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Evolution of acute myocarditis in a pediatric population: An MRI based study

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ABSTRACT

Background: Cardiac Magnetic Resonance (CMR) data regarding myocarditis presentation and disease course is still lacking in pediatric patients. We evaluate baseline CMR and evolution of functional and tissue abnormalities in children with acute myocarditis.
Methods: CMR was performed in 125 patients with clinical diagnosis of acute myocarditis. Clinical follow-up was performed for a median of 498 (214–923) days.
Results: LVEF was depressed (<55%) in 56 cases (45%) upon baseline CMR. LGE was found in 93 patients (77%) of cases. LGE was exclusively subepicardial in 29 patients (23%), while other LGE patterns (midwall/mixed) were present in 64 (51%). CMR was repeated in 92 (74%) patients. 67% presented recover of function at a median of 170 (70–746) days after onset of symptoms. Midwall/mixed LGE pattern had a statistically significant correlation with absent recover of function (OR 0.20 p 0.036).
Thirteen patients (16%) had recovery from LV dysfunction but with persistence of LGE.
Sub-epicardial pattern of LGE (OR 3.33, 95% CI 1.08–10.2, $p = 0.036$) and the presence of fever at admission (OR 4.67, 95% CI 1.16–18.7, $p = 0.03$) were associated with a significantly higher likelihood of complete normalization while midwall/mixed LGE pattern was associated with non-recovery.
Conclusions: In pediatric myocarditis, midwall/mixed LGE pattern is associated with absent recover of function. Patients with recover of function may still have persistence of LGE, while a complete recovery from functional and tissue abnormalities is found only in a third of patients. Midwall/mixed pattern of LGE at first MRI was associated to worse outcome.

1. Introduction

Myocarditis is defined as inflammation of the myocardial tissue [1] with an estimated incidence rate in pediatric population under 15 years of 2–3 cases/100,000 person-years [2,3]. It is, however, generally accepted that this is probably an underestimation due to an unknown yet significant proportion of sub-clinical disease. Indeed, clinical presentation is highly variable, ranging from subclinical to fulminant disease requiring mechanical circulatory support shortly after disease onset.

With current supportive therapies, clinical and echocardiographic recovery from acute myocarditis is common, attained in 52 to 66%

Abbreviations: CI, Confidence Interval; CMR, Cardiovascular Magnetic Resonance; DCM, Dilated Cardiomyopathy; ECMO, Extracorporeal Membrane Oxygenation; IQR, Inter-Quartile Range; LGE, Late Gadolinium Enhancement; LV, Left Ventricle; LVEDV, Left Ventricular End-Diastolic Volume; LVEF, Left Ventricular Ejection Fraction; OR, Odds Ratio; RV, Right Ventricle; RVEDV, Right Ventricular End-Diastolic Volume; RVEF, Right Ventricular Ejection Fraction; SSFP, Steady State Free Precession; STIR, Short-Tau Inversion Recovery; VT/VF, Ventricular Tachycardia /Ventricular Fibrillation.

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children affected [4,5]. The remaining survivors will progress to dilated cardiomyopathy (DCM). In fact, biopsy-proven myocarditis is reported in up to 46% of children with an identified cause of DCM [6]. The progression to DCM carries significant morbidity, accounting for 12 to 15% of pediatric hospitalizations for heart failure [7]. Foerster et al. evaluated echocardiographic data at presentation, suggesting left ventricular dilatation as a negative predictor and septal thickness as a positive predictor of recovery [5]. On the other hand, Belkaya et al. elegantly suggest a genetic basis of progression to DCM [8].

An endomyocardial biopsy (EMB) with research for Dallas criteria has been considered the gold standard for diagnosis of acute myocarditis, but its current role has been largely debated and is still controversial. The risk of EMB in young children with severe left ventricular dilatation is high. Moreover, its sensitivity is poor because of the patchy nature of inflammatory process in acute myocarditis. Previous studies found no differences in outcomes in pediatric patients with biopsy-proven myocarditis vs. those with clinically diagnosed myocarditis while others did [9–11]. EMB is therefore infrequently performed in current clinical practice, due to its invasivity and comparable sensitivity to Cardiovascular magnetic resonance (CMR) [12].

CMR imaging allows non-invasive assessment of myocardial inflammation as defined by the Lake Louise criteria [1,9]. CMR permits tissue characterization of the entire myocardium and accurate evaluation of ventricular volumes and global and regional ventricular function. Recent CMR guidelines recommend the use of routine mapping in cases of suspected myocarditis [13], but in children data about value of mapping CMR in acute myocarditis are scarce [14] because of significant practice variability between institutions as well as technical challenges in children such as motion artifacts and heart rate variability.

Adult data also suggest a prognostic role in for CMR in acute myocarditis, with an association of septal intramyocardial late gadolinium enhancement (LGE) with worse prognosis [15–18]. One pediatric study found a correlation between persistent dysfunction and larger left ventricular end-diastolic volume and lower left and right ventricular ejection fraction [19].

In the present study we aim to identify predictors of recovery from functional and tissue abnormalities in a large cohort of children with acute myocarditis.

2. Methods

2.1. Patients

All children <18 years submitted to cardiovascular magnetic resonance imaging with a clinical diagnosis of acute myocarditis at three tertiary European Pediatric Cardiology Centers from March 2007 to January 2019 were included in the analysis.

Myocarditis was defined on a clinical base by experienced clinicians in patients with acute onset of chest pain and/or heart failure and evidence of myocardial injury (elevated troponin, de novo ECG changes). Exclusion criteria were associated disease such as treatment with chemotherapeutic agents or pharmacological cardiotoxicity, endocrine disorders known to cause myocardial damage, chronic cardiac arrhythmias, immunologic diseases (maternal lupus or Sjogren syndrome), and any vasculitis, presence of structural heart disease, such as known genetic or ischemic cardiomyopathy or congenital heart diseases and contraindication for CMR.

A complete diagnostic evaluation was performed in all patients. No patient had contraindications (allergy or renal failure) to gadolinium administration.

2.2. CMR imaging

Cardiac magnetic resonance was performed using a 1.5 Tesla magnet (MR450 General Electric Medical systems, Milwaukee, USA) and a 3 Tesla scanner (Ingenia, Philips Medical Systems, the Netherlands). Images were acquired with a 32-channel phased-array cardiac coil and a vector electrocardiogram for R wave triggering using a standard CMR imaging protocol. All exams were performed in free-breathing using sedation in children under 25 kg. LV dimensions and function were obtained from stack short-axis steady-state free precession images, as well as 2 and 4 chamber views. Black-blood prepared T2-weighted (T2-STIR) were acquired along the 4-chamber view, 2-chamber view and the short-axis planes of the left ventricle. These were followed by contrast-enhanced images (intravenous administration of a bolus of gadolinium chelate, Dotarem, Guerbet, 0.2 mmol/kg body weight). Enhanced cine-SSFP were acquired along the 4-chamber, 2-chamber and short-axis stack of the left ventricle. Delayed enhancement images were acquired with an inversion recovery gradient echo pulse sequence, 8–10 min after injection of contrast media. in the short axis covering the entire left ventricle from the mitral valve plane to the ventricular apex. The inversion time was optimized to nullify normal myocardium (range 240 to 300 ms for 1.5. 300–400 ms for 3 T).

All images were analyzed with a dedicated workstation (ADW 4.5, GE Medical system).

Myocardial inflammation was diagnosed based on Lake Louise criteria [1]: 1) evidence of regional or global myocardial edema with T2 hyperintensity (T2 ratio > 2, where T2 ratio = Signal intensity $_{\text{myocardium}}$/ Signal intensity $_{\text{skeletal muscle}}$); 2) evidence of myocardial hyperemia and capillary leak with early gadolinium enhancement on cine-SSFP as compared to the skeletal muscle (EGE) [20]; or 3) evidence of myocardial necrosis and fibrosis (visual assessment) with non-ischemic regional distribution at LGE imaging.

The evaluation of EGE was done on cine-SSFP sequence (visual assessment) soon after contrast injection. Hyperemia was evaluated using an early post-contrast cine-SSFP sequence (visual assessment) as previously reported [20].

Myocardial inflammation was diagnosed when at least two criteria were present.

2.3. Follow-up and outcomes

Follow-up was performed according to regional policies, involving regular clinical and echocardiographic examinations (at least every three months for the first year of follow-up and at least every six months in case of persistent LV dilatation or dysfunction).

Recover of function was defined as the first description, either MRI-based or echo-based, of normalization of ventricular function (LVEF>55%, RVEF >54% or TAPSE z score > −2), of ventricular dimensions (LVEDVi <104 ml/m^2 male <95 ml/m^2 female, RVEDVi<108 ml/m^2 male <94 ml/m^2 female, z score < 2) and of regional wall function. Recovery of function based only on echocardiographic data was not considered if infirmed in subsequent CMR studies.

CMR normalization was defined as the first evidence of recovery of function associated to absence of myocardial edema and LGE on follow-up.

Major cardiac events such as death, heart transplantation and relapse of myocarditis were also recorded.

2.4. Statistical analysis

Normal distribution was tested using a D'agostino Pearson test. Normally distributed continuous variables were expressed as mean ± SD, otherwise as median (25th–75th centiles) while categorical variables were expressed as frequency and percentage. Student's independent *t*-test, ANOVA analysis or Mann-Whitney nonparametric test were used to compare continuous variables when appropriate. Categorical variables were compared using the Chi-square. Logistic regression models were fitted for multiple predictors of categorical variables. Due to the large number of covariates, models based on clinical and CMR data were assessed separately. A value of $p < 0.05$ was accepted as

significant. Event-free survival curves were estimated using the Kaplan-Meier method and analyzed by chi-square log-rank test. The significance level of all analyses was set at $p < 0.05$. Statistical analyses were performed using MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Patients characteristics and baseline evaluation

Demographic and clinical data from patients are summarized in Table 1.

Age followed a trimodal distribution, with peak incidence in the first year of life, a moderate peak in early scholar age (6–11) and a late peak in adolescence (Fig. 1 A). Chest pain at presentation was associated with older age (OR 1.48, CI 1.3–1.7 $p < 0.001$) and higher echocardiographic LVEF (OR 1.13, CI 1–1.2, $p < 0.001$). On the other hand, heart failure at presentation was associated to younger age (OR 0.74, CI 0.6–0.8, $p < 0.001$) and lower echocardiographic LVEF (OR 0,84, CI 0.7–0.9, $p < 0{,}001$). Clinical presentation, as shown in Fig. 1 A, changes from early infancy to adolescence, with a transition period between 6 and 11 years of age. In early infancy HF was a more frequent form of presentation, whereas in adolescence the chest pain dominated clinical presentation. Fifteen patients (12%) were admitted to an intensive care unit for inotropic and/or ventilatory support. Of these, 10 patients were ultimately connected to extracorporeal circulatory support.

Table 1
Baseline Patient Characteristics, according to first available evidence of LV systolic function.

	Total population	Impaired LVEF	Preserved LVEF	p
n (%)	125 (100)	56 (44.8)	69 (55.2)	
Gender (male)	90 (72.0%)	34 (60.7%)	56 (81.2%)	0.011
Age (years)	12.8 (6.3–15.8)	7.8 (2.3–14.8)	14.4 (10.2–16.6)	<0.0001
Weight (kg)	46.8 + −27.5	34.5 + −26.5	57.2 + −24.0	<0.0001
Height (cm)	142.6 + −40.1	126.2 + −41.0	155.9 + −34.2	<0.0001
Presentation				
Chest pain	60.6%	36.4%	87.8%	<0.001
Fever	50.0%	54.6%	44.9%	0.326
Heart failure	35.5%	64.8%	5.7%	<0.001
ECG changes	80.7%	83.7%	77.8%	0.480
Repolarization changes	75.6%	79.1%	71.8%	0.444
VT/VF	8.8%	15.9%	0.0%	0.013
Conduction delay	12.0%	14.3%	9.1%	0.492
Troponin elevation	97.9%	95.7%	100%	0.136
LVEF at admission (%)	41.5 + −18.7	33.0 + −15.6	61.8 + −3.8	<0.0001
Pericardial effusion	36.8%	34.0%	42.9%	0.486
Known aetiology	34.2%	40.8%	22.2%	0.102
Treatment				
IV Immunoglobin	44.3%	72.6%	5.4%	<0.001
Steroids	50.6%	78.4%	13.2%	<0.001
Betablockers	71.7%	86.3%	53.7%	0.001
Diuretics	22.5%	37.8%	2.9%	<0.001
ACE inhibitors	49.3%	69.4%	11.5%	<0.001
ECMO	12.8%	20.0%	0.0%	0.011
Baseline CMR				
Time from onset (days)	8 (6–31)	9 (3−32)	7 (7–28)	0.972
LVEF (%)	54.4 + −13.8	44.2 + −14.4	62.9 + −4.2	<0.0001
LVEDVi (ml/m^2)	86.9 + −28.9	94.2 + −39.5	81.0 + −13.4	0.0136
RVEF (%)	55.9% + −11.1%	49.8 + −12.7	60.6 + −6.5	<0.0001
RVEDVi (ml/m^2)	78.1 + −23.3	75.2 + −27.5	80.4 + −19.6	0.2311
Lake Louise Criteria	94 (76.4%)	41 (74.6%)	53 (77.9%)	0.659
Positive T2 criterium	81 (68.6%)	33 (63.5%)	48 (72.7%)	0.281
Positive EGE criterium	89 (73.0%)	39 (72.2%)	50 (73.5%)	0.872
Positive LGE criterium	93 (76.9%)	44 (81.5%)	49 (73.1%)	0.279

Echocardiographic impaired LV function (LVEF ≤55%) was present in about 45% ($n = 56$) of the cohort at hospital admission, and was associated with worse immediate outcomes, such as ventricular arrhythmias (p 0.013) and the need for extracorporeal support (p 0.011).

The majority (88%) of the baseline CMR studies were performed in the acute phase of the disease, with a median delay of 8 (6–31) days from clinical onset.

Baseline CMR LVEF was depressed in 33.6% ($n = 42$) of the cases, reflecting a quick LVEF recovery in about 30% of those presenting with impaired LV function at admission. Lake Louise criteria were positive in 76% of the cohort. Patients with positive Lake Louise criteria were older, median age 14 (range 8–16) years vs 7 (range 1–14) years, ($p < 0.0001$) (Fig. 1B). LGE was found in 93 cases (76.9%). In 46.2% of cases LGE involved only one or two segments. Edema, translated by T2 hyperintensity criterium, was more commonly positive in older children (OR 1.16 $p < 0.001$). T2 positivity was also more common in earlier studies, as translated by a median time from onset of symptoms to mri of 39 days in T2 negative studies and 7 days in T2 positive studies ($p < 0.001$). LGE was evenly distributed from base to apex but was more commonly found in the anterolateral and inferolateral segments (Fig. 2). The distribution of LGE was exclusively subepicardial in 29 patients (23.2%), while other patterns of LGE (midwall alone or mixed with subepicardial LGE) were found in 64 (51.2%).

3.2. Follow up data and major cardiovascular events

Clinical follow-up time lasted for a median of 498 days (214–923). During this timeframe, 73.6% of the cohort performed at least one additional CMR study (up to a maximum of 6 studies). There were no significant differences between patients with or without follow-up CMR (Supplementary Table S1) concerning clinical presentation, ventricular volumes and function. However, as expected, patients with follow-up CMR were more likely to have 2 positive Lake Louise criteria at baseline CMR (90% vs 13%, $p < 0.001$).

Three deaths were recorded (2.42%), at a mean follow-up time of 817 days. No cardiac transplantation events were recorded.

Thirteen patients (10.4%) experienced ≥1 relapse of myocarditis at a median of 11.5 months after the first episode. Those patients were more likely to be male ($p = 0.012$), presented more often with chest pain (92 vs 53%, $p = 0.007$) and had more diffuse LGE at baseline CMR, as evaluated by the number of segments affected (median 5 [4–7] vs 2 [0–4], $p = 0.02$). We also found a non-significant tendency towards a higher prevalence of ECG abnormalities in these patients (92 vs 77%, $p = 0.243$).

Of the 42 subjects with baseline LV dysfunction, 28 (67%) presented recovery of function, at a median of 170 (70–746) days after onset of symptoms.

Factors associated with recovery of function are listed in Supplementary Table S2. Considering data from the acute-phase CMR study, RVEDV, LGE extent as expressed by the total number of segments affected and a midwall or mixed LGE pattern all correlated negatively with recover of function. The midwall or mixed LGE pattern had a statistically significant association with absent recover of function in the multivariate analysis (OR 0.20 CI 0.05–0.98 p 0.036) and was associated to a significantly lower likelihood of recover of function in survival analysis ($p < 0$, 0001, Fig. 3A).

At follow-up, CMR was performed in 79 (63%) patients with pathological CMR at baseline. All 79 patients had a positive Lake Louise criteria at their first CMR. The median time from baseline and follow-up CMR

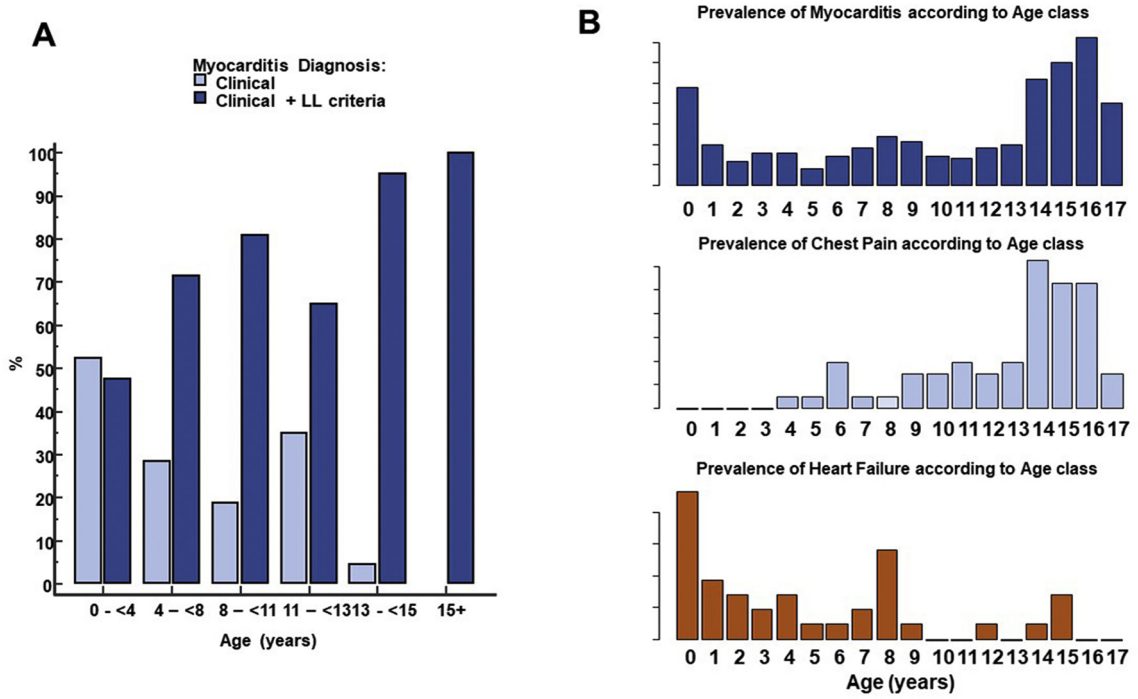

Fig. 1. A: Prevalence of Lake Louise Criteria for acute myocarditis in different classes of age. B: Age distribution of acute myocarditis in our cohort of patients in red, clinical presentation (chest pain in green, heart failure in blue) according to age groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was 10 (5.4–18.4) months. Among these patients who repeated CMR, 21 (28%) presented normalization of ventricular volumes, systolic function and resolution of edema and LGE (all of them had a positive LGE at first CMR). A subgroup of 10 patients with coalescent intramyocardial and subepicardial LGE on the acute-phase CMR (Fig. 2D) had persistent LGE on subsequent studies and therefore none achieved CMR normalization. Thirteen patients (16%) had recovery from LV dysfunction but with persistence of LGE.

A sub-epicardial pattern of LGE (OR 3.33, 95% CI 1.08–10.2, $p = 0.036$) and the presence of fever at admission (OR 4.67, 95% CI 1.16–18.7, $p = 0.03$) were associated with a significantly higher likelihood of CMR normalization, while other types of LGE (midwall/mixed) were associated to non-recovery (Fig. 3B).

4. Discussion

To the best of our knowledge, this is the largest multicenter exclusively pediatric study on CMR evaluation of acute myocarditis. A large proportion of the patients (74% of the sample) was submitted to at least one follow-up CMR study.

4.1. Baseline presentation

We report patient characteristics similar to those previously described in the literature [19]. We have observed a trimodal rather than bimodal age distribution, already seen in previous series [21]. Younger patients presented predominantly with heart failure and lower LVEF, while older patients presented predominantly with chest pain and higher LVEF. A third intermediate age group, between 6 and 11 years, presented with a transitional phenotype. We believe this observation may reflect a different response and a higher sensitivity to inflammatory triggers in infants. Nevertheless, we cannot exclude the hypothesis of a selection bias, as clinical myocarditis could only be suspected in younger children when heart failure symptoms were evident, and the true prevalence of myocarditis may be much larger in this subgroup of patients.

We have obtained positive Lake Louise criteria in 76% of the sample. This is slightly lower than previously described by Banka et al. [19], which in turn can be due to the younger age of our cohort, as we have found Lake Louise criteria to be more commonly positive at older age (Fig. 1A). One explanation might be the lack of capability to perform breath-holds at younger ages impacting the image quality and thus the sensitivity of cardiac MRI to detect myocardial inflammation. Furthermore, the higher incidence of heart failure upon presentation in younger patients could impact the prevalence of Lake Louise criteria and therefore the sensitivity of CMR, as previously demonstrated by Francone and colleagues [22]. Moreover, Stermaier and coworkers demonstrated that in myocarditis with heart failure only <4% of cases had signs of acute myocarditis (inflammatory cells infiltration associated with evidence of myocardial damage or necrosis) as defined by biventricular endomyocardial biopsy, while the majority of patients had chronic inflammation (without signs of damage or necrosis of myocytes) [23]. Thus, in many patients presenting with heart failure, myocarditis could already be in chronic phase at the time of symptom onset and myocardial edema might therefore be absent. Finally, consideration should be taken to the fact that Lake Louise criteria were not specifically validated in the pediatric population.

In adults with acute myocarditis, LGE was most frequently distributed with a sub-epicardial inferior-lateral pattern [18]. In contrast, in our cohort of pediatric patients, we found a higher prevalence of a mid-wall or mixed pattern of LGE. The mid-wall or mixed pattern of LGE is associated with worse evolution and higher complication rate than the sub-epicardial inferior-lateral pattern. As previously discussed, we cannot forget the possibility of underdiagnosis of acute myocarditis in the younger population. In these patients, a heart failure or arrhythmic phenotype was more frequent than uncomplicated chest pain. In this setting, only those patients whose clinical conditions require medical attention would be admitted and undergo CMR. This could explain a

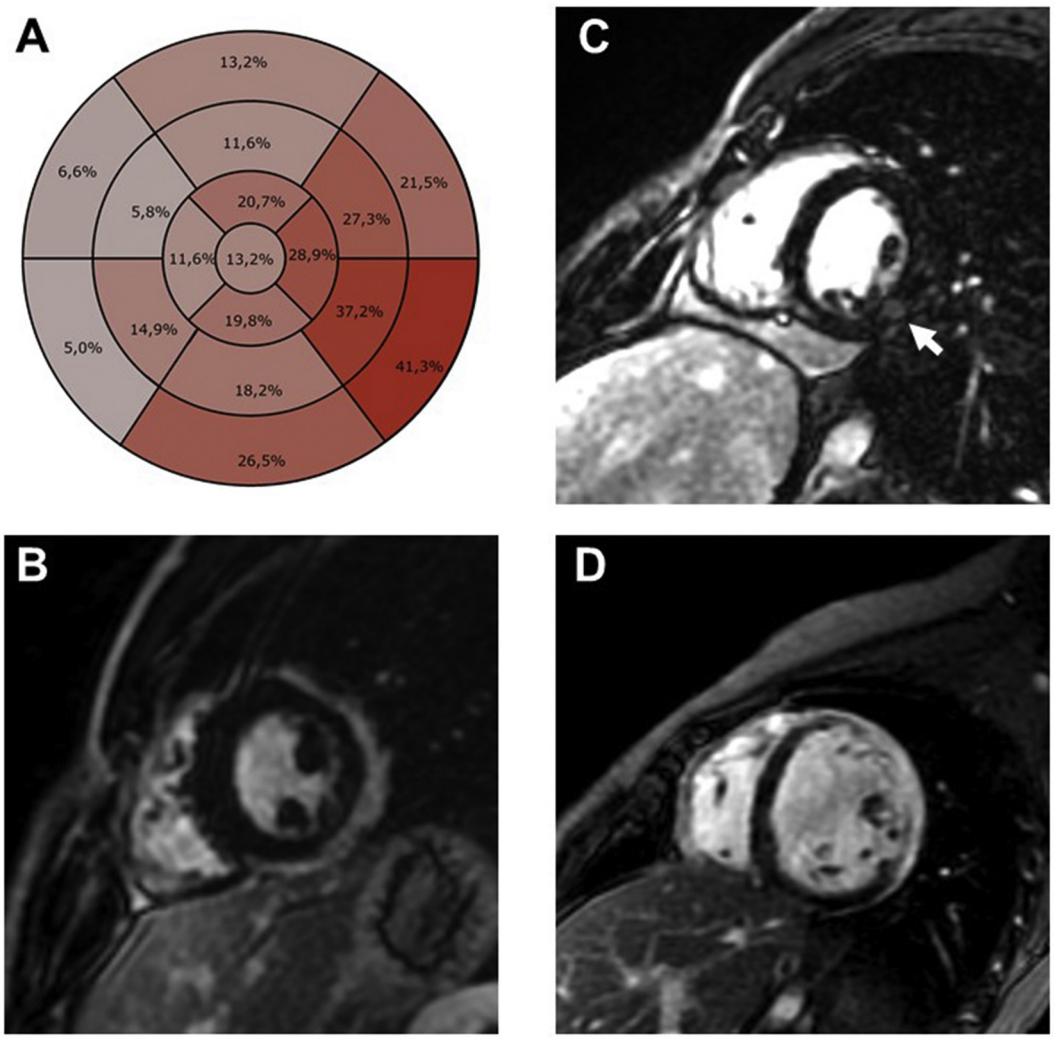

Fig. 2. LGE distribution and patterns. A. 17 segment AHA model displaying LGE distribution among all analyzed subjects. B. Typical subepicardial LGE pattern. C. Midwall LGE patch (arrow). D. Mixed-type LGE pattern, with coalescent subepicardial and intramyocardial LGE.

higher prevalence of mid-wall or mixed pattern LGE compared to subepicardial LGE alone.

4.2. Follow-up

During the follow-up the incidence of cardiac death and transplantation was relatively low, especially when compared to previous studies [4,5]. A reason for this may be selection bias, as only hemodynamically stable patients off mechanic circulatory support could have undergone baseline CMR.

We have found some patients with recidivating myocarditis. This subgroup of patients is an interesting one, as they probably have some degree of genetic susceptibility to cardiac injury, and some may ultimately present with cardiomyopathy [8,24,25]. Their greater extent of LGE at baseline CMR speaks to this association. These patients also have a non-significant tendency towards a higher prevalence of ECG abnormalities. Although highly unspecific, ECG abnormalities reflect myocardial abnormalities. Recent studies have correlated the presence and localization of LGE in the context of acute myocarditis with QRS fragmentation [26].

In this study, we evaluated the likelihood of recovery of function in the cohort of patients with LV dysfunction at baseline. In this group of patients, recovery of function was achieved by 67% of cases, which is similar to the previously described prevalence of 52–66% [4,5]. recovery of function happened in a range of 70–746 days, so we may suggest the possibility to assess the likelihood of recover of function at the end of the second year of follow-up. About LGE evaluation, midwall or mixed LGE pattern was associated with absent recover of function (OR 0.20 p 0.036) in patients with LV dysfunction at baseline.

We want to point out that 16% of patients who had recovery of function with normalization of LVEF showed persistence of LGE, highlighting the need for follow-up CMR in the evaluation of complete healing from myocarditis in pediatric patients.

Moreover, midwall or mixed LGE pattern at baseline CMR was associated also to lack of complete normalization, supporting the prognostic importance of this subtype of tissue lesion in the acute phase as already showed in adults (12).

The prognostic value of residual fibrosis in the absence of functional disease is still uncertain in the pediatric population, so future studies are needed to assess long term impact of myocardial scars in children. Regarding the association of fever in the acute phase of myocarditis and with complete CMR normalization, we could postulate that fever is usually found in the classic presentation of myocarditis with chest pain and infarct-like ECG changes, which is generally associated to better prognosis than atypical presentations as heart failure or arrhythmia.

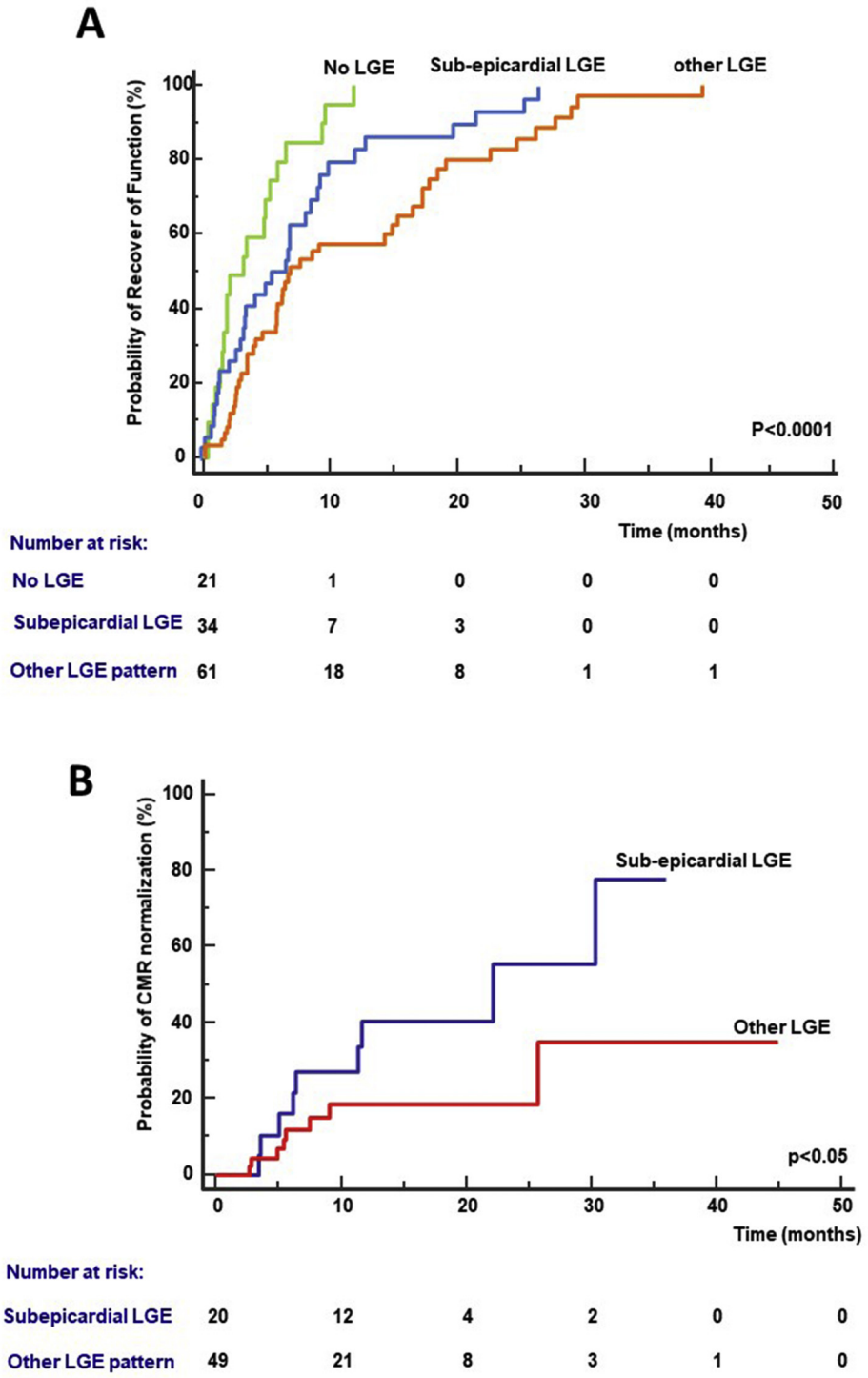

Fig. 3. Kaplan Mayer analysis showing (A) differences in probability of recovery of ventricular function in patients without LGE vs subepicardial LGE pattern vs patients with other LGE patterns (midwall or mixed); (B) differences in probability of complete CMR normalization in patients with subepicardial LGE pattern vs patients with other LGE patterns (midwall or mixed).

5. Limitations

The main limitation of this study concerns T1 and T2 mapping evaluation, which was performed only in a minority of patients and was not included in the analysis.

Recent evidence suggests that native T1 and T2 measurements may be used to evaluate the convalescent phase of AM to detect complete healing from inflammation, which can be confirmed when T1 and T2 values return to normal range [27]. However, in this multicenter retrospective study mapping techniques were not available in all the scanners at the time of initial patient enrolment.

Another limitation was that CMR was repeated in only 74% of patients. This may be explained by the fact that the decision to perform a follow-up CMR was taken by the referral cardiologist of each patient, who often decided to not perform CMR in presence of a recovery of function. However, we found that 16% of patients had recovery of

function with normalization of LVEF but persistence of LGE. Consequently, this study highlights the need for follow-up CMR in the evaluation of complete healing from myocarditis in pediatric patients.

6. Conclusion

We present the results of a large multicentric cohort of pediatric patients submitted to CMR for clinical acute myocarditis and followed for a mean time of 745 days. Recovery of function was common, achieved by 67% of the patients. Midwall/mixed LGE pattern was associated with absent recovery of function. Patients with recovery of function may still have persistence of LGE, while a complete recovery from functional and tissue abnormalities is found only in a third of patients.

Moreover, the sub-epicardial pattern of LGE, mostly involving the lateral and/or inferior wall, is associated to higher likelihood of complete recovery than a mid-wall or mixed pattern.

Credit author statement

Lamia Ait-Ali: Conceptualization, Formal analysis, Investigation, Writing - Original Draft. **Duarte S Martins:** Conceptualization, Formal analysis, Investigation, Writing - Original Draft. **Diala Khraiche:** Investigation. Pierluigi Festa: Investigation. **Andrea Barison:** Investigation. **Nicola Martini:** Investigation. **Yasmine Benadjaoud:** Investigation, Data Curation. **Rui Anjos:** Writing - Review & Editing. **Nathalie Boddaert:** Writing - Review & Editing. **Damien Bonnet:** Writing - Review & Editing. **Giovanni D Aquaro:** Conceptualization, Formal analysis, Supervision, Writing - Review & Editing. **Francesca Raimondi:** Conceptualization, Formal analysis, Supervision, Writing - Review & Editing.

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No relations with the industry to disclose by any of the authors.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.12.052.

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