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ORIGINA PAPER

Incremental value of extracellular volume assessment by cardiovascular magnetic resonance imaging in risk stratifying patients with suspected myocarditis

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Abstract

Cardiovascular magnetic resonance imaging (CMR) has become a key investigative tool in patients with suspected myocarditis. However, the prognostic implications of T1 mapping, including extracellular volume (ECV) calculation, is less clear. Patients with suspected myocarditis who underwent CMR evaluation, including T1 mapping at our institution were included. CMR findings including late gadolinium enhancement (LGE), left ventricular ejection fraction (LVEF), native T1 mapping, and ECV calculation were associated with first major adverse cardiac events (MACE). MACE included a composite of all-cause death, heart failure hospitalization, heart transplantation, documented sustained ventricular arrhythmia, and recurrent myocarditis. One hundred seventy-nine patients with a mean age of 49 ± 15 years were identified. Seventy nine individuals (44%) were female. Mean LVEF was 48 ± 16. At a median follow-up of 4.1 [interquartile-range (IQR) 2.2–6.1] years, 22 (12%) patients experienced a MACE. Mean ECV (per 10%) was significantly associated with MACE (HR 2.09, 95% CI 1.07–4.08, $p = 0.031$). Presence of ECV ≥ 35% demonstrated significant univariable association with MACE (HR 3.3, 95% CI 1.43–7.97, $p = 0.005$) and such association was maintained when adjusted to LVEF (HR 3.42, 95% CI 1.42–7.94, $p = 0.006$). ECV ≥ 35% portended a greater than threefold increased hazards to MACE adjusted to LGE presence (HR 3.14, 95% CI 1.29–7.36, $p = 0.012$). In patients without LGE, ECV ≥ 35% portended a greater than sixfold increased hazards (HR 6.6, $p = 0.010$). In the multivariable model including age, LVEF and LGE size, only ECV ≥ 35% maintained its significant association with outcome. ECV calculation by CMR is a useful tool in the risk stratification of patients with clinically suspected myocarditis, incremental to LGE and LVEF.

Keywords Myocarditis · Outcome · CMR · Cardiovascular magnetic resonance imaging · Extracellular volume · T1 mapping

Abbreviations

CMR	Cardiovascular magnetic resonance imaging
ECG	Electrocardiogram
ECV	Extracellular volume
EMB	Endomyocardial biopsy
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction

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Introduction

Myocarditis is defined as an inflammation of the heart and is a frequent underlying cause of dilated cardiomyopathy [1]. Establishing the diagnosis of myocarditis is challenging clinically because of the lack of reliable noninvasive tests [2] and the non-specificity of the symptoms [3, 4]. Cardiovascular magnetic resonance imaging (CMR) has become the primary imaging tool for diagnosis [5] and risk stratification [6]. Tissue characterization by CMR late gadolinium enhancement (LGE) imaging is a key component of the Lake Louise criteria for the diagnosis of myocarditis [5].

However, LGE detects myocardial scars with markedly heterogenous spatial patterns and it may not capture the spectrum of tissue changes due to myocarditis [6]. Extracellular volume (ECV) using serial CMR T1 mapping has been validated against quantitative myocardial collagen content by histopathology [7, 8]. It has been shown that T1 mapping and ECV characterize myocardial fibrosis [9] and provide a higher diagnostic sensitivity and specificity to myocarditis [5, 10]. However, prognostic value of these CMR measurements remain lacking in this clinical setting. Characterizing the spectrum of myocardial fibrosis is important because it may have implication to potential therapeutic targets in the future [11] and shape the treatment approach to myocarditis. In the present study, we aimed to evaluate the benefit of CMR tissue characterization including T1 mapping and ECV in risk profiling patients referred for CMR with clinically suspected myocarditis.

Methods and results

Study population

This is a sub-study of our previously published cohort, where we retrospectively included patients with suspected myocarditis who underwent a CMR scan [6]. In the current study, we only included patients from the initial study cohort who underwent pre- and post-contrast T1 mapping. Since 2009, T1 mapping and ECV calculation were incorporated into our protocol and were performed in all consecutive referred patients as clinically possible. All patients were without any evidence of coronary artery disease (CAD). CAD was excluded using invasive angiography in 34% of the patients, stress perfusion CMR in 5% of the patients, single photon emission computed tomography in 7% of the patients, photon emission tomography in 1% of the patients, stress echocardiography in 1% of the patients and exercise treadmill in 13% of the patients, while the remaining 39% showed a clinically very low pretest probability for CAD according to age, gender and symptoms. We included patients with clinical suspicion of myocarditis and with presenting signs/symptoms of either of the 2 groups: (A) acute chest pain syndromes with symptom onset < 2 weeks prior to CMR, (B) subacute (onset ≥ 2 weeks) of dyspnea or signs of left ventricular (LV) dysfunction or ventricular arrhythmias syncopal spells or abnormal ECG. Exclusion criteria were any prior clinical evidence or with CMR detected infiltrative cardiomyopathy such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, cardiac sarcoidosis and cardiac amyloidosis. Further, patients with constrictive pericarditis, Loeffler endocarditis, LV non-compaction, cardiac tumor, pulmonary embolism, severe valve disease, and stress cardiomyopathy were excluded. One hundred eighty-nine patients with the referral of suspected myocarditis fulfilling the inclusion and exclusion criteria between 2009 and 2015 were identified. Ten (5%) patients were excluded due to low T1 mapping image quality, resulting in the final cohort of 179 patients. Clinical data, cardiac biomarkers, and ECG at the time of the CMR were analyzed.

CMR imaging protocol and image post-processing

Patient scanning was performed with 3T (Tim Trio, Siemens, Erlangen, Germany). A standardized CMR consisted of cine steady-state free precession (SSFP) imaging (TR, 3.4 ms; TE, 1.2 ms; in-plane spatial resolution, 1.6 × 2 mm) for LV function and LV mass was used. Cine imaging was obtained in 8–14 matching short-axis (8 mm thick with no gap) and 3 radial long-axis planes. All patients underwent an LGE imaging protocol to detect fibrosis, using a segmented inversion-recovery pulse sequence starting 10 to 15 min after a weight-based injection of gadolinium diethylenetriamine pentaacetic acid (Magnevist, Bayer HealthCare Pharmaceuticals Inc., Wayne, New Jersey). Our hospital policies were as following: a dose of > 0.1 mmol/kg Magnevist was applied to patients with normal eGFR > 60, a reduced dose of 0.1 mmol was applied to those with eGFR 30–60 and those with eGFR < 30 were excluded from getting any contrast. T1 measurements were acquired using a validated cine Look-Locker sequence [12], with a non-slice-selective adiabatic inversion pulse, followed by segmented gradient-echo acquisition for 17 cardiac phases/times after inversion (TE = 2.5 ms; TR = 5.5 ms; flip angle = 10°; 192 × 128 matrix; 6 mm slice), spread over two cardiac cycles (TI increments for T1 measurements of 100 ms pre-contrast, and 55 ms post-contrast, slice thickness 8 mm, TR > RR intervals pre-contrast and 3 RR intervals post-contrast). The Look-Locker sequence was performed in short axis slices at basal, mid and apical LV levels. T1 mapping images were acquired in the same LV short-axis slices, once before and up to three times after the injection of gadolinium spanning across a post-contrast period of approximately 30 min. CMR variables were calculated. Further wall motion abnormalities, pleural and pericardial effusion were visually assessed. Epicardial and endocardial contours were placed manually on all LGE images, then LGE mass was quantified by using the full width half maximum signal intensity threshold cut-off (FWHM) technique above the mean intensity of remote myocardium in the same slice [13]. LGE extent (%) was calculated by dividing the LGE mass by the end-diastolic LV mass. LGE being present or absent in the segment defined the visual presence score (LGE–VPS) was further applied. CMR findings that were immediately reported to the caring physicians included global and regional left and right ventricular function and presence and segmental locations of LGE.

ECV measurements

For each Look-Locker T1-mapping sequence the endo- and epicardial borders of the LV were traced. Mean native T1 of all segments and mean native T1 with only the septal segments calculated were reported. Using commercially available software (QMASS MR, version 15, Medis Medical Imaging Systems, Leiden, the Netherlands), signal intensity versus time-after-inversion (TI) curves were generated from regions of interest in the LV and blood pool. The signal intensity versus TI curves for each segment and the blood pool were fitted to an analytical expression for the inversion recovery to obtain T1*, and corrected for the effects of radiofrequency pulse during inversion recovery to calculate T1. The reciprocal of T1 (R1 = 1/T1) was used to plot the myocardial R1 against the R1 in the blood pool. Subsequently, the slope of least-squares regression line for R1 in tissue versus R1 in blood (limited data points with R1 in blood less than 3.5 s^{-1}) was used to estimate the partition coefficient for gadolinium (λ_{Gd}). This represents an extension of the formula: $\lambda_{Gd} = (1/T1_{Myo\ Post} - 1/T1_{Myo\ Pre})/(1/T1_{Blood\ Post} - 1/T1_{Blood\ Pre})$. λ_{Gd} was then multiplied by blood plasma fraction (1 minus the hematocrit expressed as a value between 0 and 1), to obtain segmental myocardial ECV. Hematocrit was derived from routine blood laboratory testing nearest to the CMR examination. The native T1 normal values were derived from a group of healthy volunteers who underwent research 3T CMR studies at our center. A cut-off of 1072 ms was used for a normal T1 value. Further, the normal reference value of ECV was reported to be 28 ± 3% and we defined abnormal elevation of ECV by a 2SD cutoff of ≥ 35% as previously published [14]. The global myocardial ECV for an individual was calculated by averaging the myocardial segmental ECV values from all the short-axis slices. Further, calculation of ECV was made by only incorporating remote segments without presence of LGE.

Follow-up of clinical endpoints

Clinical events in all subjects were assessed by an interrogation of Social Security Death Index of the United States and a detailed review of all available electronic medical records. When electronic medical records were insufficient, subjects were evaluated by a standardized checklist based patient questionnaire by mail and/or followed up by conducting a scripted telephone interview based on the same standardized checklist. Primary major adverse cardiac events (MACE) included: (a) all cause death, (b) heart failure decompensation requiring hospital admission as defined in prior trials [15, 16], (c) heart transplantation, (d) documented sustained ventricular arrhythmia (> 30 s), and (e) recurrent acute myocarditis based on clinical, biomarkers and CMR definition [5]. When more than one event occurred in a patient subject, the first event was used. The study protocol was reviewed and approved by our Institutional Review Board in accordance with our institutional guidelines. The clinical trial number of the study is: NCT03470571.

Statistical analysis

Categorical variables were presented as percentages of the entire cohort or as a percentage of the corresponding group if relevant data were missing. Continuous variables were expressed as mean ± standard deviation (SD) or as median values with interquartile range [IQR] depending on normality of distributions. Categorical variables were compared using the Chi^2 or Fisher exact test (depending on the field numbers) whereas comparisons for continuous data were performed using a 2-sample Student t test or Wilcoxon rank-sum test, when appropriate. A two-sided P value of < 0.05 was deemed significant. Time to event was measured from the date of CMR study. Univariable and multivariable associations of risk covariates with clinical events were determined by Cox proportional hazards regression. Survival and cumulative hazard function curves were displayed using Kaplan–Meier. Annualized event rates were expressed as the number of patients experiencing MACE as a proportion of the number of patients at risk divided by the number of patient-years follow-up. IBM SPSS Statistics 22 (IBM, Armonk, NY, USA) and SAS (version 9.4, SAS Institute Inc., Cary, North Carolina) was used for all statistical analysis.

Patient characteristics

The final cohort consisted of 179 patients with a median follow-up of 4.1 (IQR 2.2–6.1) years. One (0.6%) patient was lost to follow-up. Mean age was 49 ± 15 years and 79 subjects (44%) were female. MACE occurred in 22 (12%) patients including 7 (3.9%) sustained ventricular arrhythmias, 6 (3.4%) heart failure hospitalizations, 5 deaths (2.8%), 3 (1.7%) recurrent myocarditis, and 1 (0.6%) case of heart transplantation. In 79 (44%) presentation was acute (< 2 weeks) and in the remaining 100 (56%) presentation was subacute (≥ 2 weeks). In 80 (45%) patients, LGE was present on CMR. Overall baseline characteristics and characteristics dichotomized by presence of MACE are depicted in Table 1. All baseline characteristics were not significantly different between the patients who suffered a MACE compared to those without. Median number of days of symptoms before CMR were 7 (IQR 3–19) days. In total, 39 (22%) patients had a recent infection (in the past 3 weeks), and were similar present in patients with MACE (4, 18% patients) compared to those without MACE (35, 22% patients, p = 0.872). The median delay between ECG and CMR study was 1 [IQR 0–6] days. CMR characteristics are depicted in Table 2.

Table 1 Baseline characteristics

	All patients (n = 179)	MACE (n = 22, 12%)	No MACE (n = 157, 88%)	P value
Baseline				
Age (year)	49 ± 15	49 ± 16	49 ± 15	0.906
Female gender	79 (44%)	11 (50%)	68 (43%)	0.571
Body mass index (kg/m^2)	27 ± 5	29 ± 6	27 ± 5	0.106
Acuteness of symptoms				
Acute presentation (< 2 weeks)	79 (44%)	13 (59%)	65 (42%)	0.168
Subacute presentation (≥ 2 weeks)	100 (56%)	9 (41%)	91 (58%)	
Referral reasons (multiple possible)				
Chest pain	40 (22%)	5 (23%)	35 (22%)	0.976
Dyspnea	47 (26%)	9 (41%)	38 (24%)	0.099
Palpitations	32 (18%)	2 (9%)	30 (19%)	0.246
Arrhythmia	27 (15%)	1 (5%)	26 (17%)	0.206
Fatigue	15 (8%)	0	15 (10%)	0.129
Asymptomatic	26 (15%)	1 (5%)	25 (16%)	0.207
Medications				
Aspirin	53 (30%)	7 (32%)	46 (29%)	0.837
ACE inhibitors	69 (39%)	12 (55%)	57 (36%)	0.110
Beta-blockers	78 (43%)	10 (45%)	68 (43%)	0.889
Diuretics	36 (20%)	6 (27%)	30 (19%)	0.388
Statins	38 (21%)	6 (27%)	32 (20%)	0.479
Insulin	5 (3%)	1 (5%)	4 (3%)	0.603
Abnormal ECG	93 (52%)	13 (59%)	80 (51%)	0.492
Laboratory tests				
Troponin abnormal	43 (24%)	9 (41%)	34 (22%)	0.768
Creatine-kinase abnormal	20 (11%)	5 (23%)	15 (10%)	0.632
White blood cell count abnormal	25 (14%)	2 (9%)	20 (13%)	0.756

Parametric data is indicated as mean ± standard deviation

LGE late gadolinium enhancement, *ECG* electrocardiogram, *ACE* angiotensin-converting enzyme

LVEF in the whole cohort was 48 ± 16% and significantly different in the MACE cohort compared to the no MACE cohort (41 ± 17% and 49 ± 16%, p = 0.021, respectively). ECG changes were present as following: ST-elevation in 6 (3%) patients, ST-depressions in 8 (5%) patients, T-wave inversion in 39 (22%) patients, Q-wave in 19 (11%) patients, low QRS in 14 (15%) patients, left bundle branch block in 15 (8%) patients, right bundle branch block in 6 (3%) patients and 43 (24%) showed a prolonged QTc. Mean total native T1 was 1051 ± 72 ms, mean septal native T1 was 1082 ± 78 ms and mean ECV 31.9 ± 0.6%.

Univariable and adjusted associations with MACE and event-free survival probability

The univariable association of CMR parameters with outcome are displayed in Table 3. The presence of ECV ≥ 35% was significantly (log-rank p = 0.003) associated with MACE in the event-free survival probability curve (Fig. 1).

Adjusted analysis to LVEF and LGE

Adjustment of ECV to LVEF or LGE presence, LGE size and LGE can be seen Fig. 2. Mean native T1 and abnormal native T1 were not associated with outcome (HR 1.00, 95% CI 0.99–1.01; p = 0.876 and HR 0.81, 95% CI 0.3–2.6, p = 0.960, respectively). When adding the variable acute/subacute presentation to the adjusted model including LVEF and abnormal ECV, acuteness of symptoms was not associated with MACE whereas ECV maintained its independent association with MACE (HR 3.4, 95% CI 1.43–8.04, p = 0.005). When adding native T1 or abnormal T1 to the adjusted model of LVEF and acuteness of presentation, native T1 or abnormal T1 were not incremental associated with MACE. Adjusting ECV to LGE presence and LVEF (%), only ECV ≥ 35% maintained its association with outcome with a HR of 3.33 (95% CI 1.35–7.71, p = 0.009). Further, we performed four multivariable models (see Table 4). In the multivariable models,

Table 2 CMR baseline characteristics II

	All patients (n = 179)	MACE (n = 21)	No MACE (n = 157)	P value
Cardiac MRI				
LVEF (%)	48 ± 16	41 ± 17	49 ± 16	0.021
LVEDVi (ml/m^2)	98 ± 34	112 ± 38	96 ± 33	0.040
LVESVi (ml/m^2)	55 ± 37	71 ± 42	52 ± 35	0.022
LV mass index (g/m^2)	58 ± 17	64 ± 15	57 ± 17	0.105
RVEF (%)	48 ± 11	43 ± 12	48 ± 11	0.019
RVEDVi (ml/m^2)	77 ± 21	78 ± 21	77 ± 21	0.850
RVESVi (ml/m^2)	42 ± 18	46 ± 19	41 ± 17	0.176
LGE presence	79 (44%)	14 (64%)	65 (41%)	0.052
LGE–VPS	1.6 ± 2.8	3.1 ± 4.2	1.4 ± 2.5	0.007
LGE extent (%)	2.1 ± 3.8	3.6 ± 4.4	2.0 ± 3.7	0.055
ECV mean	0.32 ± 0.06	0.35 ± 0.06	0.32 ± 0.06	0.018
ECV mean (≥ 35%)	50 (28%)	12 (55%)	38 (24%)	0.003
ECV remote mean	0.32 ± 0.06	0.34 ± 0.05	0.31 ± 0.06	0.050
ECV remote mean (≥ 35%)	44 (25%)	9 (41%)	35 (22%)	0.060

Parametric data is indicated as mean ± standard deviation

CMR cardiac magnetic resonance imaging, *LVEF* left ventricular ejection fraction, *LVEDVi* left ventricular end diastolic volume indexed, *LVESVi* left ventricular end systolic volume index, *RVEF* right ventricular ejection fraction, *RVEDVi* right ventricular end-diastolic volume index, *RVESVi* right ventricular end-systolic volume index, *LGE* late gadolinium enhancement, *LGE–VPS* LGE visual presence score, *ECV* extracellular volume

Table 3 Univariable association tissue characterization in CMR for MACE

Potential predictors	MACE HR (95% CI)	P value
Cardiac MRI (all patients, n = 179)		
LGE presence	2.02 (0.84–4.87)	0.119
LGE–VPS	1.15 (1.04–1.27)	0.007
LGE extent (%)	1.06 (0.98–1.16)	0.161
Native T1 mean (ms)	1.00 (0.99–1.01)	0.874
Native T1 septal mean (ms)	1.00 (0.99–1.00)	0.607
ECV mean (per 10%)	2.03 (1.07–4.08)	0.031
ECV mean (≥ 35%)	3.38 (1.43–7.97)	0.005
ECV remote mean (per 10%)	2.03 (0.96–4.29)	0.065
ECV remote mean (≥ 35%)	2.38 (0.98–5.76)	0.055
Cardiac MRI (LGE negative patients, n = 99)		
Native T1 mean (ms)	1.01 (0.98–1.01)	0.236
Native T1 septal mean (ms)	1.01 (0.99–1.01)	0.264
ECV mean (per 10%)	3.36 (1.04–10.82)	0.042
ECV mean (≥ 35%)	6.60 (1.57–27.67)	0.010

CI confidence interval, *ECV* extracellular volume, *HR* hazard ratio, *LGE* late gadolinium enhancement, *LGE–VPS* LGE visual presence score, *MACE* major adverse cardiac event

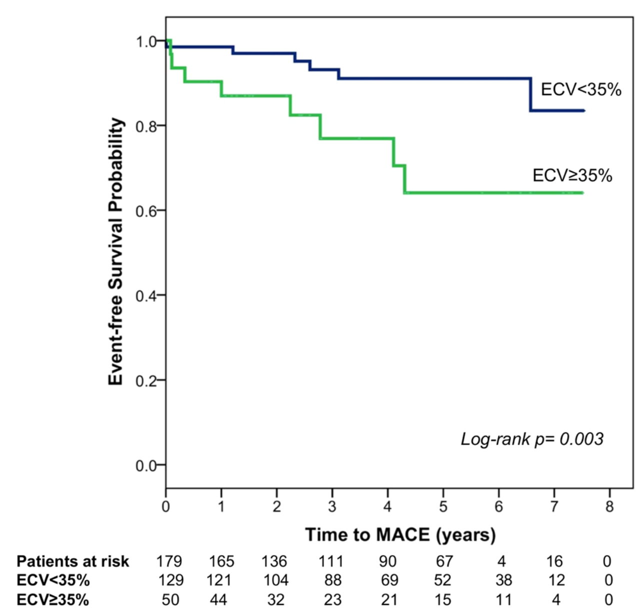

Fig. 1 Event-free (MACE) survival probability curve of patients with suspected myocarditis dichotomized by ECV ≥ 35% and ECV < 35%. Patients with clinically suspected myocarditis and ECV ≥ 35% have a significantly worse prognosis compared to those with ECV < 35%. *ECV* extracellular volume, *MACE* major adverse cardiac event

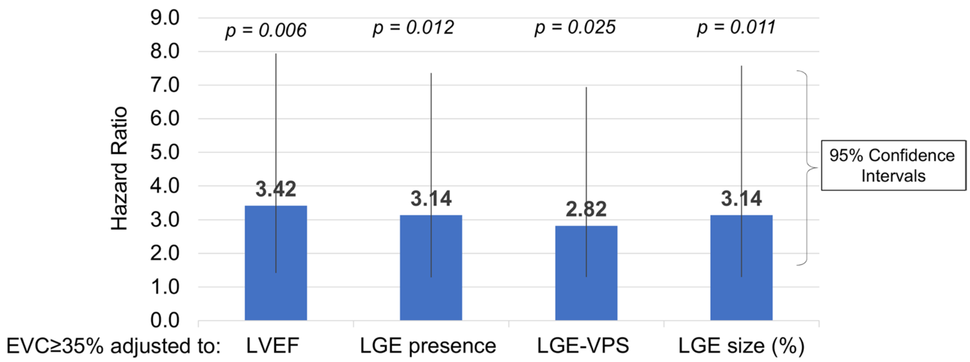

Fig. 2 Adjusted association of abnormal ECV to LVEF and LGE for MACE. Abnormal ECV (≥35%) was incremental increased associated with MACE when adjusted to either LVEF, LGE presence, LGE–VPS or LGE size. ECV ≥ 35% adjusted to LVEF, was independently associated with MACE with a HR of 3.42 (95% CI 1.42–7.94, p = 0.006). ECV ≥ 35% adjusted to LGE size, was independently threefold associated with MACE (ECV ≥ 35% HR 3.14, 95% CI 1.30–7.58, p = 0.011). ECV ≥ 35% adjusted to LGE–VPS was also independently associated with MACE (ECV ≥ 35% HR 2.82, 95% CI 1.14–6.94, p = 0.025). ECV ≥ 35% adjusted to LGE presence was independently associated with MACE (ECV ≥ 35% HR 3.14, 95% CI 1.29–7.36, p = 0.012). *ECV* extracellular volume, *LVEF* left ventricular ejection fraction, *MACE* major adverse cardiovascular event, *VPS* visuals presence score

Table 4 Association of tissue characterization in CMR for MACE in the multivariabel model

Model 1			Model 2		
Variables	HR (95% CI)	P value	Variables	HR (95% CI)	P value
Age (years)	1.01 (0.98–1.04)	0.698	Age (years)	1.01 (0.98–1.04)	0.671
LGE presence	1.32 (0.514–3.40)	0.562	LGE size (%)	1.02 (0.94–1.10)	0.645
LVEF (%)	0.98 (0.95–1.00)	0.086	LVEF (%)	0.98 (0.95–1.00)	0.077
ECV ≥ 35%	3.15 (1.31–7.60)	0.011	ECV ≥ 35%	3.1 (1.23–7.67)	0.013
Model 3			Model 4		
Variables	HR (95% CI)	P value	Variables	HR (95% CI)	P value
Age (years)	1.01 (0.98–1.04)	0.573	LGE presence	1.15 (0.54–4.04)	0.443
LGE–VPS	1.08 (0.97–1.21)	0.165	LVEF (%)	0.97 (0.95–1.00)	0.051
LVEF (%)	0.98 (0.95–1.00)	0.978	Mean native T1	0.99 (0.99–1.00)	0.067
ECV ≥ 35%	2.79 (1.12–7.00)	0.028	ECV ≥ 35%	4.29 (1.54–11.95)	0.005

ECV extracellular volume, *LGE* late gadolinium enhancement, *LGE–VPS* LGE visual presence score

only ECV ≥ 35% maintained a significant association with outcome.

Sub-population analysis in patients with preserved and depressed LVEF

In subsets of subjects with LVEF ≥ 35% (n = 137, 77%), ECV ≥ 35% was associated with MACE (log-rank p = 0.036) and likewise ECV ≥ 35% was associated with MACE in LVEF < 35% (n = 42, 33%) (log-rank p = 0.026), see Fig. 3.

Sub-analysis of patients with clinically suspected myocarditis and negative LGE

In a sub-analysis of LGE negative patients (n = 100, 56%), ECV ≥ 35% maintained its prognostic association with MACE (log-rank p = 0.003) and a HR of 6.6 (p = 0.010), see also Fig. 4. However, in LGE positive patients ECV ≥ 35% was not an independent discriminator (log-rank p = 0.251).

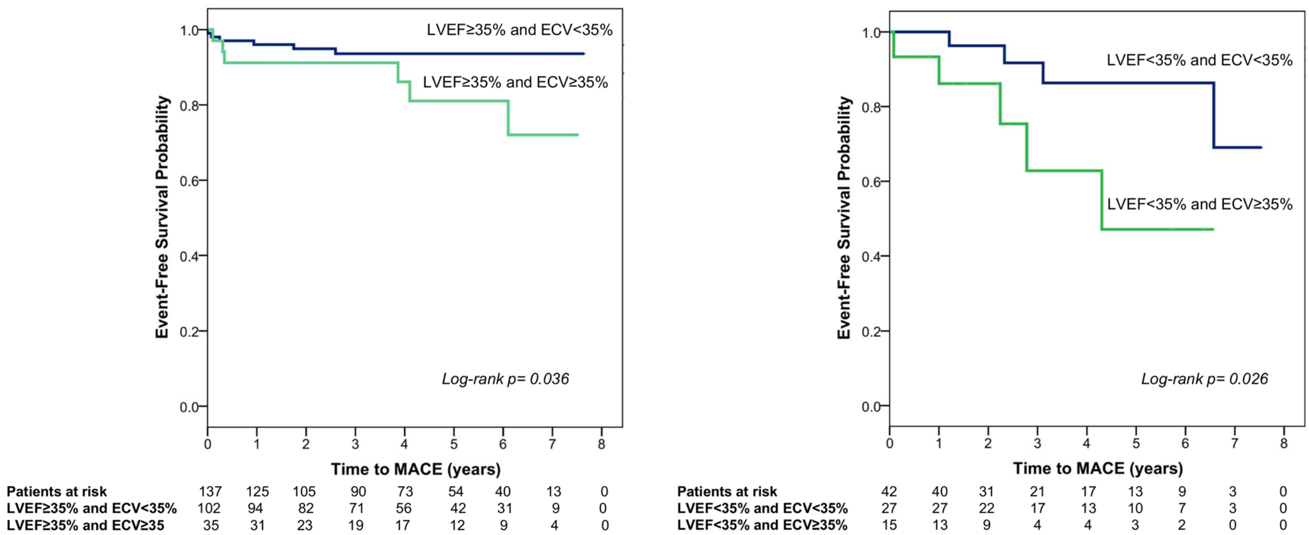

Fig. 3 Event-free (MACE) survival probability curve of patients with suspected myocarditis and combination of LVEF and ECV. Patients with LVEF ≥ 35% and ECV < 35% have a significantly better prognosis compared to those with LVEF ≥ 35% and ECV ≥ 35%. Also in patients with low LVEF (LVEF < 35%), those with ECV < 35% have a significant better prognosis compared to those with LVEF < 35% and ECV ≥ 35%. *ECV* extracellular volume, *LVEF* left ventricular ejection fraction, *MACE* major adverse cardiovascular event

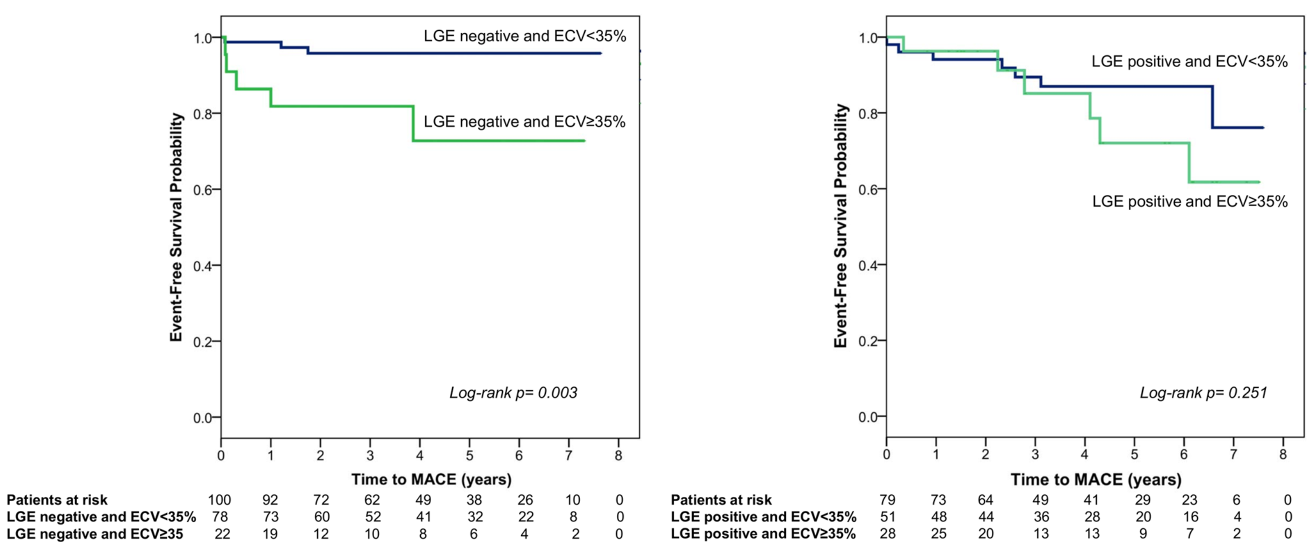

Fig. 4 Event-free (MACE) survival probability curve of patients with suspected myocarditis and combination of LGE presence and ECV. In patients without LGE, those presenting with ECV < 35% have a significant better prognosis compared to those with ECV ≥ 35%. However, in patients with LGE presence ECV < 35% and ECV ≥ 35% was not a discriminator of outcome. *ECV* extracellular volume, *LGE* late gadolinium enhancement, *MACE* major adverse cardiovascular event

Annualized event rates

Annualized event rates were 1.8% in patients with ECV < 35% versus 7.1% in patients with ECV ≥ 35% ($p < 0.001$). Annualized event rates with a cut-off of 35% LVEF and LGE presence or absence in combination with an ECV ≥ 35% or ECV < 35% are displayed in Fig. 5.

Acute versus subacute presentation

In Tables 5 and 6, the CMR characteristics and its association to outcome were analyzed in subgroups of acute and subacute presentation. We could observe in the "acute" group a predictive value only for ECV. In comparison, native T1 was not significant in both groups. On the contrary, LVEF,

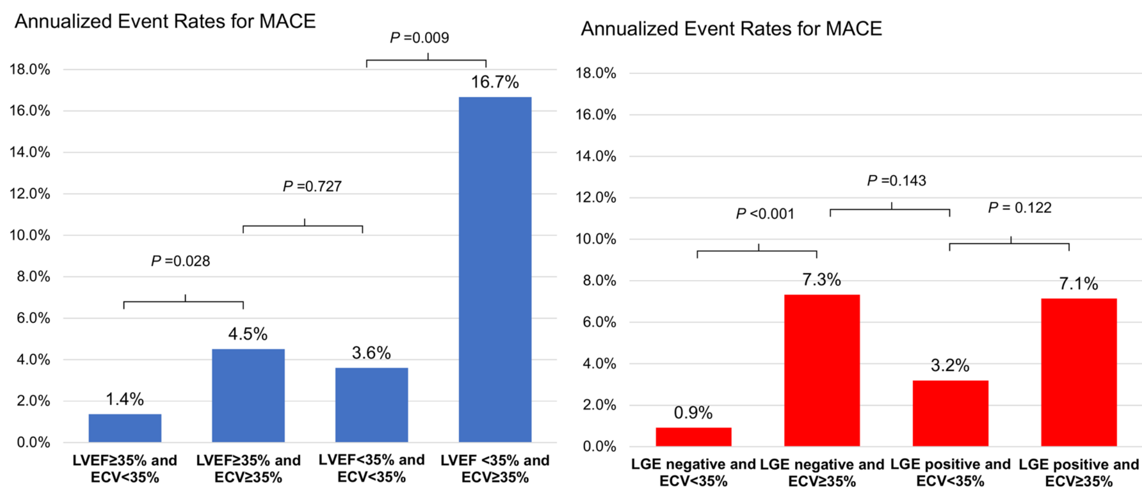

Fig. 5 Annualized event rates between ECV ≥ 35% and ECV < 35% in patients with LVEF ≥ 35% and LVEF < 35% and LGE positive or LGE negative patients with suspected myocarditis. *ECV* extracellular volume, *LGE* late gadolinium enhancement, *LVEF* left ventricular ejection fraction *MACE* major adverse cardiovascular event

Table 5 CMR baseline characteristics in patients divided by acute and subacute presentation

	Acute (n = 79)	Subacute (n = 100)	P value
LVEF (%)	46 ± 18	49 ± 14	0.403
LVEDVi (ml/m^2)	102 ± 41	96 ± 28	0.235
LVESVi (ml/m^2)	60 ± 44	51 ± 29	0.126
LV mass index (g/m^2)	63 ± 17	55 ± 16	0.004
RVEF (%)	48 ± 13	47 ± 10	0.968
RVEDVi (ml/m^2)	78 ± 24	77 ± 18	0.761
RVESVi (ml/m^2)	42 ± 22	41 ± 14	0.531
LGE presence	43 (44%)	37 (37%)	0.023
LGE–VPS	2.1 ± 3.0	1.2 ± 2.6	0.035
LGE extent (%)	2.4 ± 4.0	1.8 ± 3.7	0.309
ECV mean (≥ 35%)	24 (30%)	26 (26%)	0.615

Parametric data is indicated as mean ± standard deviation

CMR cardiac magnetic resonance imaging, *LVEF* left ventricular ejection fraction, *LVEDVi* left ventricular end diastolic volume indexed, *LVESVi* left ventricular end systolic volume index, *RVEF* right ventricular ejection fraction, *RVEDVi* right ventricular end-diastolic volume index, *RVESVi* right ventricular end-systolic volume index, *LGE* late gadolinium enhancement, *LGE–VPS* LGE visual presence score, *ECV* extracellular volume

LV-dimensions, LGE presence was associated with outcome in the subacute group, and ECV showed only a trend towards outcome (p = 0.096).

Discussion

ECV has been proposed to scale the spectrum of myocardial fibrosis or inflammation not well characterized by LGE myocarditis [9, 10]. In the current study, we demonstrated an independent prognostic association of ECV in patients with suspected myocarditis at various stages beyond LGE and LVEF as assessed by CMR. Specifically, in patients with suspected myocarditis and negative LGE, ECV demonstrated an association with outcome. ECV measurement in patients with suspected myocarditis might be an important modifiable therapeutic target for contemporary and emerging treatment in such clinical settings.

ECV stratifies the risk of patients with suspected myocarditis

T1 mapping and ECV calculation emerged as a new promising tool to characterize fundamental disease processes occurring in the myocardium that reflect alterations in tissue composition and structure [11]. The ECV technique introduces a potentially important new method to examine the myocardium because it is sensitive to the distribution of the LV myocardium into its cellular (dominated by myocyte mass) and extracellular interstitial (extracellular matrix (ECM)) compartments. As the most frequently used gadolinium-based contrast media in CMR are purely extracellular agents, the T1 shortening that these agents exert on the myocardium is directly linked to their tissue concentration and thus to the volume they occupy in the extracellular space. In the histological validation, there was a significant correlation between ECV and mean histological collagen volume fraction [17]. Expansion of the collagen volume fraction is

Table 6 Univariable association tissue characterization in CMR for MACE in acute and subacute groups

Potential predictors	Acute (n = 79)		Subacute (n = 100)	
	HR (95% CI)	P value	HR (95% CI)	P value
Cardiac MRI				
LVEF (%)	0.98 (0.96–1.01)	0.113	0.96 (0.91–0.99)	0.047
LVEDVi (ml/m^2)	1.00 (0.99–1.02)	0.709	1.02 (1.00–1.04)	0.022
LVESVi (ml/m^2)	1.00 (0.99–1.02)	0.584	1.02 (1.00–1.04)	0.016
LV mass index (g/m^2)	1.00 (0.98–1.03)	0.997	1.03 (1.00–1.06)	0.048
RVEF (%)	0.97 (0.93–1.01)	0.271	0.95 (0.89–1.02)	0.183
RVEDVi (ml/m^2)	1.00 (0.98–1.03)	0.539	0.99 (0.96–1.03)	0.767
RVESVi (ml/m^2)	1.01 (0.99–1.04)	0.258	1.01 (0.96–1.06)	0.659
LGE presence	0.98 (0.33–2.92)	0.972	5.06 (1.02–25.07)	0.047
LGE–VPS	1.10 (0.95–1.27)	0.203	1.26 (1.05–1.51)	0.015
LGE extent (%)	1.00 (0.86–1.12)	0.999	1.07 (0.93–1.23)	0.333
ECV mean (≥ 35%)	3.26 (1.08–9.8)	0.036	3.25 (0.812–13.01)	0.096
Native T1 mapping	1.00 (0.99–1.01)	0.759	1.00 (0.99–1.01)	0.817

responsible for most ECM expansion [18], which culminates in mechanical [19], electrical [20] and vasomotor [21] changes, which are key elements of cardiac vulnerability [22]. In contradistinction to native T1 (whole myocardium), ECV detects diseases limited to the interstitial space (including myocardial vasculature) and are less altered by edema. Recent work from large cohorts [23–25] suggests that the interstitium may be a principal determinant of vulnerability [26, 27], governed more by diffuse myocardial fibrosis measured by ECV than a disease classification scheme (e.g. dilated cardiomyopathy, acute myocarditis, chronic myocarditis) or a traditional disease description such as aortic stenosis [28], diabetes [25] or heart failure [29]. In conjunction with our data, in other studies ECV measures are as prognostically important as LVEF and independently associated with hospitalization for heart failure and death [24, 25]. Other investigators have reported "vulnerable interstitium" in sudden cardiac death victims [30]. Therefore, ECV may represent a principal phenotype of cardiac injury that improves risk stratification and fibrosis maybe considered as the final common pathway of myocardial disease (also in patients with myocarditis) from a variety of insults [9]. While LGE is a key determinant in CMR-driven diagnostic of myocarditis, biopsy-proven myocarditis reported only a LGE presence in up to 60% [3, 31] of the cases with a broad variability depending on the clinical presentation [31]. A recent study has shown that ECV is an estimate for diffuse myocardial fibrosis, but only in the absence of significant myocardial inflammation and therefore assuming that various degrees of myocardial inflammation and fibrosis coexist in suspected myocarditis, the measured ECV will reflect a sum of these different pathologies [32]. The findings of this study with regard to native T1 are specific to the Look-Locker technique that was used here, while other techniques such as MOLLI may render native T1 more sensitive to tissue pathology, e.g. the connective tissue components by modulation of T1 by magnetization transfer effects. Though we could not identify a significant predictive effect for native T1 mapping in the acute and subacute groups, future prospective studies using different and/or more advanced T1 mapping techniques, or looking at different clinical settings (acute, subacute, chronic), are needed to further ascertain the relative prognostic value of ECV, native T1, and T2.

Native T1 does not risk stratify patients with suspected myocarditis

Recent studies have shown that native T1 mapping is useful by detecting myocardial inflammation in patients with myocarditis [33] and yielded higher diagnostic accuracy in the detection of myocardial injury due to myocarditis than any conventional CMR approach [34, 35]. Native T1 values are a cumulative signal of myocytes and extracellular space and are altered in processes related to excess of water [9, 34–36]. As cellular edema, increased extracellular space and water, inflammation, and myocyte necrosis are common features of acute myocarditis [5, 37], all of these pathophysiological processes may prolong native T1 values. Although native T1 proved to be an outcome predictor in other cardiac diseases [23, 38], it might be postulated that the T1 alteration mainly driven by reversible edema in myocarditis patients does not per se help for risk stratification in this particular clinical setting. In patients with suspected myocarditis the combination of pre- and post-contrast T1 data may describe more accurately the interstitial fibrosis and the possible substrate at risk. It has to be mentioned that like many cardiac parameters, abnormalities in native T1 need to be interpreted within the clinical context. As native T1 seems to be helpful in discrimination of acute and convalescent stages of myocarditis [33], most probably due to the presence or absence of edema, its outcome prediction needs to be elaborated more upon in different clinical settings and phases of the disease. T2 mapping has been shown to be clinically relevant for the accuracy in diagnosing myocarditis due to its high sensitivity to edema [10, 39]. T2 mapping demonstrated to be the best parameter for differentiating chronic myocarditis [10]. However, it was not an independent prognostic marker, yet edema resolution was eventually related to cardiac recovery [40]. Beside the need for future prospective studies looking at different stages of the disease, the role of serial CMR scanning in these patients are unclear. Future trials will provide a more robust body of evidence for the prognostic value of these mapping techniques in patients with suspected myocarditis.

Conclusions

ECV by using CMR is beyond LGE and LVEF a useful tool in the risk stratification of patients with clinically suspected myocarditis. An ECV ≥ 35% may be useful to identify a new subset of patients with myocarditis who did not demonstrate LGE but pejorative outcome.

Limitations

Our study has several limitations. First, our study has the limitations of a single center, retrospective study. Further, the clinical suspicion of myocarditis was according to the referring physician. However, we believe our current cohort represents a typical real-world setting where CMR is considered a diagnostic test-of-choice while the prognostic implications of respective CMR pulse sequences have not been firmly established. Second, we used a segmented T1-mapping gradient-echo sequence, which is not widely available or used by other centers. Different sequences weigh T1 relaxation mechanisms differently, thus, generalization of our study results may be limited. The more widely used modified Look-Locker inversion recovery (MOLLI) gives a shorter T1 than our segmented Look-Locker technique because the gradient-echo read-out for the segmented Look-Locker technique produces at best only a weak magnetization transfer effect, while with the steady-state free precession read-out of MOLLI the magnetization transfer effects are significant and cause a reduction of T1 [41]. Nonetheless, our segmental Look-Locker pulse sequence has been validated for assessment of myocardial T1 and agrees reasonably well with the MOLLI sequence [42]. Third, we used a 3.0 T system, and it is unclear how field inhomogeneity has influenced our results. Further, generalizability to 1.5 T systems may be limited. Fourth, it is uncertain how the CMR findings might have influence the clinical outcomes of the patients due to their impact on management decisions by the clinicians. Fourth, it is unclear whether using a different contrast agent would have effected in different results. Therefore, more studies are needed to compare the ECV results between different agents.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards.

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