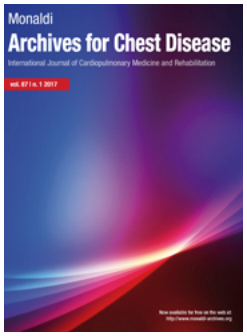

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Cardiovascular magnetic resonance in muscular dystrophies: looking ahead

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Abstract

Cardiac magnetic resonance (CMR) is an established tool for risk stratification in several cardiomyopathies, and its role in muscular dystrophies (MuD) looks promising. We sought to assess how CMR performs in predicting cardiac events in a real cohort of MuD patients.

A prospective single-center study with the enrollment of consecutive adult MuD patients referred to cardiac screening from 2012 to 2018 with the collection of clinical and CMR data. During follow-up (FUP), major adverse cardiac events were considered a composite of device implantation, ventricular tachycardia (VT), hospitalization due to heart failure, and death.

Sixty-five patients were included (mean age of 32±16, 51% female); the majority had myotonic dystrophy (34; 52.3%); most were asymptomatic (60; 92.3%) and at sinus rhythm (64; 98.5%). CMR was abnormal in 23 (43.3%) patients: left ventricle ejection fraction (LVEF) <55% was found in 7 patients, and late gadolinium enhancement (LGE) was present in 23 patients, mainly intra-myocardial or subepicardial (10 and 8 patients, respectively).

During a median FUP of 77 months (interquartile range: 33), there were 7 deaths, 8 implanted devices, and one sustained VT.

LVEF<55% and the presence of LGE were associated with the occurrence of all events (log rank test, p=0.002 and p=0.045, respectively). LVEF<55% was associated with a 6-fold higher risk of events (crude hazard ratio of 6.15; 95% confidence interval of 1.65-22.93), that remained significant after adjusting for LGE presence (adjusted hazard ratio of 4.81, 95% confidence interval of 1.07-15.9).

In our cohort, CMR LVEF<55% and the presence of LGE were significantly associated with adverse events during follow-up, reinforcing the role of this technique on risk stratification of MuD populations.

Key words: muscular dystrophy, cardiac magnetic resonance, risk stratification.

Introduction

Muscular dystrophies (MuD) represent a heterogeneous group of inherited disorders characterized by progressive muscle weakness and atrophy due to defects in one or more genes required for normal muscle function [1,2]. Myotonic dystrophy (MyD) is the most frequent type of muscular dystrophy in adults, followed by Duchenne, Becker, and facioscapulohumeral dystrophies [3]. MuD are frequently accompanied by cardiac involvement, including myocardiopathy and/or rhythm and conduction system disturbances [4]. Cardiac disease is a major source of morbidity and mortality, with heart failure currently being the leading cause of death in MuD patients. While most cardiac manifestations occur

between childhood and the second decade of life, individuals are often asymptomatic in the early stages. It is critical to detect early signs of cardiac involvement to institute cardioprotective therapy, prevent progression, and avoid life-threatening events [2,4].

Cardiovascular magnetic resonance (CMR) is the gold standard non-invasive technology for assessing ventricular volumes, mass, and global systolic function, as well for non-invasive tissue characterization. It has a well-established role in the diagnosis and risk stratification of a wide range of cardiomyopathies; some series also show promising results for MuD, as it can detect subclinical cardiac involvement when electro and echocardiograms are unrevealing [5]. CMR has the potential to improve long-term outcome prediction for several cardiac conditions; nevertheless, in MuD, the association between CMR abnormalities and the occurrence of future life-threatening events remains unsolved [5,6].

We sought to assess how CMR performs in predicting MACE in a real-world cohort of MuD patients. The main aim of the study was to explore the prognostic value of CMR findings for adverse clinical events prediction, considering cardiac function and LGE presence and extend; secondarily, we also explored potential differences in the CMR findings in myotonic dystrophy and non-myotonic dystrophies subtypes.

Materials and Methods

Study design

We conducted a prospective study involving all consecutive adult patients (18 years of age or older) with MuD who were referred to the Cardiomyopathies Cardiology Consultation at Centro Hospitalar e Universitário de São João, Porto, from September 2012 to December 2018, for cardiac disease screening. We excluded patients with previous clinical cardiac event, such as myocardial infarction, pacemaker implantation, malignant arrhythmias/conduction disease and heart failure hospitalization.

Clinical evaluation, electrocardiogram, echocardiogram, Holter monitoring, B-type natriuretic peptide (BNP) and CMR were performed.

Patients' medical records were analyzed for demographics, information on disease background, CMR data and adverse cardiac events.

Outcomes

A composite clinical endpoint was considered, comprehending all-cause death, hospitalization due to heart failure or the development of malignant arrhythmias/conduction disease requiring implantable cardiac defibrillator/permanent pacemaker, as well as appropriate shock therapy.

The date from the CMR scan until the latest known communication with the patient was used to calculate the duration of clinical follow-up. Patients´ outcomes were assessed up until 31 December of 2022. We considered events based on informatics registries of admissions to Emergency and Cardiology Departments, as well as clinical and device revision appointments.

Cardiovascular magnetic resonance

CMR imaging was performed using a 3-T system (Siemens Magnetom Trio, Washington DC, USA). CMR image acquisition and analysis were performed by two experienced investigators blinded to patient data. Electrocardiogram-triggered balanced steady-state free precession cine images were acquired throughout the cardiac cycle in breath-hold. Pulse sequences for a standard ventricular function examination were obtained with the following parameters: field of view 320 mm^2; matrix 153×208; voxel size 2.1×1.5×6.0mm; repetition time 52.9 ms; echo time 1.4 ms; flip angle 60◦; slice thickness 6 mm; no gap; temporal resolution 41 ms. Ventricular volumes were assessed using short-axis cine imaging at end-diastole and end-systole, by applying Simpson's method. For left ventricular (LV) mass calculation a combination of semi-automated and manual correction of contours of the endocardial and epicardial borders was used, excluding the papillary muscles.

A breath-hold, T2-weighted dark blood sequence to evaluate myocardial edema was also acquired. Early gadolinium enhancement images were obtained 3-5 minutes after contrast administration. Late gadolinium enhancement (LGE) imaging was performed 10-15 min after gadolinium administration using a phase-sensitive inversion-recovery sequence. The extent of LGE was quantified by the LGE index (%), a ratio of number of segments affected to total of 17 segments. The presence and distribution of LGE were independently accessed by one radiologist and one cardiologist, experienced in CMR, blinded to the study.

Statistical analysis

Statistical analysis was performed with SPPS® 27 program. Continuous variables that were normally distributed are presented as mean±standard deviation, while non-normally distributed as median (interquartile range - IQR). Comparisons of study characteristics between different groups of patients were performed using unpaired t-test or Wilcoxon Signed Rank Test as appropriate for 2 groups. Comparison of continuous variable between 3 or more groups were done by ANOVA or Kruskal–Wallis as appropriate. Categorical variables were compared by using chi-square test as appropriate. To test for independent predictors of the composite clinical endpoint we used cox survival models. Kaplan–Meier curves for the survival time free from the composite clinical endpoint were constructed with strata; a two-tailed p-value <0.05 as statically significant was considered.

Results

Baseline characteristics

A total of 65 patients were included, 33 (50.7%) were women, with a mean age of 32 ± 16 years. Most patients had myotonic dystrophy (34, 52.3%), followed by limb–girdle MuD (22; 33.8%); Becker MuD (4, 6.2%), Duchenne MuD (3, 4.6%), Myotonia congenita (1, 1.5%) and Emery-Dreifuss MuD (1, 1.5%). Two-thirds of patients exhibited predominant impairment of inferior limb muscles, with 73.8%, 24.6%, and 1.6% falling into mRankin categories 0-3, 4, and 5, respectively.

Nineteen (29,2%) patients had at least one cardiovascular risk factor; specifically, 11 (16.9%) had hypertension, 10 (15.4%) had dyslipidemia, 4 (6.2%) had a history of smoking, 3 (4.6%) had diabetes, and 1 (1.5%) had a familial history of coronary artery disease.

Regarding cardiac manifestations, 22.7% patients had cardiac symptoms (12.1% had dyspnea, 4.5% fatigue, 3.0% palpitations and 1.5% syncope); 96.9% were in sinus rhythm, the remaining were in atrial fibrillation (mean heart rate of 70±15 beats/minute). Median PR and QRS intervals duration were 169 (47) and 101 (11) milliseconds (ms), respectively. Ten (15.4%) patients had first-degree atrioventricular block, 6 (9.2%) had unspecific intraventricular conduction disturbance, 5 (7.7%) had left bundle branch block, 2 (3.1%) had left anterior fascicular block, and 1 (1.5%) patient had right bundle branch block. Additionally, 4 (6.2%) patients met the criteria for left ventricular hypertrophy.

Analytically, we registered median values of BNP, aldolase and creatinine kinase of 26 (25) pg/ml, 4.2 (6.2) mg/dl and 166 (228) mg/dl, respectively.

At echocardiogram, median telediastolic and telesystolic diameters were 45(6) and 28 (7) mm, respectively; median basal septum and posterior wall measures were both 8 (2) mm; median E/A ratio was 1,7 (1,0) and median LV ejection fraction (LVEF) was 64% (7); three patients had LVEF lower than 55%.

Concerning the CMR study, there were 23 (43.3%) patients with at least one abnormality - 6 (9.2%) patients had left ventricle (LV) dilation; 7 (10.8%), had LVEF lower than 55%; 3 (4.6%) had significant hypertrophy (12 mm) of at least one myocardial segment; one patient had LV hypertrabeculation, other had segmental alterations and other had right ventricle (RV) dilation.

Regarding tissue characterization, 2 (3,1%) patients had myocardial edema in T2-weighted sequences, 8 (12.3%) had early gadolinium enhancement (EGE) and 23 (35,4%) had late gadolinium enhancement (LGE). Of the patients with LGE, it was mainly intramyocardial (10; 43.4%) or subepicardial (8; 34.7%) and the most affected segments were the basal and mid inferolateral (13 pts, 56,5%) – see Figure 1.

Table 1 shows CMR parameters according to subgroups of myotonic dystrophy (MyD) and non-myotonic dystrophies (non-Myd) – no statistically significant difference was found.

Follow up

During a median follow up of 77 (33) months – minimum of 4 and maximum of 121 months, a total of 15 events occurred. There were 7 deaths (in the context of pneumonia in 4 patients, stage IV renal carcinoma in 1 patient and stroke in another; cause of death is unknown for 1 patient) and 8 devices implantations (4 pacemakers and 4 CRT-D); concerning cardioverter-defibrillators, three were implanted for primary sudden cardiac dead prevention and one in secondary prevention, after detection of one sustained ventricular tachycardia by Holter Monitoring. There were no shock therapies nor heart failure hospitalizations during follow-up.

Table 2 describes some CMR variables according to the occurrence or not of MACE; of the continuous parameters, only LVEF and Left Ventricle End-systolic volume index were different between the groups. Also statistically different was the presence of late gadolinium enhancement, with 16 (32.0%) patients in the no-event groups and 7 (46.7%) patients in the event group, p=0.035.

Using Kaplan Meier curves, there were associations between LVEF lower than 55% and presence of LGE with occurrence of all events (log rank test, p=0.002 and p=0.045, respectively) – see Figures 2 and 3. No associations were found with age, sex, LGE pattern nor number/distribution of affected segments and MACE (p>0.05).

Using Cox Regression, we found that the LVEF<55% was associated with a 6 fold higher risk of events, with a crude Hazard Ratio (HR) of 6,15; 95%, and confidence interval (CI) of 1,65-22,93, that remained significant after adjusting for LGE (adjusted HR of 4,81, 95% CI of 1,07-15,9).

Discussion

Our study included 65 adult patients with MuD and the most frequent subtype was MyD, accordingly to other series. Only a small fraction of the patients were symptomatic and had abnormalities in their initial ECG and echocardiogram at the start of the clinical evaluation. Median BNP was normal, suggesting an early stage of disease in our sample. This is relevant since our objective was to predict which patients were more likely to have events during follow up.

With the widespread use of CMR in clinical practice, this technique has proven to be a robust tool for risk stratification in several cardiac diseases.

Dystrophinopathies (e.g., Duchene and Becker muscular dystrophies) represent most of the published work incorporating CMR data investigation in neuromuscular disease. CMR can detect occult ventricular dysfunction and fibrosis in these muscular dystrophies at an early stage of cardiomyopathy, when other abnormalities cannot be recognized by standard cardiologic evaluation [7].

More recently, in a CMR study, Hermans *et al*, described functional or structural abnormalities in 44% of 80 patients with type 1 MyD. LV systolic dysfunction was found in 20 cases, LV dilatation in 7 patients, and LV hypertrophy in 6 patients. Myocardial fibrosis was seen in 10 patients (12.5%) [8].

However, due to the rarity of MuD and subsequently scarce literature data, CMR is only marginally recommended for this subset of patients, being more frequently performed in the absence of adequate echocardiographic window [9].

Based on our experience, and in line with the evidence at our disposal, we believe that every MuD patient should benefit from at least one CMR at baseline to identify the extent of cardiac involvement. According to baseline findings and further cardiac status, the cardiologist should individualize the frequency of subsequent CMR – if the patient remains stable, usually every 3 to 5 years intervals; sooner if de novo heart failure symptoms, echocardiographic evidence of LV diastolic or systolic dysfunction, rhythm and conduction disorders, etc. [2].

On our sample, nearly half of patients had some abnormality at baseline CMR. This is consistent with earlier studies, since these patients displayed morphological abnormalities such as LV and RV dilatation, LV hypertrophy, and LV systolic dysfunction.

In terms of tissue characteristics, more than one third patients had LGE, that was mostly intramyocardial or subepicardial in location; the most frequently involved segments were basal and mid inferolateral (56,5%), as commonly described [10].

MuD patients exhibit a distinctive myocarditis-like pattern of non-ischemic late LGE, initiating in the subepicardium/mid-wall of the lateral/inferolateral wall. Typically, this pattern progresses over the course of years, extending towards transmurality and affecting other myocardial segments, such as the septum [11]. As a genetic muscular disease, it would be expected to affect all myocardium equally in a diffuse manner and not to have this preferential segmental distribution. Whether the inferolateral wall is more vulnerable owing to regional molecular changes caused by the mutations or whether this regional susceptibility results from exposure to higher mechanical stress remains to be elucidated [12].

We found that CMR LVEF<55% and presence of LGE (irrespective of pattern) were significantly associated with higher risk of device implantation, ventricular tachycardia and mortality during a median follow up time of 6.4 (2.75) years.

It is believed that therapeutic action before to the onset of symptoms has a stronger impact, and hence the discovery of abnormal LVEF provides a chance to intervene [13]. As our data raises the hypothesis that even mild LVEF compromise is associated with the risk of events, LVEF lower than 55% in CMR may lead to prompt start of cardioprotective drugs. On the other hand, as the presence of fibrosis evaluated by LGE is also associated with adverse events, a stricter clinical vigilance may be prudent in these patients. CMR abnormalities can contribute

for risk stratification in addition to standard clinical, electrocardiogram and echocardiogram data and help in the selection of patients for invasive evaluation, namely for electrophysiological study. Therefore, our study supports the potential of cardiac magnetic resonance for risk stratification of patients with MuD.

Limitations

This is a single-center analysis of a small sized cohort of a rare group of disorders, with its inherent limitations. Given the small sample, we analyzed all subtypes of dystrophies with possible variable prognosis, which is a limitation of our study.

We did not systematically exclude coronary artery disease, conducting ischemic tests only in cases of angina or suggestive findings on exams. Still, the population was young, with a low prevalence of cardiovascular risk factors, and none exhibited typical ischemic pattern on CMR.

Unfortunately, data on T1 Mapping is unavailable due to the absence of the sequence at the time of data collection. This could have provided us with additional information on diffuse interstitial fibrosis, enabling even earlier identification of subclinical structural cardiac involvement. Nonetheless, it mirrors real-world experience with a fair period of follow-up, presents substantial associations even in a small sample study, and adds some information to a topic is still not fully understood. Larger, multicentric studies are need are required to corroborate this data for a more comprehensive cardiac phenotype characterization, which integrated with genotype-phenotype correlations can in the future improve risk stratification, helping to define more individualized protocols for clinical surveillance of these patients.

Conclusions

In our cohort, CMR LVEF<55% and the presence of LGE were significantly associated with a higher risk of device implantation, ventricular tachycardia, and mortality during follow-up, reinforcing the role of this technique in the risk stratification of patients with Muscular Dystrophies.

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Table 1. Cardiac magnetic resonance related variables according to subgroups of myotonic dystrophy and non-myotonic dystrophies.

CMR variables	Total n=65	Myotonic dystrophy n=34	Non-myotonic dystrophies n=31	p value
Left ventricle ejection fraction (LVEF), %	62 (8)	63 (8)	61 (9)	0.894
Left Ventricle End-diastolic volume index (LVEDVI), mL/m²	65 (21)	64 (20)	68 (26)	0.972
Left Ventricle End-systolic volume index (LVESVI), mL/m²	23 (12)	21 (11)	26 (13)	0.872
Left Ventricle Stroke volume index (LVSVI), mL/m²	39 (14)	39 (14)	40 (15)	0.775
Cardiac index (CI), L/min/m²	2.6 (1.0)	2.7 (1.0)	2.6 (0.9)	0.865
Left Ventricle Mass Index (LVMI), g/ m²	47 (15)	43 (13)	49 (18)	0.392
Right ventricle ejection fraction (RVEF), %	62 (8)	62 (7)	62 (11)	0.894
Right Ventricle End-diastolic volume index (RVEDVI), mL/m²	60±17	56 (17)	58 (23)	0.972
Right Ventricle End-systolic volume index (RVESVI), mL/m²	22 (12)	21 (12)	23 (14)	0.872
Right Ventricle Stroke volume index (RVSVI), mL/m²	36±9	36±7	36±10	0.749
Presence of LGE, n (%)	23 (35.4)	12 (35.3)	11 (35.4)	1.000
Pattern of LGE, n (%) - **Subendocardic** - **Intramyocardic** - **Subepicardic** - **Diffuse**	 1 (1.5) 10 (15.4) 8 (12.3) 4 (6.2)	 0 (0.0) 5 (14.7) 6 (17.6) 1 (2.9)	 1 (3.2) 5 (16.1) 2 (6.5) 3 (9.8)	0.930
LGE índex* , %	5.8 (11.7)	5.8 (8.8)	11.7 (20.6)	0.058

LGE, late gadolinium enhancement; *LGE índex as a percentage ratio of the number of affected LGE segments to the total of left ventricle segments**.** Continuous variables expressed as medians (interquartile range), except right ventricle stroke volume index, expressed as mean ± standart deviation.

Table 2. Cardiac magnetic resonance related variables, divided according to occurrence of major adverse cardiovascular events

CMR variables	Total n=65	No-event group n=50	Event group n=15	p value
Left ventricle ejection fraction (LVEF), %	62 (8)	63 (8)	50 (27)	**0.004***
Left Ventricle End-diastolic volume index (LVEDVI), mL/m²	65 (21)	64 (19)	71 (47)	0.205
Left Ventricle End-systolic volume index (LVESVI), mL/m²	23 (12)	22 (10)	40 (36)	**0.018***
Left Ventricle Stroke volume index (LVSVI), mL/m²	39 (14)	40 (14)	38 (16)	0.291
Cardiac index (CI), L/min/m²	2.6 (1.0)	2.6 (1.0)	2.8 (1.0)	0.827
Left Ventricle Mass Index (LVMI), g/ m^2	47 (15)	46 (15)	47 (23)	0.361
Right ventricle ejection fraction (RVEF), %	62 (8)	62 (8)	59 (14)	0.097
Right Ventricle End-diastolic volume index (RVEDVI), mL/m²	60±17	60±17	55±18	0.984
Right Ventricle End-systolic volume index (RVESVI), mL/m²	22 (12)	22 (11)	25 (19)	0.627
Right Ventricle Stroke volume index (RVSVI), mL/m²	36±9	37±9	33±9	0.286
Presence of LGE, n (%)	23 (35.4)	16 (32.0)	7 (46.7)	**0.035***
Pattern of LGE, n (%) - **Subendocardic** - **Intramyocardic** - **Subepicardic** - **Diffuse**	 1 (1.5) 10 (15.4) 8 (12.3) 4 (6.2)	 1 (2.0) 7 (14.0) 5 (10.0) 3 (6.0)	 0 (0.0) 3 (20) 3 (20) 1 (6.7)	0.668
LGE índex, %	5.8 (11.7)	5.8 (11.7)	8.8 (16)	0.254

LGE, late gadolinium enhancement; *LGE índex as a percentage ratio of the number of affected LGE segments to the total of left ventricle segments. Continuous variables expressed as medians (interquartile range), except right ventricle stroke volume index, expressed as mean ± standart deviation.

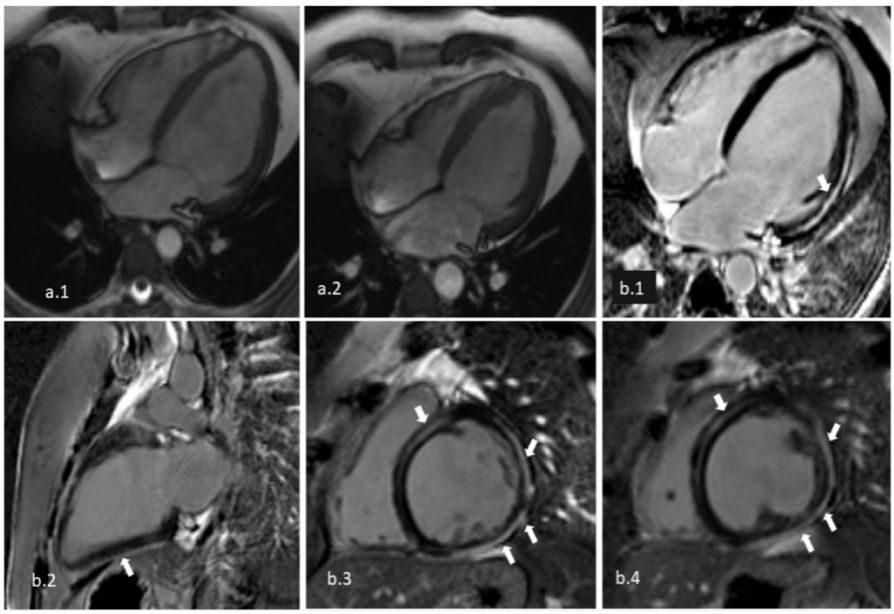

Figure 1. Cardiac magnetic resonance findings in a patient with Becker muscular dystrophy. a) SSFP sequence still images in long axis horizontal view in end-diastole (a.1) and end-systole (a.2) show left ventricular systolic dysfunction (LFEV 35%); b) LGE PSIR sequence in long-axis views in 4-chambers (b.1) and 2 chambers (b.2) and short-axis view (b.3, b.4). The arrows in these images demonstrate areas of focal fibrosis as mid-wall LGE in interventricular septum and also subepicardial LGE in lateral and inferior wall.

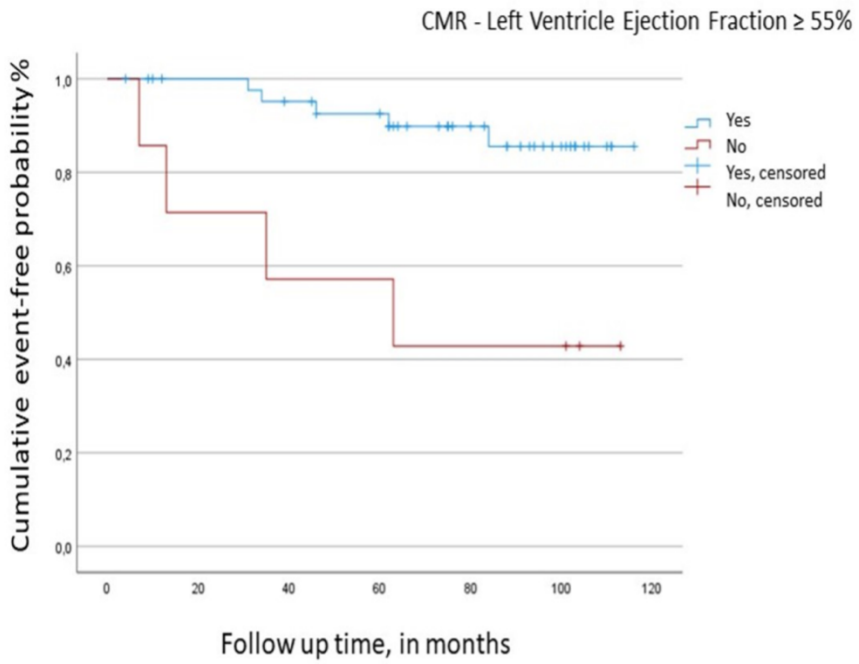

Figure 2. Kaplan Meier curve of cumulative event-free probability of the composite major adverse cardiovascular events (MACE)* according to cardiac magnetic resonance (CMR) measured left ventricle ejection fraction (LVEF) lower than 55%. *MACE comprehending all-cause death, hospitalization for heart failure, malignant arrhythmias, conduction disease requiring implantable cardiac defibrillator/permanent pacemaker, and appropriate shock therapy

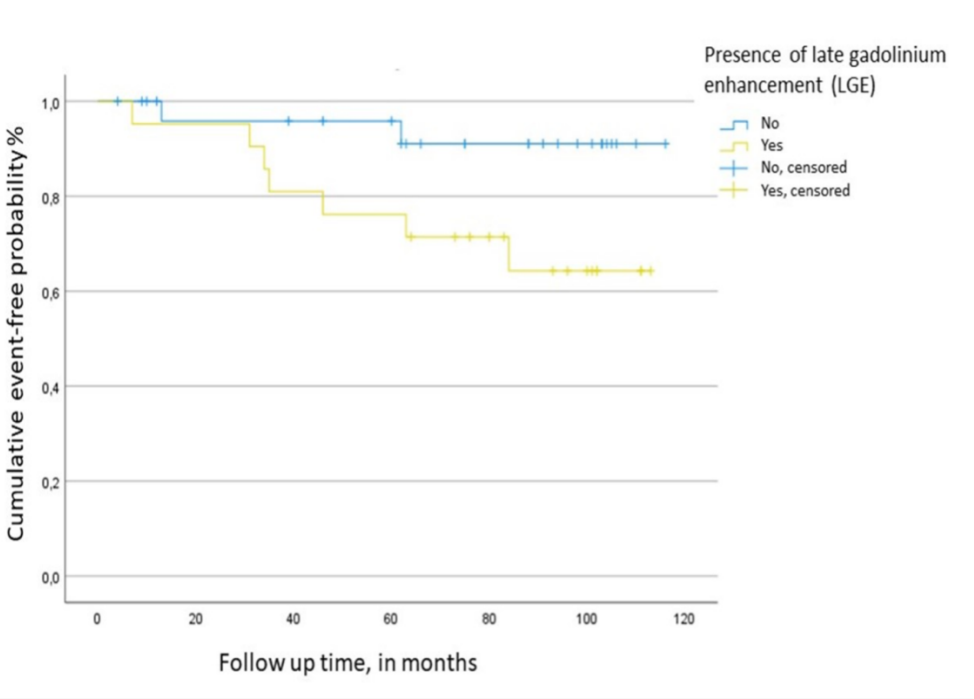

Figure 3. Kaplan Meier curve of cumulative event-free probability of the composite major adverse cardiovascular events (MACE)* according to the presence of late gadolinium enhancement (LGE) assessed by cardiac magnetic resonance (CMR). *MACE comprehending all-cause death, hospitalization for heart failure, malignant arrhythmias, conduction disease requiring implantable, cardiac defibrillator/permanent pacemaker, and appropriate shock therapy.