 2) and psychomotor deficit (unknown etiology: n = 2).

The majority of the other patients (≥6 years) who participated showed normal neurological examination results using the MND assessment protocol (n = 11 out of 13).

In the cohort, one patient had a simple MND and one patient presented with a complex MND. A simple MND is a common finding in children and may be grouped with normal neurological findings. Simple MND s can be considered a slight neurological difference and may only have limited clinical significance.[29,59] Peters et al showed that in a general population many children were found to have simple or complex MNDs (27% vs 22%). Broström et al examined prematurely born patients using the MND assessment tool. It was found that 64% presented with a normal neurology, 28.7% with a simple MND and 7.5% with a complex MND.[50] In another study, Kavas et al assessed children with a birthweight <1500 g. The analysis of this prospective longitudinal study showed that, among several potential factors, a low Apgar score, history of sepsis, and a long duration of hospitals stay correlated with an increased risk for a simple MND.[60] However, these results are not directly comparable to ours due to the investigation of different diseases and risk factors. Nonetheless, compared to results of these and further studies, our findings show good results in the MND examination of this cohort. They are comparable to those of a healthy population.[50,59-61]

On the one hand, studies of the motor and executive functioning of patients treated with a VAD suggest a benefit of this therapy due to better cerebral perfusion.[21,62,63] On the other hand, VAD therapy

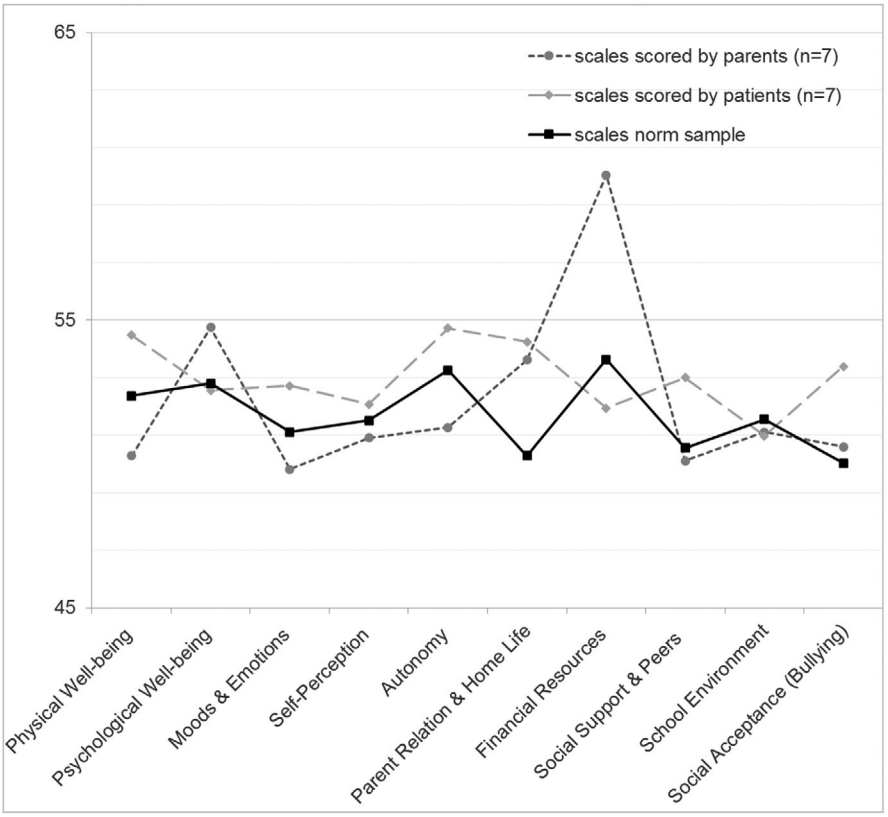

FIGURE 2 Quality of life (mean) scored by patients (n = 7), their parents (n = 7), and the German reference population

TABLE 6 Differences between child's quality of life scored by patients (n = 7) and their parents (n = 7) assessed by the nonparametric Wilcoxon signed-rank test

Kidscreen dimensions	*P*-value
Physical well-being	.5781
Psychological well-being	.2969
Moods and emotions	.5781
Self-perception	1.0000
Autonomy	.3750
Parent relation and home life	.6563
Financial resources	.0313*
Social support and peers	.1563
School environment	.5469
Social acceptance and bullying	.0156*

*$P < .05$ are considered to be significant.

and Htx are still associated with a high risk of brain injury and thus neurological complications. VanderPluym et al previously described neuroimaging results, obtained during and after VAD therapy, screening for brain injuries in children under 6 years old, bridged with the Berlin Heart excor®. 75% of patients were reported to show brain injury during neuroimaging at some point in their life, while 31% were found to have brain injuries during VAD therapy. In this study, abnormal neuroimaging generally correlated with an abnormal neurological and physical examination. It was also found that abnormal physical examination often correlated with lower IQ scores. Only 2 patients (out of 10) had abnormal neuroimaging results with a neurological and physical examination within normal limits.[64]

Neurological impairment may be of a motoric nature, but can also affect executive functioning. With this in mind, the cognitive state of our patients was examined. Though the Epitrack® was originally designed to monitor attention and executive functioning in patients with epilepsy, it is a promising screening test in patients with other neurological disorders, also.[26] In clinical practice, detected deficits should be further investigated through a comprehensive neuropsychological examination, while considering the context of the child´s educational and social performance.

In this cohort, Epitrack® testing revealed slight impairments in some cases; however, results generally indicated quite positive results considering the high risk for neurological events during this therapy. On average, children performed 7.36% and adults 13.82% lower than the reference population.[22,27]

Other studies about the cognitive outcome after VAD therapy are very promising. Chinnock et al described the developmental outcome of children after Htx as within a low to average range.[65] Jahnukainen et al found that the cognitive outcome of children bridged with an assist device was not worse than that of children who did not need an assist device before their Htx.[9]

As neurological impairment and cognition problems can greatly affect patients´ lives, a main objective of this study was to examine patients' subjective assessment about their QoL.

There are few studies evaluating HRQoL after Htx in childhood or adolescence (with or without VAD as a bridge to transplantation).[66-69] In this study, patients reported an average daily QoL

of 79.38 (68.32-90.42) in the VAS of the EQ5D-5L. Compared to the results of the INTERMACS report, where patients reported an average daily QoL of 35.3 before VAD implantation and 70.3 12 months after implantation, the QoL seems to be higher among this cohort.[52]

TABLE 7 Answers in the descriptive part of the EQ-5D-5L questionnaire (8 patients, ≥18 y old)

EQ-5D dimension	Level	N = 8 (%)
Mobility	No problems	8 (100.0)
	Slight problems	
	Moderate problems	—
	Severe problems	—
	Unable to	—
	Missing value	—
Self-care	No problems	8 (100.0)
	Slight problems	—
	Moderate problems	—
	Severe problems	—
	Unable to	—
	Missing value	—
Usual activity	No problems	5 (62.5)
	Slight problems	1 (12.5)
	Moderate problems	2 (25.0)
	Severe problems	—
	Unable to	—
	Missing value	—
Pain/discomfort	No pain	5 (62.5)
	Slight pain	2 (25.0)
	Moderate pain	1 (12.5)
	Severe pain	—
	Unable to	—
	Missing value	—
Anxiety/depression	Not anxious	5 (62.5)
	Slightly anxious	2 (25.0)
	Moderately anxious	1 (12.5)
	Severely anxious	—
	Extremely anxious	—
	Missing value	—

In summary, results are discrepant: While some studies found a similar QoL in heart transplant recipients, compared to a reference sample of healthy persons, others detected significantly lower psychosocial and physical functioning scores.[52,70] Wille et al asked 756 German children about their QoL using a VAS which was scored with an average of 83.7.[71] In this cohort, all patients scored their HRQoL comparable to the German reference population, which underlines that they do not suffer from significant limitations in their daily life. Interestingly, parents estimated social acceptance and bullying as a significant problem in their children´s lives, compared to the children themselves. Parents also estimated "autonomy" of their children as being significantly reduced compared to healthy children—again, in contrast to normal scores in the children's own questionnaires. The fact that parents estimate QoL as lower in some categories than patients themselves has also been described for other chronic diseases, such as migraine, and may reflect parents´ own fears and concerns.[72]

Generally, far lower results were expected, given the fact that both procedures (Htx and VAD implantation/therapy) are significant risk factors for neurological events.[65,73] Other factors, such as the chronic hypoxemia due to heart failure, the anesthetic drugs used during surgery, and long hospital stays, were also considered as having a potentially negative impact on children's cognitive development.[11,17] Nonetheless, these findings match the findings of previous studies.[63,65] Altogether, the overall motor and executive development, as well as QoL in the 22 included patients, were high.

A limiting factor of this study is the small sample size. This may be due to the fact that while VAD therapy has increased in importance over the past years, it still remains, similar to Htx, a relatively rare procedure. The only possibility for achieving a bigger sample size would be to conduct large, multicenter studies. It should also be considered that 10 out of 39 patients died during VAD therapy and 7 patients died in the following years after Htx (10-year post-transplant survival rate: 78.57%). Although survival data from other studies in similar populations showed the same result, this still remains a therapy with a high mortality rate and therefore obtaining larger samples may continue to be difficult.[19,74-79]

Due to the long observation period, the continuous technical medical development, and the heterogeneous patient group, different assist devices were used. A specific assessment, considering the properties of the different VADs, could be interesting. It must also

TABLE 8 Calculated EQ-5D-5L Index values and EQ-5D-5L VAS of 8 adult patients (5 patients <25 y) compared to the German index value set

	Adult study population (n = 8)		Reference population (Germany)								
			Age 18-24 (n = 264)			Age 25-34 (n = 551)			Total (n = 3552)		
	Mean	95% CI	Mean	SE	95% CI[a]	Mean	SE	95% CI[a]	Mean	SE	95% CI[a]
EQ-5D-5L Index Value	0.96	0.92-1.00	0.972	0.008	0.96-0.99	0.973	0.003	0.97-0.98	0.938	0.002	0.93-0.94
EQ-5D-5L VAS	79.38	68.32-90.42	85.3	1.1	83.14-87.46	84.0	0.8	82.43-85.57	77.3	0.4	76.52-78.08

[a]Estimated CI of reference population with CI=(mean ± 1.96 × standard error [SE])

be considered that the age range of our patients is very variable. It could therefore be interesting to analyze results of future studies in the context of patient age.

In most studies on assist device therapy and Htx, the main focal points are survival and general health outcomes. Especially, the executive and motor outcomes are decisive for the integration of a child into its' educational, later professional, and social environment. Therefore, the Epitrack® testing in particular, which is easy and quick to perform, should be an inherent part of the post- Htx follow-up, in order to detect executive deficits as soon as possible. Further studies for exploring potential follow-up programs are warranted.

5 | CONCLUSION

The main objective of this study was to examine the motoric and executive functioning outcomes, as well as the HRQoL of patients who received an assist device as a bridge to transplantation or BTR at the department of pediatric cardiology between 1992 and 2016 at the university hospital in Munich. To assess this, we used a battery of tests composed of the MND neurological examination, Epitrack® test, and Kidscreen 52/EQ-5D-5L QoL questionnaires.

Our results suggest, that in children with VAD for bridge to transplantation or BTR, overall executive and motor development is encouragingly strong, which may be reflected in a high QoL. Most patients seem to achieve normally functioning social, academic, and professional lives. Further studies to confirm these findings are warranted.

AUTHORS' CONTRIBUTIONS

L-CB, LG, and RD-P conceptualized and designed the study, and LG and RD-P supervised all aspects of the work. L-CB, LG, and RD-P contributed to analysis and interpretation of the data. RW performed statistical analysis. L-CB drafted the initial manuscript. NH, CH, IS-N, SU, AL, FH, and LH contributed to interpretation of the data and reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

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