

Age-associated clinical patterns in paediatric myocarditis: left ventricular function as the key early risk stratifier

Short title: Age-associated clinical patterns in paediatric myocarditis

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Disclosure of interest

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Abstract

Background and Aims

In myocarditis, early identification of high-risk patients is essential, robust prognostic markers are lacking. We aimed to identify early clinical risk stratifier at index hospitalization for major adverse cardiovascular events (MACE).

Methods

We analysed 725 paediatric patients with possible/definite myocarditis enrolled in the prospective multicentre MYKKE registry (2013–2024). MACE included mechanical circulatory support (MCS), heart transplantation, or death during initial admission. Model-based recursive partitioning (MOB) and bootstrap-based logistic regression with multiple imputation were applied for risk stratifier selection out of 20 baseline variables. The model was externally validated in the Swedish SWEDCON- cohort (n=243). Discrimination was assessed by the area under the curve (AUC).

Results

Among 725 patients (median age 14.3 years [IQR 4.0–16.4]; 33% female), 88 (12.2%) experienced MACE (MCS 10.9%, transplantation 4.3%, death 2.2%). MOB identified left ventricular ejection fraction (LVEF) $\leq 39\%$ as the only stable risk stratifier, delineating a “heart failure type” in younger children (1.9 years; LVEF 24%), and a “chest pain type” in adolescents with preserved LVEF (15.6 years; LVEF 59%). LVEF was confirmed as the sole robust risk stratifier (OR per 1% increase: 0.90 ;95% CI 0.881-0.917; $p < 0.01$; AUC 0.90, 95% CI 0.896–0.903). In SWEDCON (7.4% MACE), discrimination was maintained (AUC 0.894, 95% CI 0.80–0.991).

Conclusion

Reduced LVEF at presentation was the only reproducible and externally validated risk stratifier of MACE during index hospitalization. Two age-associated clinical patterns were observed: a high-risk “heart failure type” in younger children and low-risk “chest pain type” in adolescents.

Keywords:

Myocarditis; heart failure; chest pain; risk groups; outcome; paediatric

Background

Myocarditis is a major cause of acute heart failure and life-threatening arrhythmias in children and adolescents. While some patients present asymptomatic or with mild symptoms and recover spontaneously, others require mechanical circulatory support (MCS), heart transplantation (HTX), or die (1, 2). Early identification of children at high risk for adverse outcomes remains a clinical challenge (3). Although cardiac magnetic resonance and endomyocardial biopsy provide important diagnostic information and might have a prognostic impact, they are usually unavailable at admission (1). Therefore, a simple, readily available risk stratification tool is urgently needed to guide early clinical decision-making. To investigate disease presentation, course, and outcomes in paediatric patients with myocarditis the multicentre registry “MYKKE” was established.

Aims

This study aimed to identify early clinical risk stratifier for major adverse cardiovascular events (MACE) in paediatric myocarditis based on readily available information at hospital admission. The goal was to develop a simple, robust tool to support early clinical decision making and to guide patient monitoring and therapeutic strategies.

Methods

This analysis was based on data from the MYKKE-Registry, a prospective multicentre study of children and adolescents hospitalized with myocarditis (4). Patients aged <18 years were enrolled with possible or biopsy- and/or cardiac magnetic resonance imaging (CMR)-proven (definite) myocarditis according to the established diagnostic criteria (1) between 2013 and 2024 from 25 paediatric cardiology centres. Written informed consent was given from parents or legal guardians. The study was approved by the ethics committee of the Charité–Universitätsmedizin Berlin (EA2/074/13) and by the local ethics boards of all participating centres.

Baseline clinical, electrocardiographic, echocardiographic, and laboratory data were prospectively collected and entered into an online study database. Left ventricular ejection fraction (LVEF) was assessed by transthoracic echocardiography at first admission at each participating centre and entered as locally reported values, echocardiograms were not centrally re-analysed. The primary endpoint was the occurrence of MACE, defined as the need for MCS, HTX, or death.

To identify subgroups with different risk profiles, we performed model-based recursive partitioning (MOB), which is a tree-based method using logistic regression with internal instability tests to define statistically robust split points. The algorithm evaluated 20 preselected variables, including demographic characteristics, medical history, clinical presentation, laboratory parameters including elevated troponin, electrocardiogram findings, malign arrhythmias, LVEF and Z-Score of the left ventricular internal diameter in diastole (LVIDd), as well as CMR-derived late gadolinium enhancement (LGE) where available (Figure 1A). Candidate variables were prespecified as parameters routinely and objectively available at first admission and recognised as markers of disease severity in myocarditis. Variables that were not meaningful for children of all ages (NYHA class, angina pectoris, feeding intolerance), and variables with >40% missingness, were not included.

A multivariable logistic regression model was then derived to calculate a numeric risk score (5). Missing baseline values for the 20 preselected variables were completed by multiple imputation using chained equations (R package 'mice', v3.7.0) (6): predictive mean matching for continuous and logistic regression for binary variables. The imputation model included MACE and all 20 preselected variables; 100 datasets were imputed. Backward selection (AIC) was applied on 100 bootstrap samples of the imputed data, and variables selected in >70% of models were retained (7). Final coefficients were pooled using Rubin's rules (8).

Discriminatory performance was assessed by the area under the receiver operating characteristic curve (AUC).

Internal validation and bias correction were performed using as well bootstrap resampling. For each bootstrap model, we calculated the difference between apparent and test performance to estimate overoptimism. Calibration was assessed using the logistic recalibration framework; intercept and slope were corrected for bias using the same resampling approach.

Patients with missing data on the primary outcome were excluded from model development.

External validation was performed in an independent cohort of 243 children and adolescents with possible or definite myocarditis from the Swedish SWEDCON registry, in whom LVEF, age, and all components of the composite endpoint were available (9). In the validation cohort, the Youden index was used to assess the sensitivity and specificity of the model of model in the validation cohort. The LVEF-based model derived from the MYKKE cohort was applied without refitting, and its discrimination was assessed by the AUC.

Results

A total of 725 children and adolescents with possible or definite myocarditis (median (IQR) age 14.3 (4.0–16.4) years; 33% female) were included in the analysis. During the initial hospitalization, 88 patients (12.2%) experienced at least one MACE. Overall, 79 (10.9%) required mechanical circulatory support, 31 (4.3%) underwent heart transplantation, and 16 (2.2%) died.

Compared with patients without MACE, those with MACE were significantly younger (median age: 1.7 vs. 15.0, $p<0.001$), more frequently presented with severe heart failure symptoms (NYHA IV: 65% vs. 11%, $p<0.001$), reduced LVEF (median 21% vs. 56%, $p<0.001$) and higher N-terminal prohormone of brain natriuretic peptide levels (NT-proBNP, 26366 vs. 400 ng/L, $p<0.001$). CRP levels were lower in the MACE group (3.0 vs. 9.3 mg/L, $p<0.001$), while Troponin T concentrations did not differ significantly ($p=0.704$). MOB identified LVEF $\leq 39\%$ at admission as the only stable split variable. In the bootstrap stability assessment, LVEF was selected in 99% of samples, whereas age at admission was selected in 57% but did not enter the final tree. Patients with LVEF $\leq 39\%$ had a 40% MACE rate compared to 1.2% in those with LVEF $> 39\%$. The individual MACE components were consistently more frequent in patients with an LVEF threshold $\leq 39\%$ vs. $> 39\%$: MCS 36.6% vs. 0.8%, transplantation 14.6% vs. 0.2%, and death 5.5% vs. 1.0%.

Based on these variables, two distinct risk groups were defined (Figure 1B):

Group 1: “Heart failure type” myocarditis – LVEF $\leq 39\%$ ($n=206$, 28.4%). These patients were predominantly infants (1.9 (0.5–11.0) years, 53.4% female), presented with heart failure symptoms (NYHA IV 49.0%), markedly elevated NT-proBNP levels (26.366 (7.810–35.001) ng/L), and significantly enlarged LVIDd (6.1 [3.6–8.3]) and severely reduced LVEF with 24.0 [20.0–30.0]%.

Group 2: “Chest pain type” myocarditis – LVEF >39% (n=519, 71.6%). This group consisted mainly of adolescents (15.6 (12.5-16.7) years) with preserved LVEF (59.0 (52.0-66.0)%), angina pectoris (present in 63.6%), ST-segment elevation (41.6%), and elevated CRP levels 13.6 (1.6-56.6) mg/L. More than two-thirds were male (75.0%).

Multivariable logistic regression with bootstrap-based backward selection confirmed LVEF as the sole robust risk stratifier for MACE. The odds ratio per one unit increase in LVEF was 0.90 (95% CI 0.881-0.917; $p<0.01$), corresponding to approximately a 10% reduction in the odds of MACE for each percentage point increase in LVEF. The model demonstrated high discrimination with an AUC of 0.90 (95% CI: 0.896-0.903).

No other clinical, ECG, or laboratory variable recorded at first admission consistently improved model performance when added to LVEF.

In the independent Swedish validation cohort (n=243; median age 15.5 years; 22% female; 18 [7.4%] MACE), the LVEF-based model retained good discrimination for MACE, with an AUC of 0.894 (95% CI 0.80–0.991). In the validation cohort, MACE occurred in 39% (n=14) of patients with LVEF $\leq$ 39% versus 1.9% (n=4) of those with LVEF >39%. The model achieved a sensitivity of 78% and a specificity of 95% for MACE.

Conclusions

In this largest prospective cohort of paediatric myocarditis to date, reduced LVEF at presentation emerged as the only stable and reproducible risk stratifier of MACE during initial hospitalisation. Among the 20 predefined variables incorporated in the model, including clinical, ECG, laboratory, echocardiographic and CMR-derived LGE, LVEF was the only variable that reproducibly improved early risk stratification for severe MACE during index hospitalisation. This finding applies to the variables available in the present model and does not contradict the value of multiparametric assessment for comprehensive diagnostic evaluation and long-term prognostication.

Two distinct clinical patterns were observed, which also mirror the two presentations described in adult patients in the ESC myocarditis guideline (1). A “heart failure type” presentation, typically occurring in infants and young children, was associated with severely reduced LVEF and a high MACE risk. In contrast, a “chest pain type” myocarditis was more common in adolescents, often with preserved ventricular function, a

marked male predominance, and features resembling infarct-like myocarditis described in adults. These age-associated clinical patterns are descriptive presentation patterns within the LVEF-defined risk groups, identified as the only stable split by the tree-based analysis, rather than independently defined biological entities. We hypothesise that their pronounced age separation reflects age-dependent mechanisms: in younger children, immune immaturity (10, 11) and genetic predisposition, such as cardiomyopathy-associated variants (12); in adolescents, hormonal influences (e.g. testosterone) and an infarct-like presentation (13), although these mechanisms were not examined in this study. Importantly, troponin levels were frequently elevated across all groups but did not distinguish outcomes, suggesting that myocardial injury markers and haemodynamic risk markers may capture different dimensions of disease severity. As LVEF may influence decisions on mechanical circulatory support and transplantation, which constitute part of the composite endpoint, a degree of treatment-related bias cannot be excluded. However, death as a decision-independent endpoint showed the same association, and external validation supported the LVEF-based model. Objective markers of systemic hypoperfusion and end-organ dysfunction, such as lactate and renal or hepatic function parameters, were not recorded in the registry, although clinical heart failure severity was partly captured by dyspnoea and NT-proBNP, and the most severe circulatory failure is captured by the composite endpoint. Aetiology-informed stratification, including viral, autoimmune, immune-mediated, and genetic causes, is essential for comprehensive long-term prognostication and targeted treatment, but was beyond the scope of this early index-hospitalization risk stratification analysis (14, 15).

Previous MYKKE reports described, descriptively, that younger age and ventricular dysfunction are associated with adverse outcomes. Confirming these associations, the present study adds a formal, externally validated multivariable risk stratification in a large updated cohort that identifies admission LVEF as the single stable early risk stratifier, defines a readily applicable LVEF threshold, and delineates two clinical patterns whose pronounced age separation has not previously been shown this distinctly in paediatric myocarditis, providing a reproducible, externally validated basis for early bedside triage rather than a purely descriptive association. External validation in an independent Swedish cohort supported the discriminative performance of the LVEF-based approach, although the validation cohort consisted predominantly of adolescents with preserved ventricular function, so confirmation in younger, heart-failure-type children in additional international cohorts

1 remains warranted. While the age-associated clinical patterns suggest different underlying mechanisms,
2 LVEF remained the single robust prognostic marker across all ages. The LVEF threshold of 39% was derived
3 from the present cohort and should be regarded as an approximate, cohort-based cut point that requires
4 confirmation in additional cohorts rather than a universally established clinical value. Children with LVEF
5 $\leq 39\%$ should be considered at substantially increased risk and managed with close monitoring and early
6 consideration of advanced therapies, whereas children with preserved LVEF represent a subgroup with a low
7 observed early event rate. Several limitations should be acknowledged. CMR-derived LGE was included
8 where available, whereas quantitative T1/T2 mapping could not be analysed because of substantial missing
9 data. Genetic testing was not included because it was not available for the full cohort and is usually not
10 present at initial early stages of initial admission. Due to different troponin assays and reference ranges
11 across centres, we used the harmonized variable “elevated troponin”, available in 700/725 patients, which
12 was included in the initial variable set but was not associated with MACE during index hospitalization.
13 Future comprehensive prognostic models, particularly for long-term outcomes, should integrate advanced
14 CMR parameters, standardized biomarkers, genetic testing, aetiological classification, and longitudinal
15 follow-up data.

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Figure legends

Figure 1

Figure 1. Development of the paediatric myocarditis risk model and identification of clinical risk groups.

A: After enrolment of 725 children with possible/definite myocarditis in the MYKKE registry, a risk model for major adverse cardiovascular events (MACE) at index hospitalization was developed using 20 preselected variables and internally validated. **B:** Model- and tree-based analyses consistently identified two clinical risk groups: (1) a “heart failure type” myocarditis, predominantly in children <2 years, characterised by severely reduced left ventricular ejection fraction (LVEF) and a high MACE risk (40%); and (2) a “chest pain type” myocarditis, typically in adolescents, presenting with preserved LVEF and a low MACE risk (1.2%). **C:** Receiver operating characteristic (ROC) of the risk model demonstrated high discrimination with an AUC of 0.90 (95% CI: 0.896-0.903). **D:** External validation in the Swedish SWEDCON cohort (n=243) confirmed good discrimination of the LVEF-based model (AUC 0.894, 95% CI 0.80–0.991). (LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal diameter end diastole) .

Alternative text:

Four-panel figure summarising the paediatric myocarditis risk model. Panel A shows model development from 725 children with possible or definite myocarditis using 20 preselected admission variables. Panel B shows two LVEF-defined risk groups: a “heart failure type” in infants with reduced LVEF and 40% MACE, and a “chest pain type” in adolescents with preserved LVEF and 1.2% MACE. Panel C shows a receiver operating characteristic curve with an area under the curve of 0.90. Panel D shows external validation in the Swedish SWEDCON cohort with an area under the curve of 0.89.

Graphical abstract

Graphical abstract. Age-associated clinical patterns in paediatric myocarditis and early risk stratification.

In the prospective MYKKE registry (n=725), 12.2% of patients experienced major adverse cardiovascular events (MACE) during index hospitalisation. Left ventricular ejection fraction (LVEF) at admission was the only stable and reproducible risk stratifier of MACE. Patients with LVEF $\leq$ 39% had a 40% event rate and predominantly presented as a “heart failure type” pattern in younger children with severely reduced ventricular function. In contrast, patients with LVEF $>$ 39% had a low MACE rate (1.2%) and mainly represented an adolescent “chest pain type” with preserved function. Logistic regression confirmed LVEF as the sole robust risk stratifier (OR per 1% increase 0.90; AUC 0.90, 95% CI 0.896-0.903). External validation in an independent Swedish cohort (SWEDCON, n=243) confirmed good discrimination of the LVEF-based model (AUC 0.894, 95% CI 0.80–0.991).

(AUC = area under the receiver operating characteristic curve; HTX = heart transplantation; MCS = mechanical circulatory support; OR = odds ratio).

Alternative text:

Graphical summary of age-associated clinical patterns in paediatric myocarditis. In the MYKKE registry of 725 children, 12.2% experienced major adverse cardiovascular events during index admission. Left ventricular ejection fraction at admission was the only reproducible early risk stratifier: patients with LVEF $\leq$ 39% were younger and had a 40% event rate (“heart failure type”), whereas patients with LVEF $>$ 39% were adolescents with a 1.2% event rate (“chest pain type”). Odds ratio per 1% LVEF 0.90; area under the curve 0.90, 95% CI 0.896-0.903.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ACCEPTED MANUSCRIPT

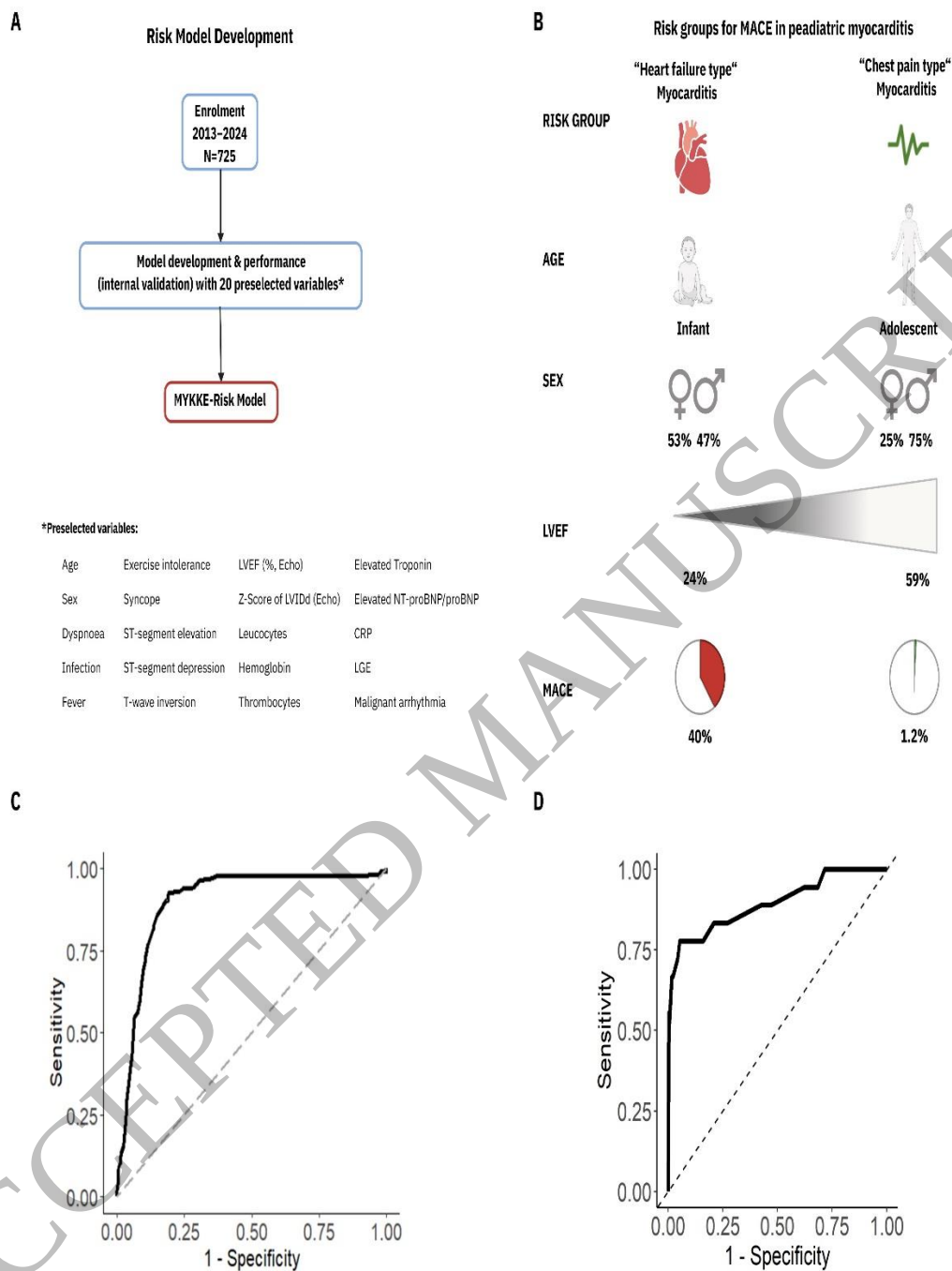
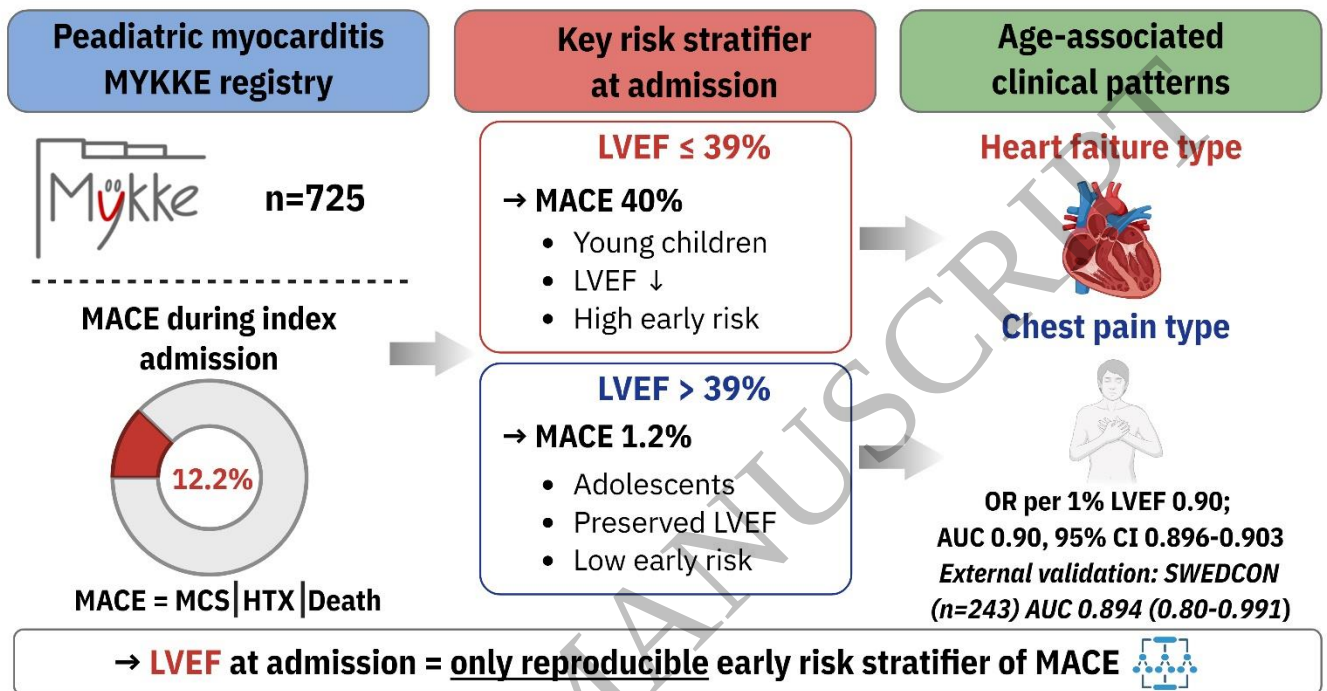


Figure 1
425x367 mm (x DPI)

Age-associated clinical patterns in paediatric myocarditis

Left ventricular function as the key risk stratifier for MACE



Graphical Abstract