


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”

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Abbreviations: CI, Confidence interval; DCM, Dilated cardiomyopathy; EBV, Epstein-barr virus; ECMO, Extracorporeal membrane oxygenation; EMB, Endomyocardial biopsy; FM, Fulminant myocarditis; HHV6, Human Herpesvirus 6; HR, Hazard ratio; HTx, Heart transplantation; IQR, Interquartile range; LVEDd, Left ventricular enddiastolic diameter; LVEF, Left ventricular ejection fraction; MCS, Mechanical circulatory support; MOF, Multi-organ failure; NYHA, New York Heart Association; PVB19, Parvovirus B19; VAD, Ventricular assist device.

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Abstract

Myocarditis represents an important cause for acute heart failure. MYKKE, a prospective multicenter registry of pediatric patients with myocarditis, aims to gain knowledge on courses, diagnostics, and therapy of pediatric myocarditis. The role of mechanical circulatory support (MCS) in children with severe heart failure and myocarditis is unclear. The aim of this study was to determine characteristics and outcome of patients with severe heart failure requiring MCS and/or heart transplantation. The MYKKE cohort between September 2013 and 2016 was analyzed. A total of 195 patients were prospectively enrolled by 17 German hospitals. Twenty-eight patients (14%) received MCS (median 1.5 years), more frequently in the youngest age group (0-2 years) than in the older groups ($P < 0.001$; 2-12 and 13-18 years). In the MCS group, 50% received a VAD, 36% ECMO, and 14% both, with a survival rate of 79%. The weaning rate was 43% (12/28). Nine (32%) patients were transplanted, one had ongoing support, and six (21%) died. Histology was positive for myocarditis in 63% of the MCS group. Patients within the whole cohort with age < 2 years and/or ejection fraction $< 30\%$ had a significantly worse survival with high risk for MCS, transplantation, and death ($P < 0.001$). Myocarditis represents a life-threatening disease with an overall mortality of 4.6% in this cohort. The fulminant form more often affected the youngest, leading to significantly higher rate of MCS, transplantation, and mortality. MCS represents an important and life-saving therapeutic option in children with myocarditis with a weaning rate of 43%.

KEYWORDS

MCS, myocarditis, pediatric, transplantation

1 | INTRODUCTION

Myocarditis as an inflammatory disease of the myocardium represents an important cause for acute heart failure and development of DCM.^{1,2} It may be responsible for up to 42% of sudden cardiac deaths in younger patients.^{3,4} FM is attended by an acute onset and a life-threatening course with acute deterioration and severe illness with need for MCS or HTx.⁵ Fulminant forms in adults show higher cardiac recovery than acute or non-fulminant forms, and a higher transplant-free survival.⁶ In children, the survival rate in FM has been reported to reach 50%-90%, although it is unclear if patients need bridging with MCS or HTx.⁷⁻⁹ According to the literature, 4%-9% of pediatric patients with myocarditis require HTx.^{10,11} The subsequent development of DCM is reported in 21%.¹² Because severe heart failure might be accompanied by both entities, the relationship between these two entities is not fully understood due to the lack of prospective data and of standardization in diagnosis.

Inflammatory changes of the myocardium may cause global or regional impairment of ventricular function.¹³ According to the degree of myocardial injury and cell damage, acute heart failure might appear early or late after the initial inflammatory response. Age-dependent differences in the clinical presentation of myocarditis are common, with a higher degree of severity in the youngest patient

group, as previously reported.¹⁴ Over the past decade, MCS by ECMO or VAD implantation has become available in a number of pediatric heart centers. So far, there are only few data published on the rate of MCS support, recovery rates, and mortality in pediatric patients with MCS.^{10,11,15} Clinical data are lacking, and the majority of publications report retrospective data.

In this study, we analyzed the characteristics and clinical course of pediatric patients (< 18 years) with suspected myocarditis from the German prospective multicenter myocarditis registry MYKKE. We focused on the incidence of severe heart failure and the need for specific treatment by MCS and/or HTx.

2 | MATERIAL AND METHODS

MYKKE is a prospective long-term registry that provides a research platform for clinical studies in pediatric myocarditis. It is hosted and technically administered by the Competence Network for Congenital Heart Defects. Inclusion criteria for MYKKE are as follows: suspected myocarditis, hospital admission, age < 18 years, and written consent from parents or legal guardians. Since 2013, 21 German centers have actively enrolled patients. Ethical approval was first obtained at the initiating center (German Heart Center Berlin, Germany) from the

ethics committee of Charité - Universitätsmedizin Berlin and subsequently confirmed by the local authorities of all collaborating centers (ClinicalTrials.gov NCT02590341).

Data entry of the prospective cohort (ie, patients with myocarditis) into a central online study database by the treating physicians at the initial admission was performed from September 2013 to September 2016. According to follow-up data, registration of the best possible information was achieved until December 2017 from all participating centers. Data from biopsy reports, MCS implantation, and HTx were collected separately and recorded by the central study team. In particular, data from patients with ECMO and/or VAD were sub-analyzed and defined the MCS group according to clinical and pathological findings.¹⁶ Patients without MCS support were defined as the non-MCS group, and their clinical data were compared to those of the MCS group.

2.1 | Diagnosis of myocarditis by endomyocardial biopsy

The diagnosis of myocarditis was made by EMB. For analysis of EMB, histopathology (including DALLAS criteria), immunohistochemistry, and viral genome detection were performed by one single accredited laboratory (Cardiopathology, Institute for Pathology and Neuropathology, University Hospital Tübingen, Tübingen, Germany). Reports were systematically reviewed for the following types of myocarditis in accordance with the WHO definition¹⁷:

- a Acute myocarditis: infiltrate of ≥ 14 leukocytes/mm² (quantitated by immunohistochemistry) and presence of myocyte damage and/or fibrosis.
- b Chronic myocarditis: infiltrate of ≥ 14 leukocytes/mm² (quantitated by immunohistochemistry) and absence of myocyte damage with or without fibrosis.
- c Status post-myocarditis: multifocal fibrosis or scarring without inflammation (0-3 leukocytes/mm²).

According to the EMB results, two groups were defined:

1. Proven myocarditis: results of acute, chronic, or status post-myocarditis in EMB
2. Myocarditis negative: no confirmed inflammation or other diagnoses in EMB.

2.2 | Statistical analysis

Analysis was performed in collaboration with statisticians of the German Heart Center Berlin and the Department of Medical Statistics at the University Medical Center Göttingen.

Categorical variables were summarized by frequencies and percentages. For continuous measures, data were presented as median values with IQR. Pearson's chi-square test or (in the case of small sample sizes) Fisher's exact test was used to compare dichotomous variables. For comparison of independent groups, the Mann-Whitney

U and Kruskal-Wallis tests were applied. Kaplan-Meier curves and log-rank tests were used for further survival analysis. The survival rates and HR were given with a 95% CI. Due to the small numbers of events, a multivariate analysis could not be performed. A probability value of <0.05 was considered statistically significant. Data were analyzed using IBM Corp. SPSS version 24.0.

3 | RESULTS

A total of 195 consecutive patients (MYKKE cohort) were prospectively enrolled by 17 centers between September 2013 and September 2016. 66.2% of the patients were male. Median age (IQR) was 13.0 (2.0-16.0) years. We defined three age groups¹⁴: 0-2 (24.6%), 2-12 (17.9%), and 13-18 years (57.4%). LVEF was $<30\%$ in 26% of the patients. Almost one third of patients presented in functional NYHA class III or IV. The incidence of fulminant myocarditis in our overall cohort was 14.3% (28/195) if using the definition of inotrope requirement and need for MCS. If using the definition of inotrope requirement only, the incidence was 34.4% (67/195).^{5-7,18,19}

3.1 | Mortality and survival

The overall mortality rate was 4.6% (9/195) during the follow-up period of 8.2 (5.3-13.0) months. An increased lethality was also documented in the patient group with the need for MCS (6/28): MOF plus bacteremia or mediastinitis (n = 4), hemorrhagic stroke and cerebral edema (n = 2). Survival was 95.4% after 6 months for patients with proven myocarditis on EMB (CI 0.90-1.00) and 85.4% in myocarditis-negative patients (CI 0.71-1.00; $P = 0.161$; n = 113).

3.2 | Risk analysis

The youngest age group (0-2 years) showed a significantly lower survival rate after 6 months (81.9% (CI 0.70-1.00) compared with children 2-12 years (90.9%, CI: 0.79-1.00) and 13-18 years of age (98.7%, CI 0.96-1.00; $P = 0.008$; Figure 1).

Patients with age under 2 years and/or severely impaired LVEF ($<30\%$) by echocardiography showed significantly lower survival rates (82.2%, CI 0.72-1.00) as compared to patients without these criteria ($P < 0.001$, Figure 2). The hazard ratios of death were 5.7 for age under 2 years (CI 1.4-22.7; $P = 0.014$) and 8.8 for LVEF $<30\%$ (CI 1.8-42.4; $P = 0.007$). All patients who died were under 2 years of age, and 78% (7/9) had an LVEF $<30\%$. The event-free survival for the combined end-point of MCS, HTx, and death was only 45.7% in the risk group compared to 100% in the non-risk group ($P < 0.001$, Figure 3).

3.3 | MCS group

3.3.1 | Patient characteristics

Twenty-eight out of 195 patients (14.4%) were supported with either ECMO and/or VAD (57% male, median age (IQR) 1.5

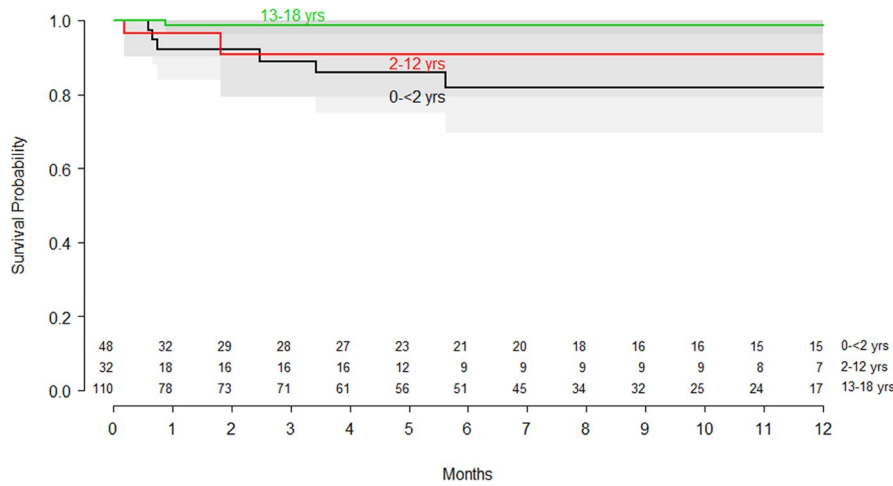


FIGURE 1 Kaplan-Meier curve for survival according to age groups 0-<2 years, 2-12 years, and 13-18 years within the MYKKE cohort (n = 195; P = 0.008). Follow-up was available in 60% (118/195)

(0.0-12.8) years). Compared to the non-MCS group, the MCS group was significantly younger (0-2 years: 29%; 2-12 years 20%; 13-18 years: 6%), showed lower LVEF, and belonged to higher functional NYHA class (P < 0.001, respectively). In transthoracic echocardiography, the median z-score of the LVEDd was significantly higher in the MCS group than in the non-MCS group with (P < 0.001; MCS group: 6.1, IQR 1.8-9.4, n = 19; non-MCS group: 0.6, IQR -0.8-3.0, n = 93). All MCS patients were on INTERMACS level 1-3 (level 1:50% (14/28); level 2:29% (8/28); level 3:21% (6/28); level 4-7:0%). Patient characteristics of the MCS group and non-MCS group are given in Table 1.

Patients in the age group 0-2 years showed the highest rate of MCS (50%). Decompensation (defined as acute right or left heart failure with peripheral edema and/or pulmonary congestion) occurred in all 28 MCS patients, and 53% (15/28) needed cardiopulmonary resuscitation.

Fourteen patients received an ECMO according to SOP and for stabilization, and three out of these patients had resuscitation within the prior 24 hours. MCS was implanted >24 hours after resuscitation in 8/28 (28%) patients.

3.3.2 | Outcome

All in all, the overall freedom from the combined end-point of MCS, HTx, and death was 80.0% (Figure 4A). For the MCS group, the overall freedom from the combined end-point of HTx and death was 31.4% compared to 96.6% in the non-MCS group (P < 0.001, Figure 4B).

3.3.3 | Type of MCS

Patients with need for MCS were treated with ECMO (10/28, 36%), VAD (14/28, 50%), or ECMO and VAD (4/28, 14%); see Figure 5. The mean duration of ECMO support was 7.4 ± 5.3 days (n = 14) and of VAD 100.4 ± 113.0 days (n = 14). ECMO cannulation was cervical in 50% (7/14), central (aorta and right atrium) in 21% (3/14), and femoral in 29% (4/14), all veno-arterial. In 50% of VAD patients (9/18), a Berlin Heart EXCOR® was implanted, in 39% (7/18) HeartWare® and in 11% (2/18) Levitronix®. Four patients were switched from ECMO to VAD after 6.3 ± 7.9 days of support. Their total MCS duration was 82.8 ± 72.3 days. Three of them could be weaned after 91.3 ± 86.0 days; one received HTx after 57 days on VAD.

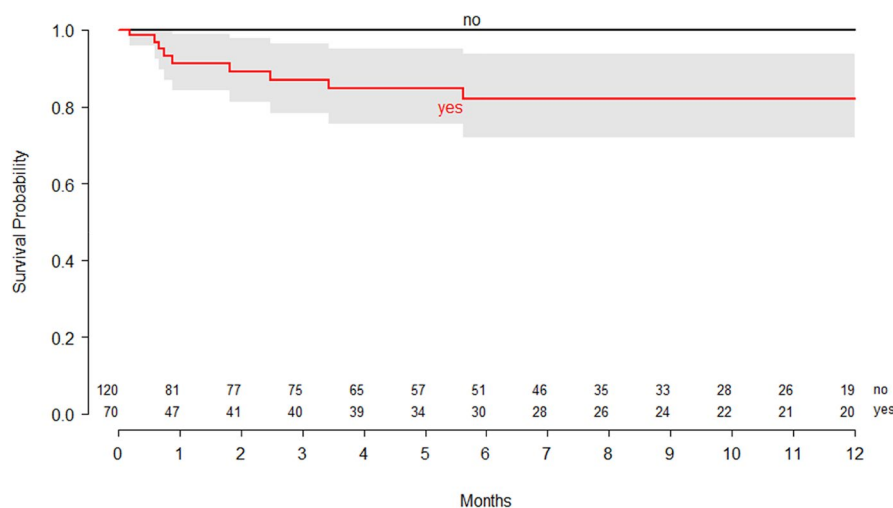


FIGURE 2 Kaplan-Meier curve for survival comparison between risk group patients (<2 years and/or left ventricular ejection fraction <30%) and no risk group patients for the MYKKE cohort (n = 195; P < 0.001). Follow-up was available in 60% (118/195)

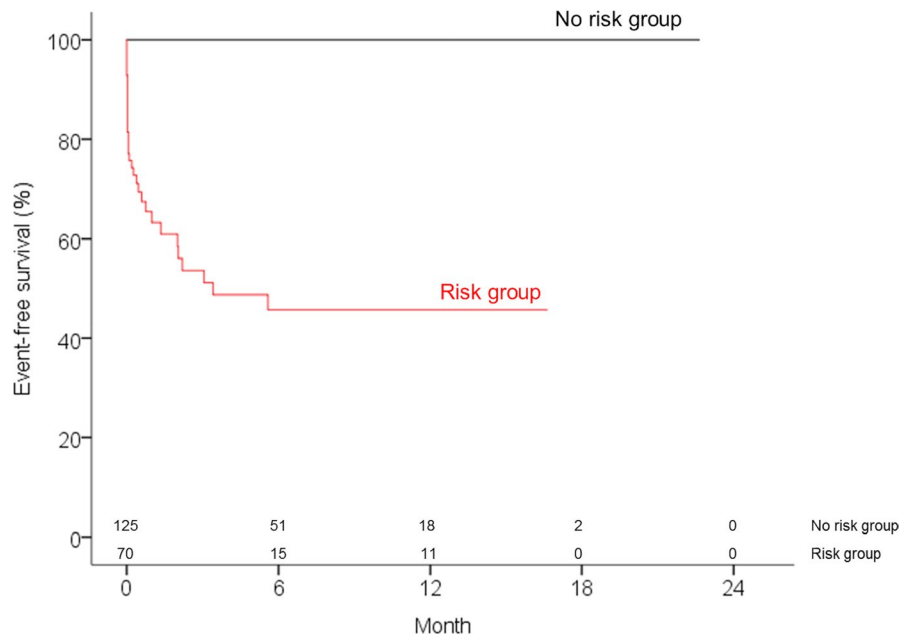


FIGURE 3 Freedom from the combined event MCS, HTx, death between the risk group (<2 years and/or left ventricular ejection fraction <30%; n = 70) and no risk group (n = 125) within the whole MYKKE cohort ($P < 0.001$)

Overall, 12 patients (12/28; 43%) were weaned from ECMO (n = 7) and VAD (n = 5) after an overall support time of 48.9 ± 75.2 days. Nine patients (32%) of the MCS group were bridged to HTx after 162.9 ± 181.0 days and a mean time on waiting list of 150.3 ± 178.3 days. One patient was still on the waiting list on VAD after 417 days of support during the preparation of the manuscript. Six patients (21%) died after a mean support time of 119.0 ± 217.9 days on MCS (Figure 5).

3.3.4 | Medication

Medical treatment included heart failure medication and catecholamines in all MCS group patients. In 96% of the patients epinephrine, in 93% milrinone, in 64% norepinephrine and in 18% dobutamine was administered. Additional medication included the following: anti-arrhythmic (32%), virostatic (14%), or immunomodulative agents (immunoglobins 46%, corticosteroids 32%, and azathioprine 7%). The administration of immunoglobins was significantly more common in the MCS group than in the non-MCS group ($P = 0.004$).

3.3.5 | Complications

Major complications during VAD and/or ECMO therapy were as follows: 25% stroke (7/28), 21% reoperation due to bleeding and hematoma (6/28), 11% infection (3/28), revision of cannula (1/28) and change to larger VAD (1/28), device dysfunction due to membrane rupture (1/28), and 21% others (6/28): cerebral bleeding, thrombosis of femoral vein, epistaxis, renal failure, paralytic ileus, or cerebral hypoxic edema.

3.4 | Role and results of endomyocardial biopsy (EMB)

EMB was performed in 113 out of 195 patients (58%). EMB results were positive for myocarditis in 73% of the patients (82/113): 17% (n = 17) acute myocarditis (lymphocytic n = 15; eosinophilic n = 1; granulocytic n = 1), 43% (n = 49) subacute/chronic myocarditis (all lymphocytic), and 12% (n = 14) status post-myocarditis (lymphocytic). According to histological analysis, 28% had other reasons for heart failure: detection of a DCM (n = 6), hypertrophic cardiomyopathy (n = 2), or non-specific myocardial changes (endocardial thickening (n = 1), perivascular fibrosis (n = 1), myocyte atrophy (n = 3), myocyte hypertrophy (n = 5), and toxic impairment (n = 3) respectively; no signs of inflammation: n = 9). No giant cell myocarditis was detected.

Patients within the groups “acute myocarditis” and “others” experienced more frequently events like MCS, HTx, or death, but without statistical significance ($P = 0.091$; Figure 6).

A virus was detected in 45% (51/113 patients with biopsy) of all patients with the following distribution: 27% PBV19; 9% HHV6; 5% PVB19/HHV6; 3% Enterovirus; and 1% EBV.

In 23 out of the 28 MCS patients, EMB was performed with a total rate of 65% of proven myocarditis (15/23): 13% acute myocarditis (all lymphocytic), 44% subacute/chronic myocarditis (all lymphocytic), and 9% status post-myocarditis (all lymphocytic). According to histological analysis, 35% had other reasons for heart failure: detection of a DCM (n = 3) or non-specific myocardial changes (endocardial thickening, myocyte atrophy, and toxic impairment: n = 1, respectively; no signs of inflammation: n = 2). For virus detection within the myocardium of the MCS and non-MCS groups, see Table 2.

Time from initial admission to EMB was 2.0 (1.0-7.0) days (whole cohort); time from symptom onset to EMB was 8.0

TABLE 1 Patient characteristics of the MCS and non-MCS groups

	MCS group (n = 28)	Non-MCS group (n = 167)	P-value
Age in y	1.5 (0.0-12.8)	14.0 (7.0-16.0)	<0.001
Gender male percent (n)	57.1 (16)	113 (67.7)	
Age groups			
0-2 y	14 (50.0)	34 (20.4)	<0.001
2-12 y	7 (25.0)	28 (16.8)	
13-18 y	7 (25.0)	105 (62.9)	
Symptoms, n (%)			
Decompensation	28 (100.0)	32 (19.2)	<0.001
Fatigue, weakness	26 (92.9)	116 (69.5)	0.01
Decrease of exercise capacity	25 (89.3)	114 (68.3)	0.023
Dyspnea	19 (67.9)	55 (32.9)	<0.001
Feeding intolerance	17 (60.7)	24 (14.4)	<0.001
Infection < 6 weeks before	16 (57.1)	90 (53.9)	0.749
Fever < 6 weeks before	9 (32.1)	59 (35.3)	0.743
Arrhythmia, documented	13 (46.4)	51 (30.5)	0.098
Arrhythmia, perceived	6 (21.4)	33 (19.8)	0.838
Syncope	3 (10.7)	24 (14.4)	0.604
Sudden cardiac death	3 (10.7)	4 (2.4)	0.029
Angina pectoris	3 (10.7)	72 (43.1)	0.001
NYHA			
I	1 (3.6)	98 (58.7)	
II	1 (3.6)	36 (21.6)	
III	3 (10.7)	13 (7.8)	<0.001
IV	23 (82.1)	20 (12.0)	
Symptom onset before admission, days	3.5 (0.25-20.0)	3.0 (1.0-9.0)	0.858
Time from symptom onset to EMB, days	10.0 (5.0-30.0)	8.0 (3.3-25.0)	0.793
Initial LVEF			
<30%	25 (89.3)	25 (15.0)	<0.001
30%-44%	2 (7.1)	28 (16.8)	
45%-54%	1 (3.6)	44 (26.3)	
≥55%	0 (0.0)	70 (41.9)	
Z-Score LVEDd	6.1 (1.8-9.4) n = 19	0.6 (-0.8-3.0) n = 93	<0.001
Medication			
Heart failure medication	28 (100.0)	95 (56.9)	<0.001
AT1-antagonists	2 (7.1)	0 (0.0)	0.02
Epinephrine	27 (96.4)	17 (10.2)	<0.001
Norepinephrine	18 (64.3)	4 (2.4)	<0.001
Milrinone	26 (92.9)	24 (14.4)	<0.001
Dobutamine	5 (17.9)	16 (9.6)	0.194
Levosimendan	15 (53.6)	9 (5.4)	<0.001
Ilomedine	8 (28.6)	0 (0.0)	<0.001
Calcium channel blockers	4 (14.3)	0 (0.0)	<0.001
Other antiarrhythmics	9 (32.1)	12 (7.2)	0.001

(Continues)

TABLE 1 (Continued)

	MCS group (n = 28)	Non-MCS group (n = 167)	P-value
Immunoglobins	13 (46.4)	35 (21.0)	0.004
Corticosteroids	9 (32.1)	9 (5.4)	<0.001
Virostatic	4 (14.3)	7 (4.2)	0.055
Azathioprine	2 (7.1)	1 (0.6)	0.055
Interferon	0 (0.0)	0 (0.0)	
Outcome			
HTx	9 (32.1)	1 (0.6)	<0.001
Death	6 (21.4)	3 (1.8)	<0.001

Values are given as n (%) or median (interquartile range).

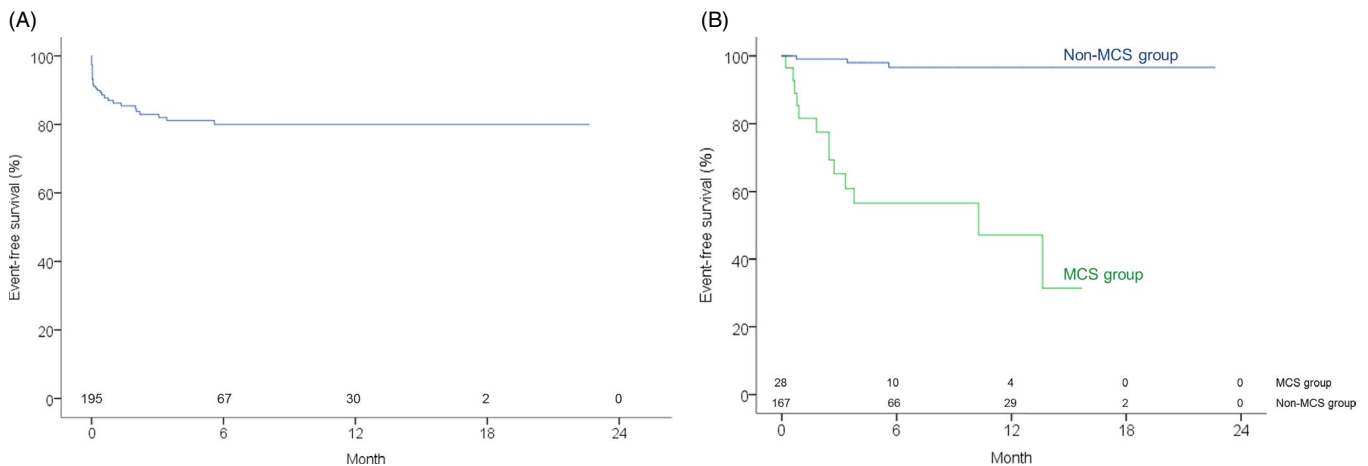
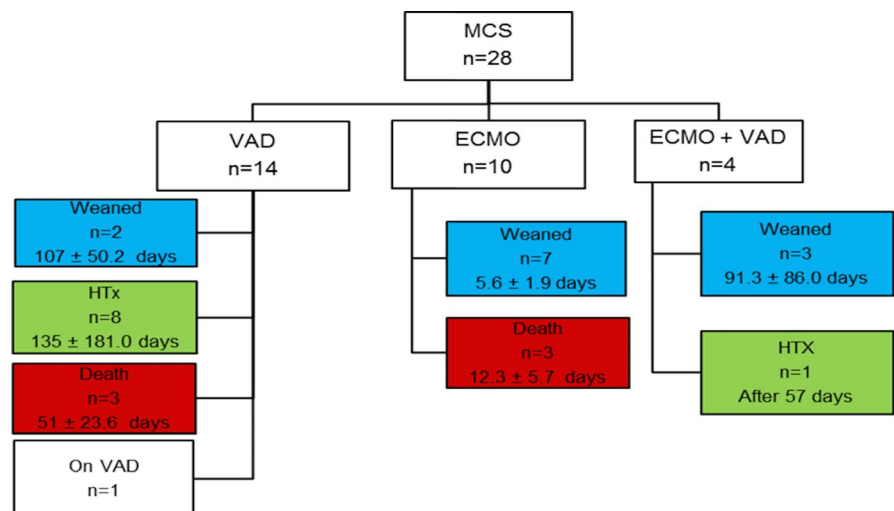


FIGURE 4 A, Freedom from the combined event MCS, HTx, death within the whole MYKKE (n = 195). B, Freedom from the combined event HTx and death between non-MCS (blue) and MCS groups (green); $P < 0.001$

FIGURE 5 Outcome of patients within the MCS group. Twelve patients were weaned, nine received heart transplantation, and six died. One patient was still on VAD at the time of manuscript preparation



(4.0-25.0) days (whole cohort); time from initial admission to MCS was 2.0 (1.0-17.0) days; and time from symptom onset to MCS was 13.5 (5.0-54.5) days.

EMB was performed in 12 patients during implantation of MCS and in 11 patients before or after initiation of MCS.

4 | DISCUSSION

Diagnostic approaches and therapeutic strategies in pediatric patients with myocarditis are still diverse, not standardized, and not supported by a large body of evidence.²⁰ Pharmacologic strategies address

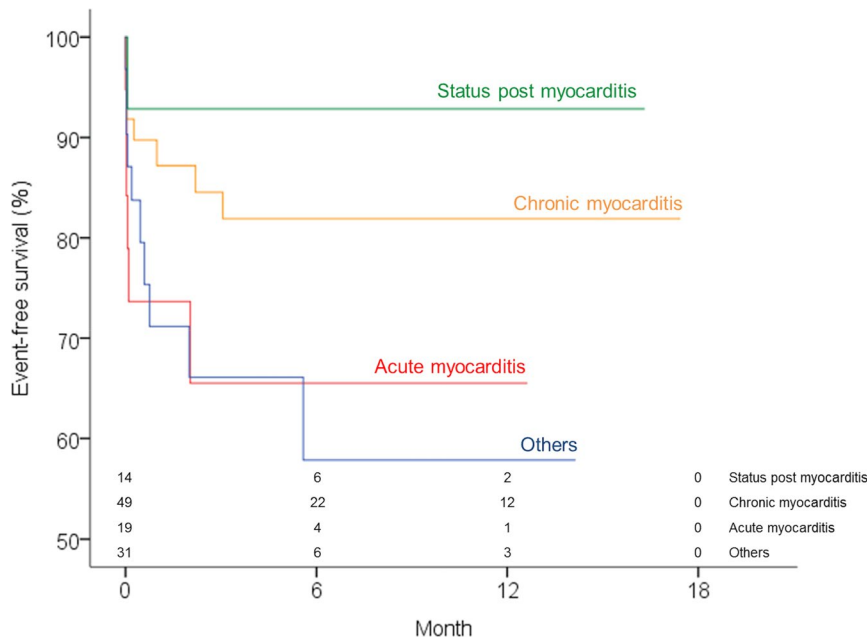


FIGURE 6 Freedom from the combined event MCS, HTx, death according to the results of endomyocardial biopsy (acute, chronic, status post-myocarditis, and others; $P = 0.091$; $n = 113$)

TABLE 2 Virus detection within the myocardium of the MCS and non-MCS groups

	MCS group (n = 23)	Non-MCS group (n = 90)
Myocardial virus detection	7 (30.4)	44 (48.8)
PVB19	2	28
HHV6	2	8
PVB19/HHV6	2	5
Enterovirus	1	2
EBV	0	1

Values are given as n (%).

different targets with cardioprotective and immuno-modulating substances. In cases of severe heart failure with progressive or fulminant course, MCS can be a life-saving additional option in the therapy of myocarditis, as it has been shown by several case reports and retrospective studies.^{10,20,21} MYKKE is the first cohort which prospectively analyzed the use of MCS in pediatric patients with myocarditis.¹⁴

Age <2 years and/or an ejection fraction <30% are indicators for a significantly higher risk for MCS, death, or heart transplantation. Both criteria were present in 39% (11/28) of cases requiring MCS, confirming the clinical impression that there was a relatively high proportion of patients in this age group with severe heart failure and a fulminant course. As myocarditis is an acquired but potentially reversible disease, MCS therapy can be applied for temporary support. This was confirmed in this patient group by an effective weaning rate of 43%. On the contrary, 32% of the MCS group and one patient of the non-MCS group received HTx.

It remains unclear which factors influence the clinical course and determine the need for MCS or transplantation in these young children.^{10,11,15,22} As long-term support has been reported as "bridge to recovery or transplantation",^{15,23} MCS might be employed until cardiac

function is stabilized. "Cardiac unloading" by MCS might influence the possibility of cardiac recovery. But, its influence on reversibility of inflammation or decrease of fibrosis has not yet been shown by prospective data. All our MCS patients presented with a progression of their disease, clinical worsening with acute decompensation, and 53% required resuscitation. Also, these factors itself might influence the outcome of the use of MCS independently. However, complications of MCS (eg, stroke, infection, bleeding) caused additional mortality and morbidity, leading to higher mortality in the MCS group than in the non-MCS group. But, we still could report a favorable survival rate of 79% in this high-risk group. Comparable data are found in the meta-analysis by Xiong et al who reported a survival rate of 62% or in reports of children with FM.²⁴

According to histopathological analysis, an inflammatory pattern was detected in 65% in the MCS group and 73% in the whole MYKKE cohort; this differs significantly from recent retrospective data. Inflammation might especially influence clinical course and need for treatment.¹⁵ The higher mortality in the non-myocarditis group might be caused by the existence or development of DCM, a coincidence or result of inflammatory disease. The diagnostic value of the Dallas criteria has been challenged because of limited interobserver reproducibility. By now, newer methods including immunohistochemistry and polymerase chain reaction (PCR) for virus detection are included in the diagnostics of myocarditis.²⁵ Viral detection by PCR in the myocardium or blood might be useful in order to better clarify the activity of the disease and may be used for therapeutic intervention, although the detection rate in the MCS group was only 30%. But, viral detection may also depend on the diagnostic approach and timing of EMB, as detection of acute virus infections might be reduced if the EMB is taken late after admission.

Depending on virus persistence and/or post-viral immune processes, chronic myocardial injury may develop.²⁶ So far, there is no explanation for fulminant myocardial inflammation in early childhood. Maybe immunological disorders, such as the development of

cardiac or myocardial antibodies, should be considered.^{27,28} On the other hand, de novo mutations or genetic predisposition may determine the course of myocarditis.^{29,30} The immunological response might be gender-dependent and differ in various age groups. The fulminant course with acute cardiac deterioration in very young children might be caused either by an incomplete or by an overshooting immune system. This still needs to be investigated. Moreover, there is still a great need for systematic pharmacological studies in order to treat acute heart failure in children and in order to prevent serious complications.

5 | LIMITATIONS

Developed as the first worldwide prospective registry, MYKKE includes all patients with suspected myocarditis admitted as an inpatient in Germany. All patients—so far—did not undergo standardized diagnostic or therapeutic approaches and were treated by center-specific protocols or each standard of care. In relation to the total number of patients, the patient group with a fulminant form of myocarditis is still small. A higher number of patients are needed in order to identify important factors influencing the risk profile of acute and fulminant myocarditis in children, and there might also be an overlap to cardiomyopathy patients.

As this registry has not included defined follow-up time points, the follow-up data were registered from clinical routine according to the clinical center protocol. Therefore, the possibility of patient's with loss to follow-up is increased in this cohort.

6 | CONCLUSION

Myocarditis is a life-threatening disease with an overall mortality of 4.6% in this prospective pediatric cohort. The fulminant form more frequently affected the youngest age group (<2 years), leading to increased events of decompensation with severe heart failure and high mortality. With the use of MCS therapy, improved survival can be achieved in patients with complicated heart failure. Ventricular unloading seems to be important and effective for recovery of ventricular function despite a lack of other specific therapies, but the pathomechanisms and underlying factors still remain unknown. For better understanding and the development of treatment strategies, additional patients and analysis are needed within a prospective cohort of pediatric myocarditis patients.

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CONFLICT OF INTEREST

None.

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REFERENCES

1. Caforio AL, Pankuweit S, Arbustini E, 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(33):2636-2648, 2648a-2648d.
2. Richardson P, McKenna W, Bristow M, 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(5):841-842.
3. Basso C, Calabrese F, Corrado D, Thiene G. Postmortem diagnosis in sudden cardiac death victims: macroscopic, microscopic and molecular findings. *Cardiovasc Res*. 2001;50(2):290-300.
4. Gore I, Saphir O. Myocarditis; a classification of 1402 cases. *Am Heart J*. 1947;34(6):827-830.
5. Gupta S, Markham DW, Drazner MH, Mammen PP. Fulminant myocarditis. *Nat Clin Pract Cardiovasc Med*. 2008;5(11):693-706.
6. McCarthy RE 3rd, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med*. 2000;342(10):690-695.
7. Amabile N, Fraisse A, Bouvenot J, Chetaille P, Ovaert C. Outcome of acute fulminant myocarditis in children. *Heart*. 2006;92(9):1269-1273.
8. Duncan BW, Bohn DJ, Atz AM, French JW, Laussen PC, Wessel DL. Mechanical circulatory support for the treatment of children with acute fulminant myocarditis. *J Thorac Cardiovasc Surg*. 2001;122(3):440-448.
9. Matsuura H, Ichida F, Saji T, et al. Clinical features of acute and fulminant myocarditis in children- 2nd nationwide survey by Japanese society of pediatric cardiology and cardiac surgery. *Circ J*. 2016;80(11):2362-2368.
10. Butts RJ, Boyle GJ, Deshpande SR, et al. Characteristics of clinically diagnosed pediatric myocarditis in a contemporary multi-center cohort. *Pediatr Cardiol*. 2017;38(6):1175-1182.
11. Ghelani SJ, Spaeder MC, Pastor W, Spurney CF, Klugman D. Demographics, trends, and outcomes in pediatric acute myocarditis in the United States, 2006 to 2011. *Circ Cardiovasc Qual Outcomes*. 2012;5(5):622-627.
12. D'Ambrosio A, Patti G, Manzoli A, et al. The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy: a review. *Heart*. 2001;85(5):499-504.
13. Canter CE, Simpson KE. Diagnosis and treatment of myocarditis in children in the current era. *Circulation*. 2014;129(1):115-128.
14. Messroghli DR, Pickardt T, Fischer M, 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;187:133-144.
15. Wilmot I, Morales DL, Price JF, et al. Effectiveness of mechanical circulatory support in children with acute fulminant and persistent myocarditis. *J Card Fail*. 2011;17(6):487-494.
16. Lieberman EB, Hutchins GM, Herskowitz A, Rose NR, Baughman KL. Clinicopathologic description of myocarditis. *J Am Coll Cardiol*. 1991;18(7):1617-1626.
17. 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(3):200-209.
18. Acker MA. Mechanical circulatory support for patients with acute-fulminant myocarditis. *Ann Thorac Surg*. 2001;71(3):S73-76; discussion S82-75.
19. Chen JM, Spanier TB, Gonzalez JJ, et al. Improved survival in patients with acute myocarditis using external pulsatile mechanical ventricular assistance. *J Heart Lung Transplant*. 1999;18(4):351-357.
20. Wheeler DS, Kooy NW. A formidable challenge: the diagnosis and treatment of viral myocarditis in children. *Crit Care Clin*. 2003;19(3):365-391.
21. English RF, Janosky JE, Etedgui JA, Webber SA. Outcomes for children with acute myocarditis. *Cardiol Young*. 2004;14(5):488-493.
22. Choi K, Pan YP, Pock M, Chang RK. Active surveillance of sudden cardiac death in young athletes by periodic Internet searches. *Pediatr Cardiol*. 2013;34(8):1816-1822.
23. George CL, Ameduri RK, Reed RC, Dummer KB, Overman DM, St Louis JD. Long-term use of ventricular assist device as a bridge to recovery in acute fulminant myocarditis. *Ann Thorac Surg*. 2013;95(3):e59-60.
24. Xiong H, Xia B, Zhu J, Li B, Huang W. Clinical outcomes in pediatric patients hospitalized with fulminant myocarditis requiring extracorporeal membrane oxygenation: a meta-analysis. *Pediatr Cardiol*. 2017;38(2):209-214.
25. Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. *Circulation*. 2006;113(4):593-595.
26. Liu PP, Mason JW. Advances in the understanding of myocarditis. *Circulation*. 2001;104(9):1076-1082.
27. Caforio AL, Angelini A, Blank M, et al. Passive transfer of affinity-purified anti-heart autoantibodies (AHA) from sera of patients with myocarditis induces experimental myocarditis in mice. *Int J Cardiol*. 2015;179:166-177.
28. Simpson KE, Cunningham MW, Lee CK, et al. Autoimmunity against the heart and cardiac myosin in children with myocarditis. *J Card Fail*. 2016;22(7):520-528.
29. Belkaya S, Kontorovich AR, Byun M, et al. Autosomal recessive cardiomyopathy presenting as acute myocarditis. *J Am Coll Cardiol*. 2017;69(13):1653-1665.
30. Campuzano O, Fernandez-Falgueras A, Sarquella-Brugada G, et al. A genetically vulnerable myocardium may predispose to myocarditis. *J Am Coll Cardiol*. 2015;66(25):2913-2914.

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