Cardiac magnetic resonance abnormalities in patients with acute myocarditis proven by septal endomyocardial biopsy

Giovanni Peretto[1,2] · Marco Merlo[3] · Piero Gentile[4] · Aldostefano Porcari[3] · Anna Palmisano[5] · Davide Vignale[5] · Paola Sormani[4] · Stefania Rizzo[6] · Monica De Gaspari[6] · Cristina Basso[6] · Paolo Della Bella[1] · Simone Sala[1] · Enrico Ammirati[4] · Gianfranco Sinagra[3] · Antonio Esposito[2,5] · Patrizia Pedrotti[4]

Abstract

Background Previous studies suggest low diagnostic sensitivity of cardiac magnetic resonance (CMR) imaging based on Lake Louise criteria (LLC) to identify patients with complicated presentations of acute myocarditis (AM). We evaluated classic and updated LLC in patients with AM proven by right ventricular septal endomyocardial biopsy (RVS-EMB).

Methods From an initial population of 499 patients with clinically suspected AM from a multicenter retrospective cohort, we included 74 patients with histologically proven myocarditis on RVS-EMB and available CMR within 30 days since admission. The prevalence of total and septal CMR abnormalities [namely, T2-weighted images (T2W), late gadolinium enhancement (LGE), T2 and T1 mapping, and extracellular volume (ECV)] were assessed in patients with complicated vs. uncomplicated AM.

Results Among 74 patients [mean age 38 ± 15 years, 65% males, left ventricular ejection fraction (LVEF) 40 ± 18%] with RVS-EMB-proven AM, 53 (72%) had a complicated presentation. The classic LLC were positive in 56/74 patients (76%), whereas the updated ones were positive in 41/41 of cases (100%). Septal involvement, documented in 48/74 patients (65%) by conventional T2W/LGE and in 39/41 cases (95%) by mapping techniques ($p < 0.001$), was more common in patients with complicated AM. In the 41 patients undergoing both evaluations, CMR sensitivity for myocarditis was 85% for the classic LLC vs. 100% for the updated LLC ($p = 0.006$).

Conclusion In patients with myocarditis on RVS-EMB, CMR using updated LLC has high sensitivity in the detection of AM when performed within 30 days. Septal abnormalities are more common in patients with complicated AM.

Keywords Myocarditis · Endomyocardial biopsy · Right ventricle · Septum · Cardiac magnetic resonance · Parametric mapping

Abbreviations

ACS	Acute coronary syndrome
AM	Acute myocarditis
CMR	Cardiac magnetic resonance
ECV	Extracellular volume
EMB	Endomyocardial biopsy
LGE	Late gadolinium enhancement
LLC	Lake Louise criteria
LVEF	Left ventricular ejection fraction
RVS	Right ventricular septum
STIR	Short tau inversion recovery

✉ Giovanni Peretto
peretto.giovanni@hsr.it

[1] Department of Cardiac Electrophysiology and Arrhythmology, IRCCS San Raffaele Scientific Institute, Milan, Italy

[2] School of Medicine, Vita-Salute San Raffaele University, Via Olgettina 58, Milan, Italy

[3] Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy

[4] De Gasperis Cardio ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

[5] Experimental Imaging Center, Radiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

[6] Department of Cardiac Thoracic Vascular Sciences and Public Health, Cardiovascular Pathology, Padua University, Padua, Italy

Introduction

Acute myocarditis (AM) can present with a relatively broad spectrum of clinical manifestations, ranging from uncomplicated presentation with isolated chest pain without left ventricular (LV) systolic dysfunction to a presentation complicated by heart failure (HF) or ventricular arrhythmias (VA) [1]. Currently, the gold standard technique to confirm AM diagnosis is endomyocardial biopsy (EMB) [2, 3]. However, the widespread use of the technique is still limited by invasiveness and technical skills, which appear even more challenging when substrate-guided left ventricular (LV) sampling is planned [4, 5], instead of the more common right ventricular septum (RVS) sampling [6]. Among the non-invasive imaging techniques complementary to EMB, cardiac magnetic resonance (CMR) imaging is currently the first choice in patients with AM [1–3]. The classic Lake Louise criteria (LLC), criteria historically used to identify patients with myocarditis on CMR [8], have shown low sensitivity in patients with clinical presentation complicated by HF and VA [9], fulfilling the operative definition of complicated myocarditis [3, 10]. In this setting, hemodynamic instability or recurrent VA often causes a forced delay in CMR performance, amplifying the likelihood of falsely negative results. Also, the low sensitivity reported for the LLC in the MyoRacer-trial [11] may be justified by subacute or chronic clinical setting. Currently, there is a lack of studies comparing EMB and CMR performed at the very early stage of the disease.

We aimed at analyzing type and localization of early-stage CMR abnormalities, in a multicenter cohort of patients with newly diagnosed AM proven by RVS-EMB. In addition, we intended to compare the sensitivity of CMR between cases with complicated and uncomplicated AM and to assess the diagnostic yield of updated over classic LLC.

Methods

Study design

We present a multicenter, retrospective study, involving three referral centers for myocarditis management. The study design was approved by the local institutional review boards.

From March 2010 to April 2019, we screened 499 consecutive patients admitted to hospital with clinically suspected AM [2] (males 63%, age 43 ± 13 years, left ventricular ejection fraction (LVEF) 39 ± 17%). We finally included adult patients with AM proven by RVS-EMB, and available CMR performed with 30 days from EMB, consistent with the current definition of active myocarditis [3]. The study flowchart is shown in Fig. 1.

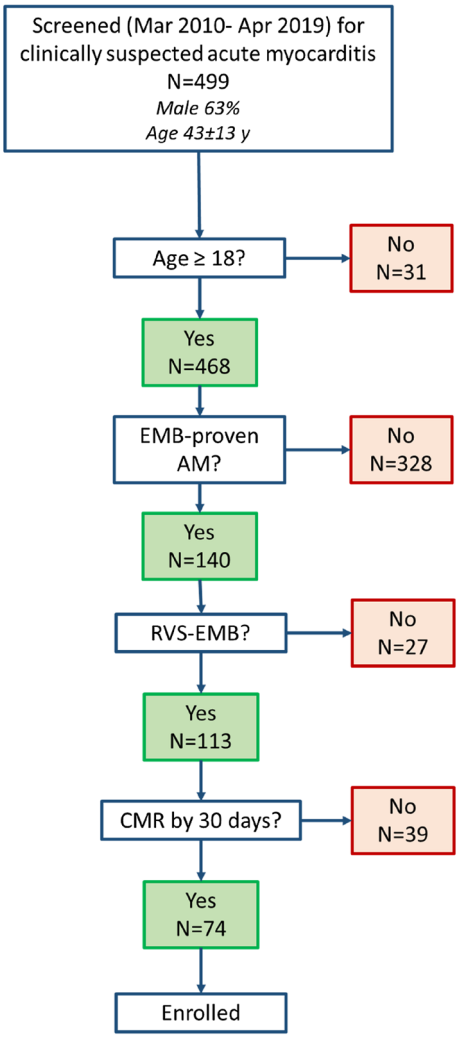

Fig. 1 Study design. The study flowchart is shown. *AM* acute myocarditis, *CMR* cardiac magnetic resonance, *EMB* endomyocardial biopsy, *RVS* right ventricular septum

All patients underwent extensive baseline diagnostic workup, including transthoracic echocardiogram, cardiac biomarkers and C-reactive protein, 12-lead ECG, and continuous in-hospital telemonitoring. In addition, patients > 40 years underwent also coronary angiography to rule out significant epicardial coronary artery disease.

EMB

In all centers, EMB was performed by deflectable bioptomes (Cordis® or ABMedica®), via percutaneous access, under either fluoroscopic or echocardiographic guidance. Samples

were uniformly obtained from the RVS. In compliance with the current recommendations [2, 3], EMB-proven myocarditis was defined by standard histological and immunohistochemical criteria, as assessed by experienced cardiovascular pathologists. In addition, polymerase chain reaction for the research of intramyocardial viral genomes was performed in 69% of patients. Indication to EMB included any of the following: LVEF < 50%, ventricular arrhythmias, advanced atrioventricular block, persistence of HF symptoms, or troponin release despite optimal cardiological treatment.

CMR

At each center, CMR was performed on a 1.5 T scanner (Achieva dStream; Philips Medical Systems, Eindhoven, The Netherlands; TS: Philips Intera MR 1.5; Siemens Magnetom Aera© Erlangen, Germany) equipped with multichannel cardiac phased-array coils. Images were acquired according to the updated Society for Cardiac Magnetic Resonance recommendations [12] implemented with the evaluation of 2009 classic and 2018 updated LLC [8, 13] according to previously described protocol [14]. Functional imaging consisted of ECG-gated balanced steady-state free precession cine sequences acquired during breath hold in horizontal and vertical long axis, LV outflow tract, and short axis, the latter covering the whole LV from base to apex for the assessment of volumes and function. Myocardial edema was assesses with black blood T2-weighted (T2W) images in horizontal and vertical long axis, LV outflow tract, and short axis, the latter covering the whole LV from base to apex, T1 mapping and T2 mapping, both acquired in the short-axis plane (base, mid-ventricle, apex). Parametric maps were acquired on 3 SA slices, before (T1 native and T2 mapping) and 15 min after contrast administration (post-contrast T1 mapping) (Table S1). Extracellular volume (ECV) was calculated as follows: $ECV = (1 - \text{hematocrit}) \times [\Delta R1\text{myocardium}]/[\Delta R1\text{bloodpool}]$, where $\Delta R1$ is the difference in pre-contrast and post-contrast relaxation rates (1/T1) [15]. Reference native T1, T2, and ECV values for each CMR laboratory are reported in Table S2. Late gadolinium enhancement (LGE) images were acquired 10 min after gadolinium-based contrast agent (gadobutrol, Bayer Schering Pharma©, Berlin, Germany; 0.15 mmol/kg) injection using 2D T1-weighted segmented inversion recovery gradient-echo sequences or PSIR (phase-sensitive inversion recovery) sequences acquired in long- and short-axis images, the latter covering the whole LV. The correct inversion time was determined using the Look-Locker technique. Extension of substrate abnormalities was quantified in terms of LV surface area in a 17-segment model. Native T1, T2, and ECV values were calculated on the 3 SA slices, according to a 16-segment LV model. All CMR images were analyzed using a dedicated semi-automatic cardiac software (CVI42v.5.6.6, Circle Cardiovascular Imaging®, Calgary, Canada). At each center, analysis was performed by experienced radiologists and/or cardiologists, and data were validated by an independent imaging reviewer.

Study groups

According to updated definitions [3, 10], complicated AM was defined in the presence of ≥ 1 of the following: heart failure presentation with LV dysfunction (LVEF < 50% on first echocardiogram), low cardiac output syndrome, cardiogenic shock, sustained ventricular arrhythmias, and advanced heart block. Otherwise, AM was defined as uncomplicated.

Endpoints

The primary study endpoint was to assess global and septal CMR abnormalities in patients with active myocarditis on RVS-EMB. We further assessed CMR findings in complicated AM vs. AM with uncomplicated presentation. Finally, in a subset of patients we determined the incremental diagnostic yield of updated LLC over classic LLC.

Statistical analysis

SPSS Version 20 (IBM Corp., Armonk, New York) was used for analysis and Prism Version 6 (GraphPad Software Inc., La Jolla, California) for graphic presentations. Continuous variables are expressed as mean and standard deviation (SD), or as median and first to third quartile (Q1–Q3), depending on the distribution of data. Accordingly, they were compared by parametric (Student *T*) or non-parametric (Mann–Whitney *U*) tests, respectively. Categorical variables were reported as counts and percentages and were compared by using the Fisher exact test, when indicated. To correct for inter-center variability for each quantitative mapping parameter (native T1, T2, and ECV), *Z*-scores were calculated as $Z = (X - \text{mean})/\text{SD}$, where *X* was the measured value and both mean and SD refer to the distribution of a healthy population (Table S2). Where relevant, 2-sided *p* values < 0.05 were considered as statistically significant.

Results

Baseline characteristics

The study cohort is composed by 74 patients (mean age 38 ± 15 y, 65% males) with AM proven by RV-EMB. Main clinical presentation was acute HF ($n = 34$, 46%), followed by infarct-like chest pain ($n = 26$, 35%) and ventricular arrhythmias ($n = 14$, 19%). The mean LV ejection fraction

(LVEF) at presentation was 40 ± 18%. In particular, 53 patients (72%) had complicated presentation, including 27 cases with a fulminant presentation requiring inotropic or temporary mechanical circulatory supports. Complete characteristics of the population, and comparison between complicated and uncomplicated groups, are shown in Table 1. The median in-hospital stay length was 14 days

Table 1 Baseline characteristics of the cohort

	Units	Total $N=74$	Complicated AM $N=53$	Uncomplicated AM $N=21$	p
General features					
Age (years)	Mean ± SD	38 ± 15	42 ± 15	30 ± 12	**0.002**
Male gender	*n* (%)	48 (65)	30 (57)	18 (86)	**0.029**
Caucasian	*n* (%)	64 (86)	44 (83)	20 (95)	0.264
BSA (m^2)	Mean ± SD	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.000
Blood exams					
WBC ($10^3/mm^3$)	Mean ± SD	13 ± 6	14 ± 6	10 ± 3	**0.003**
Neutrophils (%)	Mean ± SD	69 ± 15	72 ± 14	61 ± 12	**0.007**
C-reactive protein (mg/l)	median (Q1–Q3)	47 (10–99)	56 (11–115)	28 (5–63)	0.313
Creatinine kinase (U/l)	median (Q1–Q3)	160 (17–593)	50 (10–562)	281 (143–623)	**0.043**
HsT-Troponin (ng/l)	median (Q1-Q3)	784 (108–3066)	513 (63–3539)	957 (319–1749)	0.744
NTproBNP (ng/l)	median (Q1–Q3)	1051 (219–5816)	2507 (398–8308)	221 (176–476)	**< 0.001**
ECG and telemonitoring					
Sinus rhythm	*n* (%)	60 (81)	40 (75)	20 (95)	0.057
Sustained VT, VF	*n* (%)	6 (8)	6 (11)	0 (0)	0.175
Non-sustained VT, PVC	*n* (%)	4 (5)	3 (6)	1 (5)	1.000
Complete AV block	*n* (%)	4 (5)	4 (8)	0 (0)	0.573
ST-segment abnormalities	*n* (%)	27 (36)	15 (28)	12 (57)	**0.031**
T-wave abnormalities	*n* (%)	23 (31)	20 (38)	3 (14)	0.057
Echocardiogram					
LVEDVi (ml/m^2)	Mean ± SD	61 ± 28	64 ± 32	53 ± 15	0.056
LVEF (%)	Mean ± SD	40 ± 18	34 ± 16	57 ± 6	**< 0.001**
LVEF < 50%	*n* (%)	42 (57)	42 (79)	0 (0)	**< 0.001**
Diastolic dysfunction	*n* (%)	33 (45)	30 (57)	3 (14)	**0.002**
Restrictive pattern	*n* (%)	13 (18)	13 (25)	0 (0)	**0.015**
RV dilation	*n* (%)	9 (12)	8 (15)	1 (5)	0.431
TAPSE < 20 mm	*n* (%)	18 (24)	18 (34)	0 (0)	**0.002**
Pericardial effusion	*n* (%)	38 (51)	22 (42)	16 (76)	**0.010**
EMB					
Dallas criteria	*n* (%)	74 (100)	53 (100)	21 (100)	1.000
IHC criteria	*n* (%)	74 (100)	53 (100)	21 (100)	1.000
Molecular criteria	*n* (%)	51 (69)	32 (60)	19 (90)	**0.013**
Lymphocytic	*n* (%)	64 (86)	45 (85)	19 (90)	0.715
Eosinophilic	*n* (%)	7 (10)	3 (6)	4 (19)	0.095
Sarcoidosis	*n* (%)	3 (4)	3 (6)	0 (0)	0.554
Viral genome	fraction (%)	14/51 (27)	11/32 (34)	3/19 (16)	0.202
Necrosis	*n* (%)	57 (77)	43 (81)	14 (67)	0.521
Replacement fibrosis	*n* (%)	19 (26)	16 (30)	3 (14)	0.239

Significant values are enhanced in bold font

Baseline characteristics of the population ($N=74$) are shown

AV atrioventricular, *BSA* body surface area, *EMB* endomyocardial biopsy, *Hs* high sensitivity, *IHC* immunohistochemical, *IQR* interquartile range, *LVEDVi* left ventricular end-diastolic volume (indexed), *LVEF* left ventricular ejection fraction, *PVC* premature ventricular complexes, *RV* right ventricular, *SD* standard deviation, *TAPSE* tricuspid annular plane systolic excursion, *VF* ventricular fibrillation, *VT* ventricular tachycardia, *WBC* white blood cells

(Q1–Q3: 9–23). Details about in-hospital and discharge treatment are reported in Table S3.

EMB and histology

EMB was performed within 1 week since admission in 62 patients (84%). Vascular access was jugular in 63 cases (85%), and femoral in the remaining. RVS sampling was guided either by fluoroscopy ($n = 65$), ultrasound ($n = 2$), or both ($n = 7$). The median procedure time was 30 (25–40) min, with no difference between complicated and uncomplicated groups. Further comparisons are reported in Table S4. No major complications occurred, accounting for cardiac tamponade, at least moderate pericardial effusion, bleeding, embolization, arrhythmias, or damage to cardiac or vascular structures. In a single case (1%), symptomatic hypotension was effectively treated by intravenous (IV) saline administration. The mean (± SD) number of fragments per patient was 4 ± 1, and the minimal cumulative sampling area was 4 mm^2 (Table 1). All patients had active myocarditis diagnosed by histologic and immunohistochemical criteria [2], including 17 cases (23%) with borderline myocarditis based on Dallas criteria [16]. In addition, molecular analysis was performed in 51 cases (68.9%), 14 (20.2%) of whom had myocardial viral genomes. Lymphocytic myocarditis was the prevalent diagnosis, and it was found in 64 patients (86.5%), whereas replacement fibrosis was found in 19 cases (25.7%).

Primary endpoint

CMR morphological and functional parameters are reported in Table 2. Overall, the classic LLC were met in 56 patients (76%). Parametric mapping analysis was available in 41 cases (55%), in 2 of whom ECV assessment was lacking. All patients in whom mapping techniques were applied (100%) fulfilled the updated LLC, having at least one segment showing elevated T2 (41/41) and at least one segment showing increase in either native T1 or ECV (39/41 and 38/39 cases, respectively).

The dominant localization of CMR abnormalities was inferolateral in 41 patients (55%) and anteroseptal in 18 (24%). However, the proportion of septal involvement by single-segment analysis was as follows: 48/74 (65%) at classic LLC vs. 39/41 (95%) at updated LLC with the acquisition of parametric mapping sequences ($p < 0.001$). A representative example of dissociation between classic and updated LLC is shown in Fig. 2. In the septum, T1 and T2 mapping and ECV were elevated (respective *Z*-score values: 4.0 ± 1.9, 3.6 ± 1.9, and 2.2 ± 1.3), despite apparently normal T2W and LGE images.

Secondary endpoint

Overall, the timespan between CMR and EMB was longer for complicated AM (median: 5, Q1–Q3: 3–11 days; vs. 3, Q1–Q3: 2–5 days; $p = 0.021$). Referring to the classic LLC, T2W images were positive in 39/53 (74%) complicated vs. 21/21 (100%) uncomplicated cases ($p = 0.007$), whereas LGE showed no significant difference (44/53 vs. 19/21, $p = 0.718$). As for the updated LLC, no differences between groups were found for T2, native T1 and ECV positivity rates; however, *Z*-score values for both native T1 and ECV were significantly higher in the complicated group (Table 2).

Patients with complicated AM had more frequently septal LGE abnormalities (35/53 vs. 3/21, $p = 0.002$), grater prevalence of abnormalities at all CMR sequences, and higher *Z*-score values for all mapping parameters (Table 2).

In the subset of patients undergoing mapping techniques assessment ($n = 41$), the updated LLC showed a higher sensitivity compared to the classic ones (overall: 100% vs. 85%, $p = 0.006$; in complicated AM: 82% vs. 100%, $p = 0.052$), as well as a greater prevalence of septal involvement. Of note, CMR positivity rate by native parameters alone (T2W, T1, and T2 mapping) was 39/41 (95%). Full data are shown in Fig. 3.

Discussion

Major study findings

Our multicenter experience, focusing on RVS-EMB-proven AM [2, 3], showed that the prevalence of septal CMR abnormalities by 30 days was high, especially at mapping techniques. Remarkably, septal involvement was more common in patients with complicated myocarditis.

CMR abnormalities

A first, relevant study finding, is that the classic LLC were not completely reliable in detecting AM, referring to histology as the gold standard diagnostic technique [2, 3]. The issue is particularly relevant for complicated myocarditis, since HF and arrhythmic presentations have been previously associated with falsely negative results at traditional CMR [9]. Even in our experience, T2W positivity was significantly lower in arrhythmic and HF presentations, compared with uncomplicated infarct-like presentation. The necessity of postponing CMR due to hemodynamic instability may have contributed to the results [17, 18]. Instead, in keeping with the better performance of the updated LLC [13], all patients undergoing mapping analysis had signs of myocardial inflammation and non-ischemic damage independently of the clinical

Table 2 CMR findings

	Units	Total $N=74$	Complicated $N=53$	Uncomplicated $N=21$	p
CMR					
Timing from EMB (days)	median	4 (2–9)	5 (3–11)	3 (2–5)	**0.021**
CMR after EMB	(IQR) *n* (%)	28 (38)	27 (51)	1 (5)	**0.001**
LVEDVi (ml/m^2)	Mean ± SD	79 ± 24	80 ± 28	76 ± 10	0.373
LVEF (%)	Mean ± SD	48 ± 16	45 ± 17	58 ± 6	**0.001**
RVEDVi (ml/m^2)	Mean ± SD	69 ± 21	67 ± 24	54 ± 12	0.088
RVEF (%)	Mean ± SD	53 ± 12	51 ± 14	59 ± 7	**0.002**
Tissue characterization					
Classic LLC	*n* (%)	56 (76)	36 (68)	20 (95)	**0.015**
Updated LLC	fraction (%)	41/41 (100)	28/28 (100)	13/13 (100)	1.000
T2W+	*n* (%)	60 (81)	39 (74)	21 (100)	**0.007**
EGE+	*n* (%)	23 (31)	17 (32)	6 (29)	1.000
LGE+	*n* (%)	63 (85)	44 (83)	19 (90)	0.718
Parametric mapping analysis	*n* (%)	41 (55)	28 (53)	13 (62)	0.606
Max T2 (*Z*-score)	Mean ± SD	4.7 ± 1.9	4.6 ± 1.8	4.9 ± 2.2	0.546
Max native T1 (*Z*-score)	Mean ± SD	5.7 ± 2.1	6.1 ± 2.2	4.6 ± 1.6	**0.006**
ECV (*Z*-score)	Mean ± SD	4.2 ± 1.8	4.9 ± 1.7	2.7 ± 1.7	**< 0.001**
Increased T2 mapping	Fraction (%)	41/41 (100)	28/28 (100)	13/13 (100)	1.000
Increased T1 mapping	Fraction (%)	39/41 (95)	26/28 (93)	13/13 (100)	1.000
Increased ECV	Fraction (%)	37/39 (95)	25/26 (96)	12/13 (92)	1.000
Localization of abnormalities					
Subepicardial	*n* (%)	47 (63)	29 (55)	18 (86)	**0.016**
Midwall	*n* (%)	19 (26)	17 (32)	2 (10)	0.074
Transmural	*n* (%)	8 (11)	7 (13)	1 (5)	0.427
Anteroseptal	*n* (%)	18 (24)	15 (28)	3 (14)	0.245
Inferolateral	*n* (%)	41 (55)	25 (47)	16 (76)	**0.037**
Diffuse[a]	*n* (%)	15 (20)	13 (25)	2 (10)	0.206
Any septal abnormality	*n* (%)	58 (78)	44 (83)	14 (67)	0.208
Septal T2W+	Fraction (%)	34 (46)	28 (53)	6 (29)	0.073
Septal LGE+	Fraction (%)	40 (54)	35 (66)	5 (24)	**0.002**
Septal T2 (*Z*-score)	Mean ± SD	3.6 ± 1.9	4.1 ± 1.9	2.2 ± 1.4	**< 0.001**
Septal native T1 (*Z*-score)	Mean ± SD	4.0 ± 1.9	4.6 ± 2.1	2.8 ± 0.9	**< 0.001**
Septal ECV (*Z*-score)	Mean ± SD	2.2 ± 1.3	2.6 ± 1.1	1.4 ± 1.4	**< 0.001**
Increased septal T2	Fraction (%)	36/41 (88)	26/28 (93)	10/13 (77)	0.304
Increased septal T1	Fraction (%)	34/41 (83)	25/28 (89)	9/13 (69)	0.181
Increased septal ECV	Fraction (%)	33/39 (85)	24/26 (92)	9/13 (69)	0.153

Significant values are enhanced in bold font

CMR abnormalities documented in the study cohort ($N=74$) are shown

CMR cardiac magnetic resonance, *ECV* extracellular volume, *EGE* early gadolinium enhancement, *EMB* endomyocardial biopsy, *IQR* interquartile range, *LGE* late gadolinium enhancement, *LLC* Lake Louise criteria, *LVEDVi* left ventricular end-diastolic volume (indexed), *LVEF* left ventricular ejection fraction, *RVEDVi* right ventricular end-diastolic volume (indexed), *RVEF* right ventricular ejection fraction, *SD* standard deviation, *STIR* short tau inversion recovery

[a]Diffuse: diffuse pattern includes features of both anteroseptal and inferolateral involvement

presentation [19]. In particular, differently from conventional T2W imaging, T2 mapping abnormalities were documented even in patients with myocarditis complicated by HF and arrhythmias. Furthermore, the updated LLC were informative, even when CMR was performed following hemodynamic stabilization or after EMB. In this setting, the improved sensitivity of the updated LLC (Fig. 3) is likely explained by the quantitative rather than qualitative analysis [13, 14]. However, results are in disagreement with the MyoRacer-trial findings [11], in which

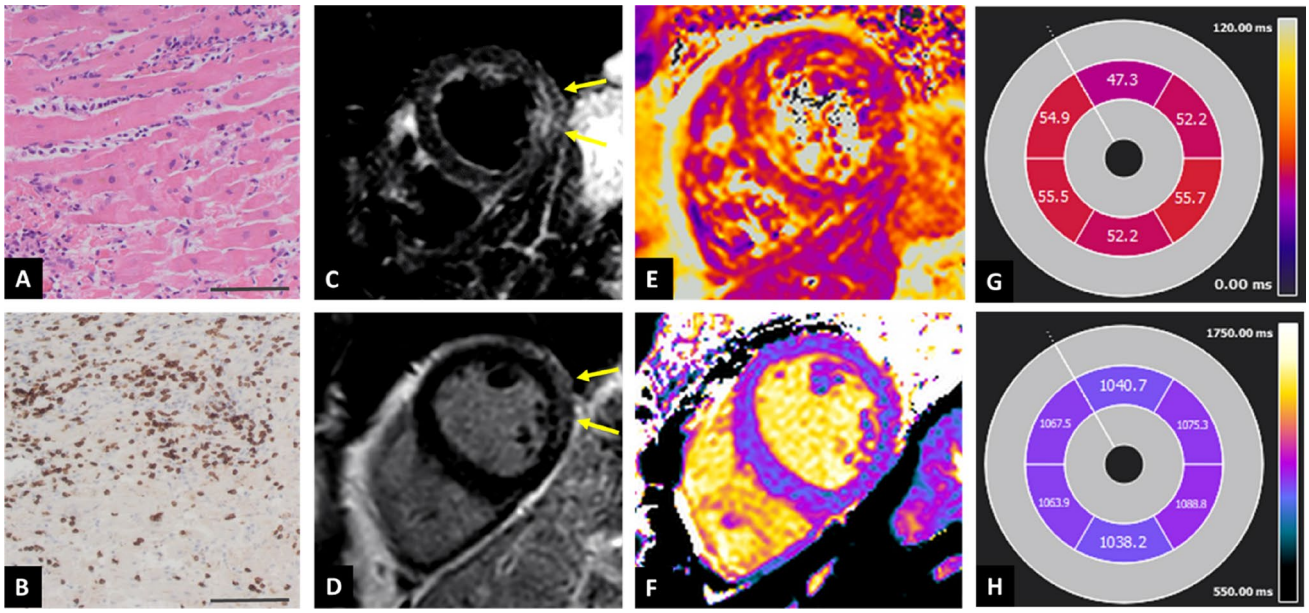

Fig. 2 CMR findings. Discordant septal involvement according to classic vs. updated Lake Louise criteria in a representative CMR from a patient with acute lymphocytic myocarditis diagnosed by right ventricular septal endomyocardial biopsy. In detail, hematoxylin eosin assay **A** shows lymphocytic inflammatory infiltrates with CD3+ > 7/mm^2 at immunohistochemistry (**B**). Scale bars 100 μm. At CMR, T2 STIR (**C**) and LGE sequences (**D**) show inferolateral distribution pattern (arrows) with septal sparing. Conversely, T2 mapping (**E**) and native T1 (**F**) show abnormal findings even at the interventricular septum. Numerical values of T2 (**G**, average *Z*-score 1.7 ± 1.1) and native T1 (**H**, average *Z*-score 1.7 ± 0.6) are shown within the same mid-ventricular slice. *CD* cluster of differentiation, *CMR* cardiac magnetic resonance, *ECV* extracellular volume, *LGE* late gadolinium, *STIR* short tau inversion recovery

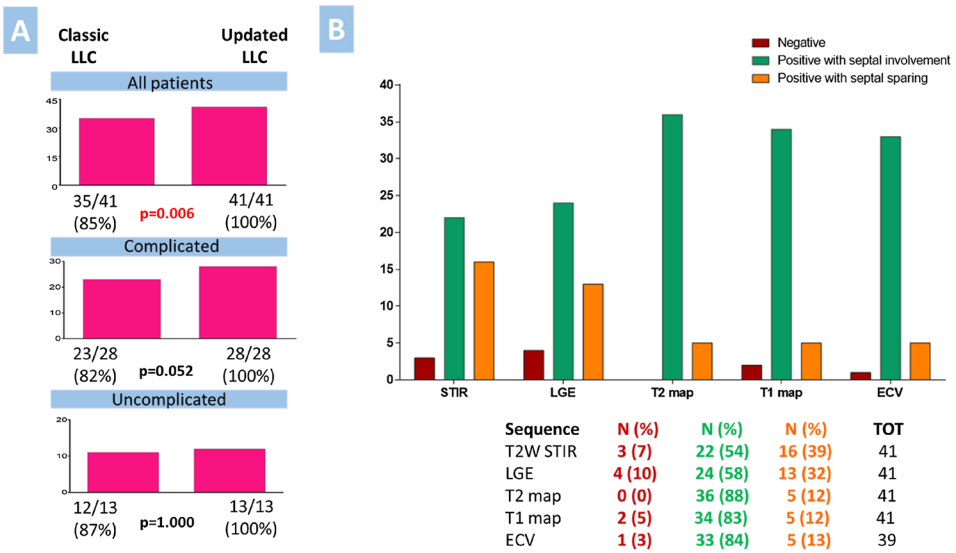

Fig. 3 Comparison between classic and updated LLC in $n = 41$ patients. Comparison between classic and updated LLC in the subset of patients studied with parametric mapping besides standard CMR protocol ($n = 41$). Panel A—sensitivity is 100% for the updated LLC, with a statistically significant difference compared to the classic ones in the whole population, but not in the complicated ($n = 18$) and uncomplicated ($n = 23$) subgroups. Panel B—The proportion of septal involvement is maximal for parametric mapping parameters (T2 map, T1 map, and ECV), as compared to the classic T2W STIR and LGE sequences. *CMR* cardiac magnetic resonance, *ECV* extracellular volume, *LGE* late gadolinium enhancement, *LLC* Lake Louise criteria, *T2W STIR* T2-weighted short tau inversion recovery

both distinction between complicated and uncomplicated presentations and septal involvement subanalysis were missing. In our experience, the application of updated LLC could overcome the lower sensitivity of CMR attributed to identify myocarditis among the causes of unexplained HF or cardiomyopathy complicated by ventricular arrhythmias. In our experience, CMR sensitivity was high (95%) even before gadolinium administration: studies are needed to evaluate the feasibility of contrast-sparing scanning.

Clinical significance of septal involvement

So far, septal abnormalities were reported in a minor proportion of patients with AM. In fact, many studies documented a dominant involvement of the inferolateral LV wall in myocarditis [7, 10]. Even in our current experience, CMR showed dominant anteroseptal pattern in less than one-fourth of the whole cohort, consistently with other reports [7, 20]. Nonetheless, segment-by-segment analysis documented septal abnormalities in a consistent proportion of cases. Consistently with MyoRacer-trial findings, we observed that native T1 and T2 mapping had a high sensitivity, whereas we found that the classic LLC had a higher sensitivity in our study (76%) compared to what observed in MyoRacer-trial (66%) [11]. In addition, modern mapping techniques allowed a significantly higher sensitivity in detecting septal abnormalities. Abnormalities were consistent with active-phase inflammation proven by RVS-EMB, which we previously demonstrated as an informative diagnostic techniques to detect active myocarditis, even when LGE shows isolated LV localization [6].

Previously, it has been shown that septal involvement at CMR bares a negative prognostic value [7, 21]. In particular, a greater occurrence of arrhythmias and heart failure episodes was reported as compared to the classic inferolateral pattern. However, data were derived from LGE and low-voltage areas as a rough approximation of myocardial scar [7, 21]. Consistently, the association with follow-up arrhythmias is high even in the post-inflammatory stage of myocarditis [17, 21]. In our study, we showed that, irrespectively of the dominant localization pattern, septal involvement by LGE was significantly associated with complicated AM. Consistently, patients with complicated AM showed higher septal *Z*-score values for all mapping parameters (Table 2). Since complicated presentation is in turn a relevant prognostic factor for AM [10, 22, 23], our findings suggest that septal abnormalities at CMR may play a primary role in risk stratification. Since most acute-phase abnormalities are reversible [19, 24], ad hoc investigation inclusive of follow-up imaging reassessment [24] is needed in the near future.

RVS-EMB technique

The diagnostic synergy between CMR and EMB in the setting of AM is well known [25]. Remarkably, all patients in our cohort had AM proven by RVS-EMB, which has been previously reported as a safe technique [6]. Even in our multicenter experience, complication rates were neglectable in both complicated and uncomplicated scenarios. The widespread prevalence of septal involvement found by mapping techniques at CMR was consistent with the diagnostic findings on RVS-EMB. Our data are also in keeping with the high sensitivity of RVS-EMB recently documented in patients with LV myocarditis proven by classic LLC [6]. At least in the acute setting, our data provide a valuable alternative to the substrate-guided LV sampling [4, 5]. Sensitivity may be increased by providing an adequate tissue sampling area: with a minimal area of 4 mm^2, our data are in keeping with previously reported cutoffs for RVS-EMB sensitivity [6].

Study limitations

Our study is primarily limited by retrospective design and a small sample size, resulting from the selective inclusion of patients with EMB-proven myocarditis. In particular, we could not estimate CMR specificity, as well as the proportion of EMB sampling errors. In turn, the high proportion of septal involvement may be overestimated by a selection bias, since patients with clinical indication to EMB may not reflect the larger population of uncomplicated myocarditis. In patients undergoing CMR scanning after EMB, as well as in those requiring mechanical circulatory support for fulminant myocarditis, iatrogenic signal abnormalities might have been superimposed to AM; however, both huge extension of CMR abnormalities and lack of subendocardial localization, make this hypothesis unlikely. In the absence of genetic investigation, the presence of underlying primary cardiomyopathy could not be excluded, especially in patients with heart failure presentation and EMB-proven fibrosis. Although CMR was independently analyzed by experienced readers at each center, the absence of a core lab analysis should be acknowledged. Due to intrinsic limitations, mapping analysis was restricted to the LV, and available only in the most recent cohort of patients. Finally, it should be acknowledged that mapping techniques are still non-uniformly available and limited by some technical issues, including lack of standardization and inter-center variability.

Conclusion

Our findings suggest that, in patients with RVS-EMB-proven AM, CMR by 30 days frequently identifies a septal involvement. Septal abnormalities are more common in patients

with complicated AM, a setting with lower LLC accuracy because of negativity of T2W conventional imaging. Due to the high sensitivity of the updated LLC, the time frame for CMR investigation in AM can be reasonably extended. In keeping with histology findings, mapping techniques are sensitive in showing septal involvement, even when the dominant substrate localization is different. These data suggest that AM is a pan-myocardial disease, and support the clinical usefulness of RVS-EMB as relatively safe procedure, able to provide definite diagnosis of myocarditis.

Funding None.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

References

1. Tschöpe C, Ammirati E, Bozkurt B et al (2020) Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nat Rev Cardiol 18(3):169–193
2. Caforio AL, Pankuweit S, Arbustini E et al (2013) Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 34(33):2636–2648
3. Ammirati E, Frigerio M, Adler ED et al (2020) Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. Circ Heart Fail 13:e007405
4. Casella M, Dello Russo A, Bergonti M et al (2020) Diagnostic yield of electroanatomic voltage mapping in guiding endomyocardial biopsies. Circulation 142:1249–1260
5. Vaidya VR, Abudan AA, Vasudevan K et al (2018) The efficacy and safety of electroanatomic mapping-guided endomyocardial biopsy: a systematic review. J Interv Card Electrophysiol 53:63–71
6. Peretto G, Cappelletti A, Spoladore R et al (2021) Right ventricular endomyocardial biopsy in patients with cardiac magnetic resonance showing left ventricular myocarditis. J Cardiovasc Med 22(7):560–566
7. Aquaro GD, Perfetti M, Camastra G et al (2017) Cardiac MR with late gadolinium enhancement in acute myocarditis with preserved systolic function: ITAMY study. J Am Coll Cardiol 70:1977–1987
8. Friedrich MG, Sechtem U, Schulz-Menger J et al (2009) International consensus group on cardiovascular magnetic resonance in myocarditis. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. J Am Coll Cardiol 53:1475–1487
9. Francone M, Chimenti C, Galea N et al (2014) CMR sensitivity varies with clinical presentation and extent of cell necrosis in biopsy-proven acute myocarditis. JACC Cardiovasc Imaging 7:254–263
10. Ammirati E, Cipriani M, Moro C et al (2018) Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: multicenter Lombardy registry. Circulation 138:1088–1099
11. Lurz P, Luecke C, Eitel I et al (2016) Comprehensive cardiac magnetic resonance imaging in patients with suspected myocarditis: the MyoRacer-Trial. J Am Coll Cardiol 67(15):1800–1811
12. Kramer CM, Barkhausen J, Flamm SD et al (2013) Standardized cardiovascular magnetic resonance protocols 2013 update. J Cardiovasc Magn Reson 15:91. https://doi.org/10.1186/1532-429X-15-91
13. Ferreira VM, Schulz-Menger J, Holmvang G et al (2018) Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol. 72:3158–3176
14. Palmisano A, Benedetti G, Faletti R et al (2020) Early T1 myocardial MRI mapping: value in detecting myocardial hyperemia in acute myocarditis. Radiology 295:316–325
15. Kellman P, Wilson JR, Xue H, Ugander M, Arai AE (2012) Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. J Cardiovasc Magn Reason 14:63
16. Aretz HT (1987) Myocarditis: the Dallas criteria. Hum Pathol 18(6):619–624
17. Ammirati E, Veronese G, Brambatti M et al (2019) Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. J Am Coll Cardiol 74:299–311
18. Peretto G, Sala S, Rizzo S et al (2020) Ventricular arrhythmias in myocarditis: characterization and relationships with myocardial inflammation. J Am Coll Cardiol 75:1046–1057
19. Ammirati E, Sormani P, Moroni F et al (2018) Changes of late gadolinium enhancement extension compared with native T1 mapping early after acute myocarditis. Int J Cardiol 257:227
20. Imazio M, Angelico G, Andriani M et al (2018) Prevalence and prognostic impact of septal late gadolinium enhancement in acute myocarditis with or without preserved left ventricular function. Am J Cardiol 122(11):1955–1958
21. Peretto G, Sala S, Basso C et al (2020) Inflammation as a predictor of recurrent ventricular tachycardia after ablation in patients with myocarditis. J Am Coll Cardiol 76:1644–1656
22. Anzini M, Merlo M, Sabbadini G et al (2013) Long-term evolution and prognostic stratification of biopsy-proven active myocarditis. Circulation 128:2384–2394
23. Caforio ALP, Calabrese F, Angelini A et al (2007) A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. Eur Heart J 28:1326–1333
24. Aquaro GD, GhebruHabtemicael Y, Camastra G et al (2019) Prognostic value of repeating cardiac magnetic resonance in patients with acute myocarditis. J Am Coll Cardiol 74:2439–2448
25. Baccouche H, Mahrholdt H, Meinhardt G et al (2009) Diagnostic synergy of non-invasive cardiovascular magnetic resonance and invasive endomyocardial biopsy in troponin-positive patients without coronary artery disease. Eur Heart J 30:2869–2879