Toward evidence-based diagnosis of myocarditis in children and adolescents: Rationale, design, and first baseline data of MYKKE, a multicenter registry and study platform

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Aims The aim of this registry is to provide data on age-related clinical features of suspected myocarditis and to create a study platform allowing for deriving diagnostic criteria and, at a later stage, testing therapeutic interventions in patients with myocarditis.

Study design and results After an initial 6-month pilot phase, MYKKE was opened in June 2014 as a prospective multicenter registry for patients from pediatric heart centers, university hospitals, and community hospitals with pediatric cardiology wards in Germany. Inclusion criteria consisted of age<18 years and hospitalization for suspected myocarditis as leading diagnosis at the discretion of the treating physician. By December 31, 2015, fifteen centers across Germany were actively participating and had enrolled 149 patients. Baseline data reveal 2 age peaks (<2 years, >12 years), show higher proportions of males, and document a high prevalence of severe disease courses in pediatric patients with suspected myocarditis. Severe clinical courses and early adverse events were more prevalent in younger patients and were related to severely impaired leftventricular ejection fraction at initial presentation.

Summary MYKKE represents a multicenter registry and research platform for children and adolescents with suspected myocarditis that achieve steady recruitment and generate a wide range of real-world data on clinical course, diagnostic workup, and treatment of this group of patients. The baseline data reveal the presence of 2 age peaks and provide important insights into the severity of disease in children with suspected myocarditis. In the future, MYKKE might facilitate interventional substudies by providing an established collaborating network using common diagnostic approaches. (Am Heart J 2017;187:133-144.)

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In patients under the age of 18 years, myocarditis despite a low prevalence is one of the leading causes for congestive heart failure and dilative cardiomyopathy, which accounts for >80% of noncongenital pediatric cases listed for heart transplantation.[1] Although these patients represent the severe end of clinical courses, there are others who experience temporary chest pain with normal ventricular function or even go unnoticed.[2] This wide and yet nonspecific set of clinical presentations is one of the reasons why establishing the diagnosis of myocarditis in many cases remains challenging.[3] Another reason is the limited diagnostic accuracy of available invasive and noninvasive diagnostic tests. Previous attempts to define standardized cutoff values for endomyocardial biopsy (EMB) or magnetic resonance imaging (MRI) based on expert consensus (Dallas criteria and Lake Louise criteria, respectively)[4,5] resulted in single-modality classifications that suffered from unsatisfactory sensitivity and specificity, producing a large number of both false-negative and false-positive results (based on clinical history and course) when applied to individual real-world patients. New developments in EMB analysis (immunohistology, viral polymerase chain reaction) and MRI acquisition strategies (T1 mapping, T2 mapping)[6,7] might help to obtain more detailed information on the myocardium but have not been tested in multicenter trials. Although there are widely accepted recommendations regarding scenarios where EMB should be performed, these recommendations do not comment on the clinical significance of potential results.[8] Recently, standardized criteria for the clinical diagnosis of myocarditis in adults have been proposed by the European Society of Cardiology Working Group on Myocardial and Pericardial Disease,[9] which are solely based on expert consensus (level of evidence C) and so far have not been validated. The authors of that document encourage a wider use of EMB in patients with suspected myocarditis. Also, the German Society for Pediatric Cardiology proposed a diagnostic flowchart for pediatric patients based on expert consensus only.[10]

The trigger mechanism in most cases of myocarditis is believed to be acute viral infection. The fact that otherwise benign viruses are involved (which only cause minor noncardiac infections in most subjects) indicates that the response of the immune system is a major determinant of the resulting injury to the myocardium.[11] Accordingly, genetic background and specific conditions affecting the immunologic state such as young age might lead to different patterns of the immune response to viral infection of the myocardium and thus to different clinical courses and outcome.[12,13]

Whereas systematic data from adult patients with myocarditis are limited, the situation in pediatric patients is even worse.[14] Most studies are based on single-center experience and/or retrospective data collection.[15-17] To our knowledge, the largest prospective study published so far involved 173 children (aged 3.7 ± 2.9 years) admitted to the National Institute of Cardiovascular Disease in Karachi/Pakistan, of which 80 were randomized to receive prednisolone or not.[18] There are no published data on normal values for invasively or noninvasively assessed parameters of myocardial tissue composition.

Rationale of the MYKKE registry

The aim of this project is to overcome the lack of prospectively collected multicenter data on epidemiology, clinical presentation, and diagnostic value of currently available diagnostic tools in children and adolescents with myocarditis to define age-specific properties and to establish clinically meaningful criteria for the diagnosis of myocarditis. To this end, MYKKE is designed to include patients with *suspected* myocarditis rather than patients with *definitive* myocarditis only, as the latter would introduce a preselection of cases and thus make an open evaluation of diagnostic criteria impossible. If successful, the infrastructure and results established in this project might serve as a platform for diagnostic and interventional substudies in myocarditis in the future.

Methods

Study design

MYKKE is a long-term prospective registry providing a research platform for clinical studies that are attached in a modular fashion. After a 1-year pilot phase including 8 centers, the registry was opened in June 2014 to all hospitals in Germany treating pediatric patients with heart disease. Although the scientific lead is with 2 study coordinators (D.M. and S.S.) and a study group consisting of principal investigators from the collaborating centers ("MYKKE Investigators"), MYKKE is hosted and technically administered by the Competence Network for Congenital Heart Defects, which was initiated in 2003 by the Federal Ministry of Education and Research of the German government and is now an associated partner of the German Center for Cardiovascular Research (DZHK). Statistical advice for MYKKE is provided by a statistician affiliated with the DZHK (T. F.). Ethical approval was first obtained at the initiating center (Deutsches Herzzentrum Berlin) and subsequently confirmed by local authorities of all collaborating centers.

The treating physicians enter basic data from patients enrolled at the study site to a central study database via an online Web interface. For each patient, a specific patient identification number is generated based on name, first name, and date of birth to store data in a pseudonymized fashion. As the patient identification numbers are generated by a specific algorithm, data from the same patient are always linked to the same dataset even when

data from different visits are entered by different institutions.

Data capturing

The Web interface provides 2 different forms for each patient. The first form ("general sheet") is filled in only at first presentation and consists of 12 items regarding disease and patient history, and initial symptoms of the disease. The second type of sheet ("current visit") can be generated once for each new patient visit and includes 52 items on characteristics of the current visit, current symptoms, diagnostic tests performed, confidence of the treating physician in the diagnosis on a subjective scale, leftventricular (LV) function, therapy, complications, and follow-up care provider after discharge. Items primarily require yes/no responses via ticking respective boxes, allowing for completing each data sheet in <5 minutes when all data are available.

Study population

The inclusion criteria are as follows:

- Suspected myocarditis as the leading diagnosis for referral/diagnostic workup and hospital admission
- Age< 18 years.

The exclusion criteria are as follows:

- Unwillingness of the adolescents, parents, or legal guardians to provide written consent allowing for storing and analyzing all clinical data of the patient in a pseudonymized way in the central study database.

Substudy on diagnostic criteria

MYKKE is a modular platform facilitating substudies with additional items. The first substudy to be built upon this platform ("MYKKE-DIAGNOSE") will consist of 2 stages and will have the aim to derive evidence-based diagnostic criteria for the diagnosis of myocarditis in children and adolescents.

Stage 1: development of diagnostic criteria. In stage 1, the basic data of the first 150 MYKKE patients that are stored in the central database will be enriched with results from clinical tests by revising clinical records at the study sites.

Myocarditis will be defined by the following findings or combinations thereof: positive EMB result, typical hyperenhancement on late gadolinium-enhanced MRI,and temporary or persisting signs of ventricular dysfunction or serologic evidence of myocardial injury within the first year after the onset of symptoms in the absence of noninflammatory causes of heart failure. Where 1-year follow-up data are incomplete, patients will be contacted and asked do undergo a follow-up cardiologic assessment at the initial site including cardiopulmonary exercise testing, echocardiography, and assessment of brain natriuretic peptide (BNP)/proBNP levels. An adjudication committee will review ambiguous cases.

Parameters to be assessed and tested for their value as diagnostic criteria include levels of C-reactive protein, troponin, and BNP/N-terminal prohormone of brain natriuretic peptide (NT-proBNP) on laboratory testing; arrhythmia and alterations of ST-segments on electrocardiogram (ECG); arrhythmia on 24-h Holter ECG; LV and right ventricular (RV) size and function on echocardiography; LV and RV function and size; presence of pericardial effusion, myocardial T1, and extracellular volume on MRI; and copies of viral DNA by PCR on EMB.

In a first step, the enriched database of these 150 patients will be used to assess the diagnostic accuracy of the diagnostic criteria for myocarditis outlined by the position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases[7] at initial presentation to identify patients with the diagnosis of myocarditis based on the definition described above. In a second step, logistic regression analysis will be applied to test which combinations of symptoms and diagnostic parameters at initial presentation yield the highest diagnostic accuracy to identify patients with the diagnosis of myocarditis. A diagnostic score will be derived based on the most specific symptoms and on the test results that retrospectively best identify patients with myocarditis in this initial cohort.

Stage 2: validation of diagnostic criteria and score. In stage 2 of this substudy, the full clinical data of the next 100 patients (expected enrolment: end of 2016 until end of 2017) will be captured, and 1-year follow-up data will be retrieved according to stage 1. Finally, the diagnostic score derived in the first cohort of patients will be applied to the second cohort, and the diagnostic accuracy (sensitivity, specificity, and positive and negative predictive values) of the score for identifying a patient with myocarditis at admission will be calculated and compared with conventional criteria[9] and with the results of EMB alone.

MYKKE as a platform for therapeutic interventions

After completion of stages 1 and 2 of the substudy on diagnostic criteria, MYKKE will serve as a study platform for interventional substudies by providing an established multicenter infrastructure with continuous access to patients with acute myocarditis. Based on this infrastructure, MYKKE patients will be invited to take part in prospective trials testing, for example, the use of angiotensin-converting enzyme inhibitors and immunoglobulins in symptomatic patients with normal LV ejection fraction (LVEF) at presentation or the effects of anti-inflammatory therapy in patients with persistent inflammatory response and impaired ventricular function.

Figure 1

Number of active recruitment sites (A) and enrolled patients (B) by quarter until end of December 2015.

Statistical analyses

General aspects of the MYKKE registry. Statistical advice is provided by a statistician who is affiliated with the DZHK (T. F.). The nature of statistical analyses will be determined by individual substudies.

Baseline data. Categorical variables are summarized by frequencies and percentages. For continuous measures, means and standard deviations are provided if they are approximately normal; otherwise, their distribution is described by appropriate percentiles.

Missing values in the baseline characteristics will be dealt with by multiple imputations. The diagnostic value of the tests and scores derived from the data of the first stage will be validated by an independent sample (stage 2). Again, sensitivity, specificity, and area under the receiver operating characteristic curve (AUROC) will be reported with 95% CIs. The prognostic accuracy of initial findings to predict hospitalization for heart failure, necessity for ventricular assist device therapy, heart transplantation, or death will be assessed in appropriate regression models. For time-to-event outcomes (eg, death), Cox proportional hazards models will be used, whereas recurrent events such as heart failure hospitalizations will be modeled by negative binomial distributions. For binary outcomes (eg, necessity for ventricular assist device therapy), logistic regressions will be used as for the primary outcome.

Severity of disease. A *severe disease course* was defined by the occurrence of at least 1 of the following events: death, survived sudden cardiac death, assist device implantation, *decompensated heart failure* (defined as acute right or left heart failure with peripheral edema and/or pulmonary congestion), heart transplantation, catecholamine therapy, or malignant arrhythmia. The outcome "severe disease course" was modeled in a logistic regression with age and gender as independent variables. The effects were assessed as odds ratios with 95% CIs.

LV ejection fraction. To the logistic regression model described above, LVEF was added as an independent variable to assess its effect on the likelihood for a severe disease course. Additionally, we modeled the likelihood of severely impaired LVEF (<30%) depending on age and gender in a logistic regression.

Substudy to develop diagnostic criteria. The diagnostic value of binary variables will be assessed by sensitivity and specificity, which will be reported with 95% CIs. The diagnostic value of continuous measurements will be assessed in receiver operating characteristics (ROC) curves. The AUROC will be reported as summary measure with 95% CI. Furthermore, the presence/absence of myocarditis will be modeled by a logistic regression with various combinations of baseline characteristics and diagnostics as independent variables to derive a prognostic score. An optimal cutpoint for the score will be determined in ROC analyses corrected by the cross-validation for bias in the estimation of the AUROC.

Table I. Baseline characteristics of the first 149 patients as collected on a baseline form for each patient via the online Web portal at the initial presentation (percentage of positive queries)

1. Gender and history	
Gender	Male: 66.4%, female: 33.6% (n = 149)
Onset of symptoms (days before admission)	16.1 ± 41.8 (n = 149)
Infection <6 wk prior to onset of symptoms	54.8% (80/146)
Fever <6 wk prior to onset of symptoms	36.7% (54/147)
Preexisting heart condition	None: 94.0%, congenital/single: 0.7%, congenital/complex: 0.0%, primary cardiomyopathy: 1.3%, other: 4.0% (n = 149)
Sports activities	Unknown: 23.6%, age-based (eg, school sport): 56.1%, recreational: 16.2%, competitive: 4.1% (n = 148)
2. Initial symptoms	
Exercise intolerance	70.9% (105/148)
Angina pectoris	41.9% (62/148)
Dyspnea	37.2% (55/148)
Arrhythmia	30.4% (45/148)
Feeding intolerance	18.2% (27/148)
Syncope	12.2% (18/148)
Sudden cardiac death	2.7% (4/148)
Other	14.8% (22/149) including nausea/vomiting (5), loss of appetite (2), fever (2), abdominal pain, zyanosis, coughing, paresthesia of left hand, increased sensitivity to touch, sinus tachycardia, hypertension, epistaxis, perspiration, upper respiratory tract infection, sore throat, erythema migrans, tick bite

Baseline characteristics of the first 149 patients as collected on a baseline form for each patient via the online Web portal at the initial presentation (percentage of positive queries).

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Logistic support and management of the research database are provided by the Competence Network for Congenital Heart Defects (Berlin, Germany), which received funding from the Federal Ministry of Education and Research, grant number 01GI0601 (until 2014), and the DZHK (as of 2015).

Results

Baseline data

By December 31, 2015, fifteen centers across Germany (4 heart centers, 10 university hospitals, 1 community hospital) were actively participating in MYKKE and had enrolled 149 patients. Figure 1 illustrates the increase in recruitment sites and patients enrolled since the beginning of the study.

Tables I and II provide the baseline data of the patients enrolled so far.

Two age groups are dominating at presentation: the first year of life and adolescence (Figure 2). In the age group 0-<2 years, there is almost an even distribution of males (n = 18) versus females (n = 14). At closer analysis, 37.5% of cases (n = 12) in this group show symptoms during the first 10 days of life, 15.6% at birth (n = 5). In the adolescent group (13 to 17 years; n = 96), males (n = 68) account for approximately two thirds of patients. Only a minority of patients (n = 21; 14%) present at age 2 to 12 years.

Severity of disease as a function of age and gender

Out of 149 patients, 57 patients (38%) met at least 1 of the following criteria: death, survived sudden cardiac death, assist device, decompensated heart failure, heart transplantation, catecholamine therapy, or malignant arrhythmia. Taking this combined endpoint as a marker for a severe course of disease, the influence of age and gender on this combined end point was examined. The odds for a severe disease course decreased statistically significantly with age by 14% per year (95% CI,8%-19%;$P < .001$) (Figure 3), and there were higher frequencies of adverse events in younger patients, especially in the 0- to <2-year group (Figure 4). The same group also had the highest frequency in severe reduction of LV function as defined by LVEF <30% (Figure 5).

There was no statistically significant difference in the overall rates of severe courses between male and female patients ($P = .3133$).

LV ejection fraction

Data on LVEF, categorized as normal (≥55%), mildly impaired (45%-54%), moderately impaired (30%-44%), or severely impaired (<30%), were available for 140 of the 149 patients (93.6%) (Table II, "5. LV function"). Most of these data were obtained from echocardiography (74.3%), followed by MRI (22.1%) and levocardiography (3.6%). Adjusted for age and gender, LVEF had a statistically significant effect on the likelihood for a severe disease course ($P < .001$), whereby patients with severely impaired ejection fraction (<30%) had the worst outcome (Figure 6). The prevalence of severely impaired ejection fraction was higher in younger patients ($P < .001$), with the odds for a severe impairment decreasing by 15% per year (95% CI,10%-21%) (Figure 7). In the analysis, we found a trend indicating that the severe impairment is more prominent in females ($P = .0522$).

Discussion

In the past, clinical research on myocarditis has primarily been performed by single centers and provided only limited insight into the epidemiology, clinical course, and impact of diagnostic and therapeutic actions for 2 reasons. Firstly, single centers do not see large numbers of pediatric patients with myocarditis. Although there are no systematic data on the prevalence or incidence of myocarditis in children and adolescents, information, for example, from analyses of admission rates and pathology databases,[19] indicates that this condition meets the formal definition of a rare disease (ie, prevalence of <5/10,000). Secondly, there is a wide range of clinical presentations; as most hospitals/departments have specific clinical core expertise, they only get to see a fraction of the spectrum rather than the full picture.

MYKKE aims to overcome these deficits by providing a long-term multicenter research platform facilitating the conduct of epidemiological, diagnostic, and interventional studies alike. The first results indicate an enrolment rate of 80-100 cases per year by the currently participating centers, for the first time providing prospective multicenter data at a volume and rate that enable epidemiologic studies and that should allow for systematic validation of diagnostic and therapeutic approaches. In rare diseases and pediatric settings, the conduct of randomized controlled trials (RCTs) can be extremely difficult. A clinical registry such as MYKKE represents an invaluable resource this situation because it provides not only efficient access to patients and vital information for trial planning of RCTs but also data that could formally be incorporated into the RCT analysis through so-called generalized or cross-design evidence synthesis approaches. These statistical methods are conceptual extensions of random-effects meta-analyses, resulting in a higher gain of information in the RCT and a more efficient use of resources.

The baseline data provide a variety of insights into the characteristics of pediatric patients with suspected myocarditis and into the utilization of diagnostic and therapeutic methods in this patient group. The age distribution clearly shows a peak in case numbers within the first 2 years of life and a second starting with the onset of adolescence. A similar age distribution has been described by a retrospective review of a large administrative database from the United States.[17] Moreover, gender distribution in the US database was comparable to that in MYKKE (64% vs 66%). Whereas that study could show that children <12 years of age had a higher mortality or transplantation rate than patients >12 years of age, the MYKKE baseline data further show that young patients not only are more likely to experience a severe course of the disease but also present with significantly lower LVEF than older patients. As young children are frequently not able to communicate mild symptoms, there might be an unknown number of young patients who go unrecognized. It is not impossible that this even holds true for patients in the midrange age group (2 to 12 years), who should be able to communicate cardiac symptoms but still might not do it, as they might not realize that their symptoms could be unusual.

Taking these findings together, we hypothesize that there are different disease mechanisms in place in these age groups. The identification of these mechanisms will be one of the fields of research the MYKKE platform will serve as a basis for.

The study design of MYKKE was centered on 2 premises. First, a critical point in any multicenter activity is recruitment that hinges on the willingness and practical ability of the investigators "on the ground" to actually enroll patients in addition to their routine clinical duties. Thus, to avoid anything that could discourage physicians from doing so, a short and simple online Web form was designed, refraining from overly complicated queries of diagnostic results etc. It was decided to focus on basic information at enrollment and to postpone the enrichment of datasets to a later time point as part of modular substudies, which then would be supported financially and staffwise in a way that would minimize the burden of extra work for the treating physicians as much as possible. Besides the envisaged substudy on diagnostic criteria, other modules in the future might cover advanced phenotyping methods, therapeutic interventions, or research into quality of life and might be directed at the entire cohort or at subgroups only.

Second, the search for standardized clinical diagnostic criteria was set as the short-term major goal of the study. To avoid any bias in this search by preselecting diagnostic criteria, we decided to refrain from asking for any specific symptoms or test findings for inclusion and rather took the genuine clinical referral diagnosis of the treating

Table II. Baseline data of the first 149 patients collected on visit forms at first admission, as entered once for each stay of the patients via the online Web portal (percentage of positive queries)

1. Visit	
Route of admission	Self: 9.4%, emergency room: 8.1%, outpatient clinic: 2.7%, private practice: 24.8%, other hospital: 55.0% (n = 149)
Outpatient	4.0% (6/149)
Inpatient	96.0% (143/149)
If yes: length of stay (d)	21.7 ± 45.80 (n = 138); median 8; range 0 to 490
If yes: intensive care	54.9% (78/148)
2. Current symptoms	
Dyspnea, NYHA class	I: 53.4%, II: 20.9%, III: 7.4%, IV: 18.2% (n = 148)
Chest pain, CCS class	0: 55.2%, I: 10.3%, II: 13.8%, III: 6.9%/IV: 13.8% (n = 145)
Arrhythmia, perceived	22.3% (33/148)
Arrhythmia, documented	36.9% (55/149)
Weakness, fatigue	73.6% (109/148)
Other	20.8% (31/149) including nausea/vomiting (5), agitation (4), feeding intolerance (4), fever (4), coughing (3), sore throat (3), headache (2), dizziness (2), cardiogenic shock (2), diarrhea, epistaxis, exanthema, perspiration, sinus tachycardia, presyncope, syncope, gastroenteritis, loss of appetite, pleural effusion
3. Diagnostics	
12-lead ECG	98.7% (147/149)
24-h Holter ECG	53.4% (79/148)
ECG monitoring	96.0% (143/149)
Laboratory: blood count	99.3% (148/149)
Laboratory: CRP	97.3% (145/149)
Laboratory: Troponin	97.3% (145/149)
Laboratory: BNP or NT-proBNP	88.6% (132/149)
Laboratory: serologic virus screening	53.4% (79/148)
Chest X-ray	70.9% (105/148)
Echocardiography	99.3% (148/149)
Cardiac MRI	53.7% (80/149)
X-ray coronary angiogram	50.3% (75/149)
X-ray angiography: EMB RV	45.6% (68/149)
X-ray angiography: EMB LV	7.4% (11/149)
Other	15.4% (23/149) including EP study (5), metabolic testing (4), virus PCR other than blood (4), borreliosis serology (3), ajmaline/catecholamine testing (3), lumbar puncture (2), exercise testing (2), electroencephalography, transesophageal echocardiography, genetic testing
4. Myocarditis diagnosis	
Certainty of diagnosis	5 = definitive, no alternative possible: 27.4% (45/144) 4 = certain, alternatives theoretically possible: 22.9% (33/144) 3 = probable, alternatives possible: 19.4% (28/144) 2 = possible, alternatives with equal certainty: 10.4% (15/144) 1 = possible, alternatives with higher certainty: 9.0% (13/144) 0 = excluded, alternatives definitely diagnosed: 6.9% (10/144)
If 0: alternatively diagnosed disease	Dilated cardiomyopathy (3), tachycardia-induced cardiomyopathy (3), hypertrophic cardiomyopathy, noncardiac infection, acute myocardial infarction due to coronary aneurysm after Kawasaki disease
If 0: diagnostic method	EMB (4), EP study (2), cardiac MRI (2), coronary angiography, genetic testing, TTE
5. LV function	
Minimal EF (%)	<30: 23.6%, 30-44: 15.0%, 45-54: 19.3%, ≥55: 42.1% (n = 140)
Applied method	Echocardiography: 74.3%, MRI 22.1%, levocardiography: 3.6% (n = 140)

(continued on next page)

Table II (*continued*)

1. Visit	
6. Therapy	
Physical rest	94.0% (140/149)
Pharmacologic therapy	Heart failure: 55.0%, catecholamines: 28.9%, antiarrhythmic: 26.2%, nonsteroidal anti-inflammatory: 26.8%, corticosteroids: 5.4%, interferon-β: 0.0%, immunoglobulins: 28.9%, virostatic: 2.7% (n = 147–149)
Ventilation	20.9% (31/148)
Device	Pacemaker: 3.4%, ICD: 4.7%, CRT: 0.0%, VAD: 8.1% (n = 149)
Other therapies	17.5% (24/149) including antibiotics (7), ECMO (7), anticoagulant therapy (2), EP ablation (4), calcium sensitizer, pericardial puncture, PFO closure, PAB
7. Adverse events	
Death	2.8% (4/144)
Heart transplantation	2.1% (3/140)
Acute heart failure	20.4% (29/142)
Heart block	5.7% (8/141)
Malignant tachycardia	14.1% (20/142)
Other adverse events	3.4% (5/149) including liver failure, pericardial tamponade, capillary leak syndrome, stroke, aspiration pneumonia, aseptic meningitis
8. Discharge	
Follow-up	Heart center: 27.9%, outpatient clinic: 37.1%, private pediatric cardiologist: 29.3%, private cardiologist: 0%, private pediatrician: 3.6%, general practitioner: 2.1%, none: 0% (n = 140)

NYHA, New York Heart Association;*CCS*, Canadian Cardiovascular Society;*CRP*, C-reactive protein; *TTE*, transthoracic echocardiography; *ICD*, implantable cardioverter/defibrillator;*EP*, electrophysiologic;*VAD*, ventricular assist device;*ECMO*, extracorporeal membrane oxygenation.

physician as inclusion criterion. Thus, MYKKE indeed is a registry of pediatric patients with suspected rather than proven myocarditis—as we believe that an appropriate way of diagnosing myocarditis is yet to be defined and the aim of this project is to collect the evidence that allows for doing so. Accordingly, some of the data recorded in MYKKE originate from patients without myocarditis and might provide important insights into alternative causes of heart failure in the young. Given the high rate of EMB (45.6%) and cardiac MRI (53.7%) performed in the patients who were enrolled in MYKKE so far, we are confident that it will be possible to identify patients with "true" myocarditis and evaluate the diagnostic performance of clinical parameters by combining the results from various analyses (see "Methods" section).

Limitations

Fifteen sites contributed to the data presented here. Although these sites represent the majority of pediatric heart centers and are located across all regions in Germany, there are some centers remaining who did not participate. Moreover, a significant number of patients might have been seen by general pediatric departments with basic cardiologic services, which do not participate in the registry. Thus, it is not possible to derive numbers on prevalence or incidence of pediatric myocarditis from MYKKE data at this stage.

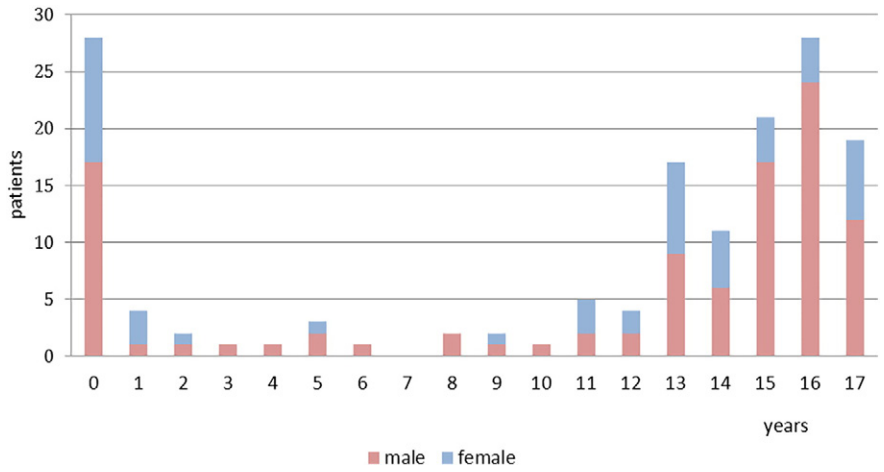
MYKKE is currently including German centers only. Given the viral component of the disease and the heterogeneous epidemic distribution of these viruses, there might be differences in clinical presentation of patients from different regions and climate zones (eg, northern vs southern Europe), which cannot be detected with MYKKE. However, we plan to extend the geographic coverage and open MYKKE to international centers with an interest in participating in this multicenter endeavor.

Although we could determine the proportion of patients who received catecholamines during their initial hospital stay, we have no data on the use of other inotropic agents such as milrinone, as this information was not requested in the online case report form. Thus, there might be a subgroup of patients who required treatment with inotropic drugs but who were not assigned to the "severe course" group of patients. For subsequent patients, MYKKE's online case report form has been extended to include an additional question asking about the use of "Inotropic agents other than catecholamines".

Conclusions

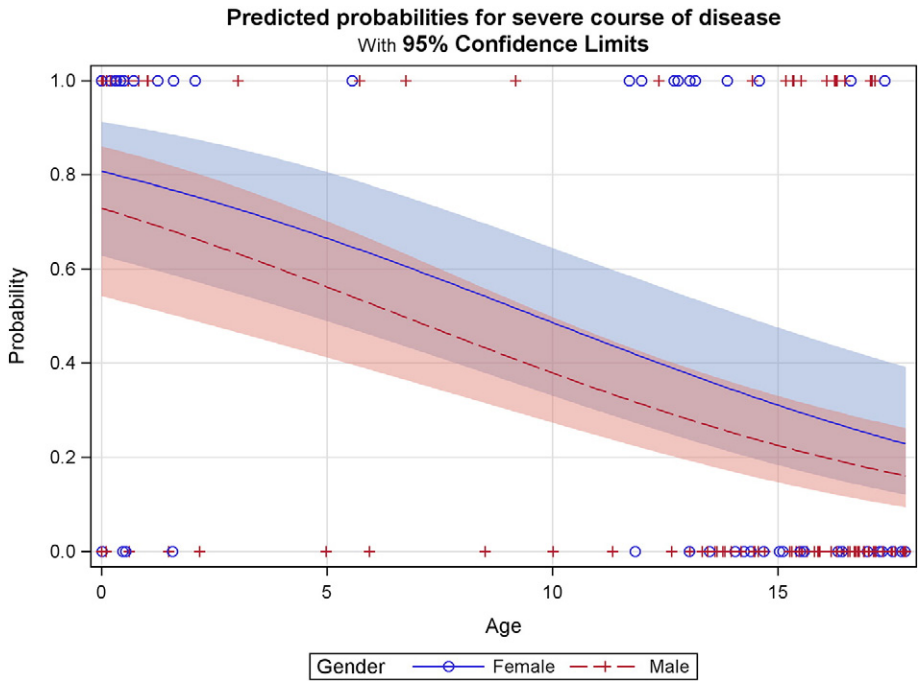
MYKKE is the first multicenter prospective registry for children and adolescents with suspected myocarditis that is designed to collect evidence on epidemiology, diagnosis, and therapy in this disease. The baseline data

Figure 2



Distribution of gender and age at initial presentation (n = 149).

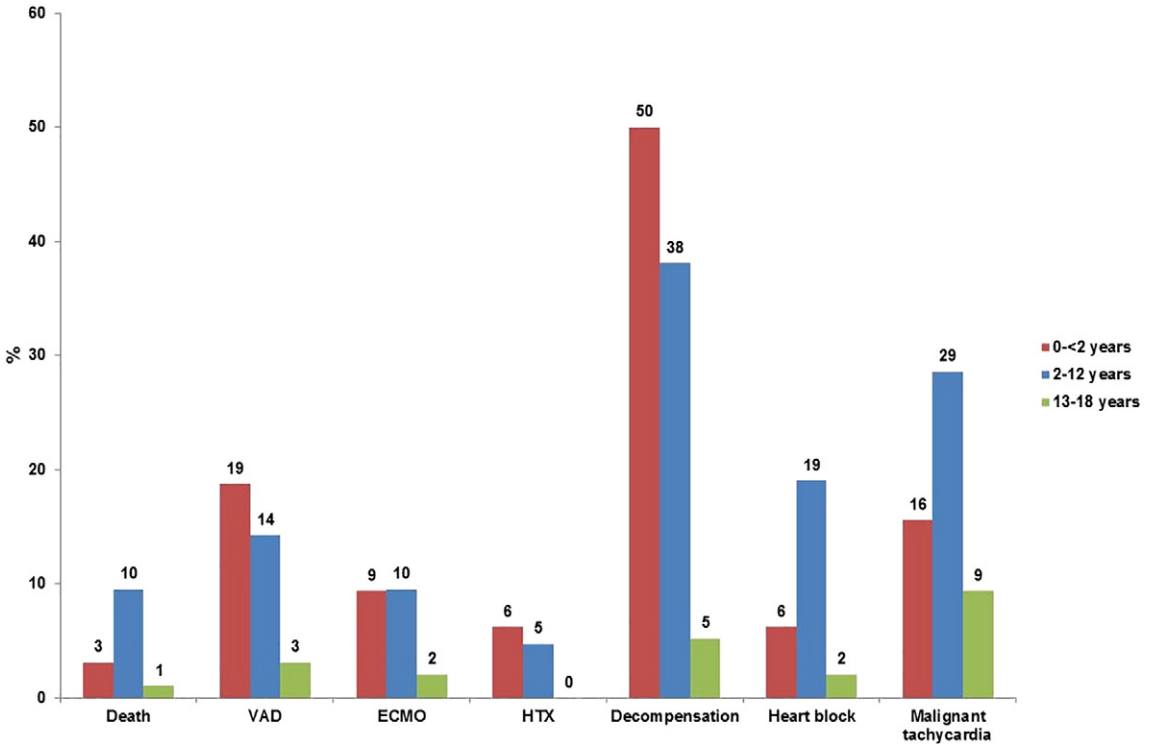
Figure 3



Probability of severe disease course depending on age (in years) by gender as predicted by logistic regression with age and gender as independent variables (see text for details). Circles and crosses indicate the observations for girls and boys, respectively.

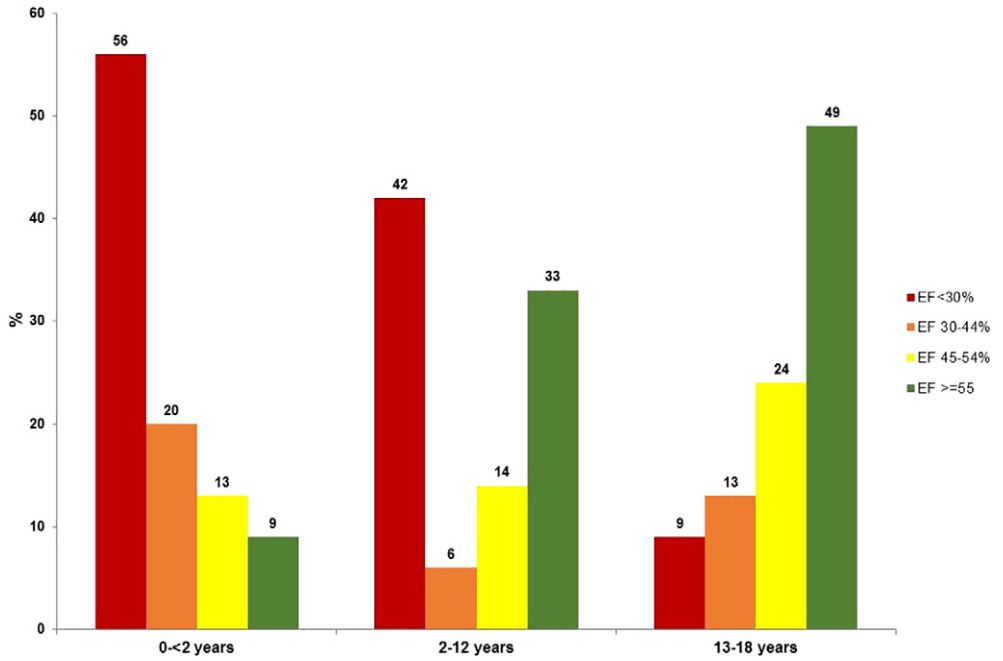
from 149 patients enrolled at 15 centers reveal 2 age peaks and a high proportion of patients with severe courses of disease and early adverse events including the need for mechanical circulatory support, heart transplantation, and death. Severe courses of disease are related to younger age and to severely impaired LVEF at the initial presentation. The major aim of the first phase of MYKKE is to establish standardized criteria for the diagnosis of

Figure 4



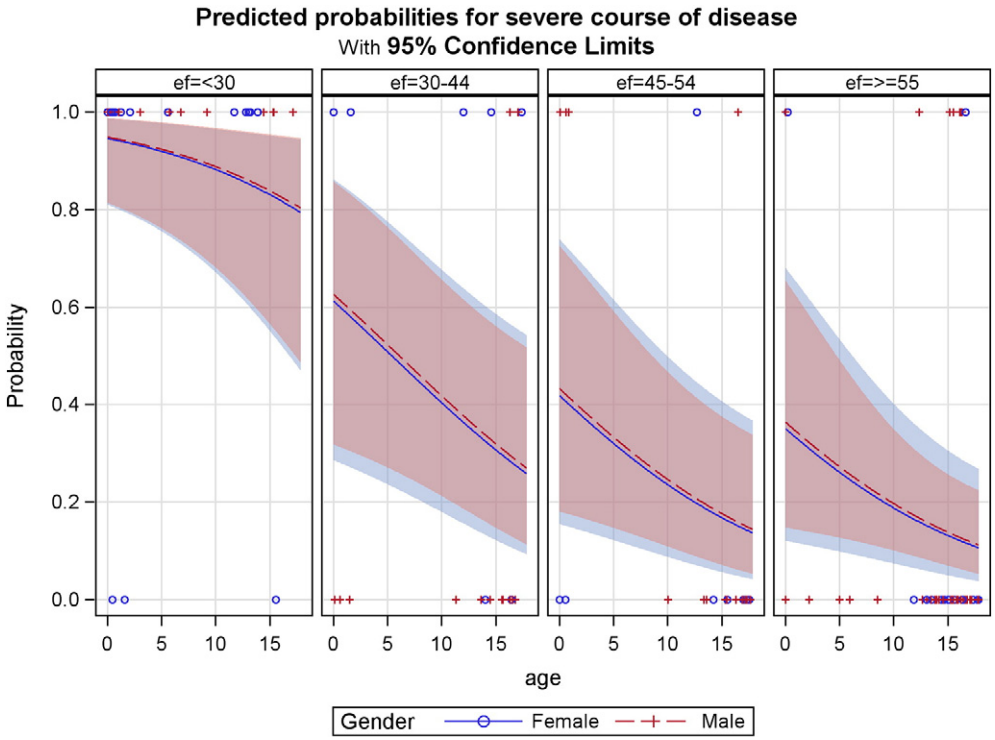
Percentage adverse events within age groups: 0-<2 years (n = 32), 2-12 years (n = 21), and 13-18 years (n = 96).

Figure 5



Distribution of LVEF within age groups 0-<2 years, 2-12 years, and 13-18 years.

Figure 6



Probability of severe disease course depending on age (in years) by gender and ejection fraction (as predicted by the logistic regression with age, gender, and ejection fraction as independent variables [see text for details]). Circles and crosses indicate the observations for girls and boys, respectively.

myocarditis. Further analyses and studies are underway to test the performance of invasive and noninvasive diagnostic tests and the outcome of patients undergoing different therapeutic strategies.

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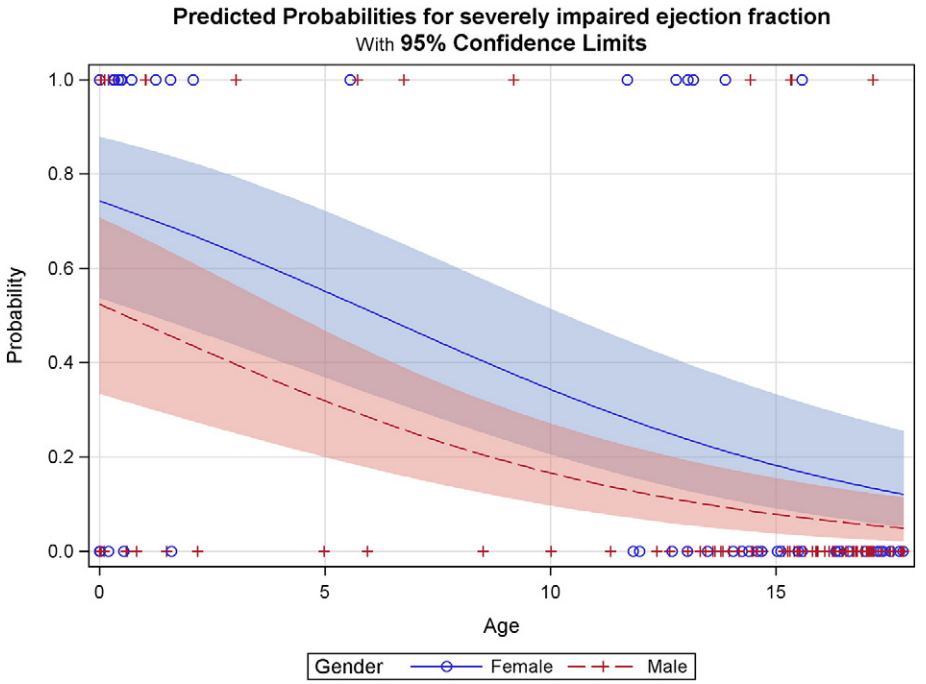
Figure 7



Probability of severely impaired ejection fraction depending on age (in years) by gender as predicted by the logistic regression with age and gender as independent variables (see text for details). Circles and crosses indicate observations for girls and boys, respectively.

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