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Clinical Presentation and Outcome in a Contemporary Cohort of Patients with Acute Myocarditis: The Multicenter Lombardy Registry

Running Title: *Ammirati et al.; Outcome of Acute Myocarditis*

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Abstract

Background—There is controversy regarding outcome of patients with acute myocarditis (AM), and lack of data on how patients admitted with suspected AM are managed. We report characteristics, in-hospital management and long-term outcome of patients with AM based on a retrospective multi-center registry from 19 Italian hospitals.

Methods—A total of 684 patients with suspected AM and recent onset of symptoms (<30 days) were screened between May 2001 and February 2017. Patients >70 years and those older than 50 years without coronary angiography were excluded. The final study population comprised 443 patients (median age 34 years, 19.4% female) with AM diagnosed either by endomyocardial biopsy (EMB) or increased troponin plus edema and late gadolinium enhancement at cardiac magnetic resonance (CMR).

Results—At presentation, 118 patients (26.6%) had either left ventricular (LV) ejection fraction (EF) <50%, sustained ventricular arrhythmias (VA) or a low cardiac output syndrome (LCOS) whilst 325 (73.4%) had no such complications. EMB was performed in 56/443 (12.6%), and a baseline CMR was performed in 415/443 (93.7%) of patients. Cardiac mortality plus heart transplant (HTx) at 1 and 5 years were 3.0% and 4.1%. Cardiac mortality plus HTx were 11.3% and 14.7% in patients with complicated presentation and 0% in uncomplicated cases (Log-rank p<0.0001). Major AM-related cardiac events after the acute phase (post-discharge death and HTx, sustained VA treated with electrical shock or ablation, symptomatic heart failure needing device implantation) occurred in 2.8% at 5-year follow up, with a higher incidence in patients with complicated forms (10.8% vs. 0% in uncomplicated AM, Log-rank p<0.0001). Beta adrenoceptor blockers were the most frequently employed medications both in complicated (61.9%) and in uncomplicated forms (53.8%, p=0.18). After a median time of 196 days, 200 patients had follow-up CMR and 8/55 (14.5%) with complications at presentation had LVEF<50% compared with 1/145 (0.7%) of those with uncomplicated presentation.

Conclusions—In this contemporary study, overall serious adverse events after AM were lower than previously reported. However, patients with LVEF<50%, VA or LCOS at presentation were at higher risk compared with uncomplicated cases that had a benign prognosis and low risk of subsequent LV systolic dysfunction.

Key Words: Acute myocarditis; outcome; endomyocardial biopsy; cardiac magnetic resonance; heart transplantation

Clinical Perspective

What is new?

- Patients with uncomplicated acute myocarditis have benign short and long-term outcome although all patients in our series have evidence of increased necrosis biomarkers and late gadolinium enhancement at cardiac magnetic resonance.
- When left ventricular ejection fraction at first cardiac magnetic resonance is preserved, the risk of developing an inflammatory cardiomyopathy at mid-term follow up is very low.
- Autoimmune or systemic inflammatory disorders must be investigated in patients with acute myocarditis, as an autoimmune disorder can be found in 7.2% of patients admitted, and in particular in those with complicated presentation (15.4%).

What are the clinical implications?

- Patients can be effectively stratified based on their initial clinical presentation: patients with left ventricular ejection fraction <50% at first echocardiogram, those with sustained ventricular arrhythmias or with low cardiac output syndrome (termed complicated acute myocarditis) are at higher risk of cardiac events, compared with those without the above manifestations (uncomplicated cases) that are at lower risk.
- Our overall approach may help identify the most effective allocation of available resources, and in particular, does not support the idea that performing an endomyocardial biopsy can improve prognosis at least in patients with uncomplicated acute myocarditis.

Introduction

Acute myocarditis (AM) is generally caused by a post-viral immune response, even if other triggers have been involved, such as hypersensitivity drug reactions, infections, immune checkpoint inhibitors or systemic autoimmune disorders.[1-5] Post-mortem examinations in young adults have demonstrated that AM was responsible of 3 to 12% of cases of sudden cardiac death.[6-8] By contrast, in-hospital and long-term outcome of patients admitted with clinically suspected AM remains undetermined. So far, most large studies on AM were carried out in tertiary referral hospitals, were monocentric and included between 100 and 200 patients,[9-12] with variable timing of diagnosis from symptom onset.

There is evidence that the prognosis of patients with AM can be predicted, at least in part, based on the clinical presentation. Patients presenting with ventricular arrhythmias (VA) and/or symptoms of heart failure (HF) have worse prognosis compared with those presenting with chest pain.[11-15] Accordingly, in the United States there is consensus that endomyocardial biopsy (EMB) should be performed primarily in those cases with VA and conduction abnormalities, or advanced HF of recent onset (i.e. within one month since symptom onset) to exclude eosinophilic and giant cell myocarditis (GCM) or cardiac sarcoidosis, that have worse outcome and benefit from immune suppression.[1, 16, 17] By contrast, European experts recommend performing EMB in all clinically suspected AM.[18] Nevertheless, in the real-world, the perceived usefulness of EBM in the setting of AM is relatively low. Overall, in the United States between 2002 and 2014, approximately 1 EMB in native heart per million patients has been performed, and in 2014 only 8% of these were carried out in clinically suspected AM.[19]

Two recent multicenter studies in over 1,000 patients[20, 21] have proven the incremental diagnostic role of cardiac magnetic resonance (CMR) in patients with suspected AM confirming

previous studies showing that the presence, location and extent of late gadolinium enhancement (LGE) allow detection and quantification of myocardial damage as well as prediction of patient outcome. [16, 22, 23,15, 22]

Finally, although there is preliminary evidence that in young children (1 to 6 years old) AM can be followed by dilated cardiomyopathy, it is still debated whether adult patients that suffered from AM are at higher risk of developing dilated cardiomyopathy during follow up.[1 24] In this retrospective, multicenter study in 443 patients with AM, we aimed to define the natural history of the condition from the time of its diagnosis up to a median follow up of 35 months. We studied patients without concurrent cardiac disorder and with symptoms' onset within one month. The diagnosis of AM was confirmed either by EMB or by the combination of positive necrosis biomarkers and CMR criteria. Compared with our previous report on patients with AM presenting with fulminant vs. nonfulminant forms admitted to 2 referral hospitals, [14] the present study is based on a multicenter registry. We enrolled symptomatic patients with a diagnosis of AM based either on histology or increased troponin plus edema and LGE at CMR. Here, we evaluated beyond cardiac mortality and need for heart transplant (HTx), also major events related to AM and in approximately half of cases the changes of volumes and LVEF at CMR. Thus, the present study illustrates the clinical characteristics, in-hospital management and long-term outcome of a contemporary cohort of patients with AM.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, as the current approval of the

Ethics does not allow to share sensible patients' data with other researches without local Institutional Review Board (IRB) approval.

Study population and diagnosis of myocarditis

Patients admitted to 19 hospitals with cath labs and CMR facilities in Lombardy, a northern Italian region with a population exceeding 10 million, from May 2001 to February 2017, with clinically suspected AM were retrospectively screened and their data centrally revised on pre-specified criteria for the final inclusion in the dataset.

Niguarda hospital in Milan was the coordinating center. The appropriate ethics committee (Milano Area C) approved the study (Identifier 120-032016), and the collection of data was obtained in accordance with IRB. All the hospitals were at a maximal distance of 100 kilometers (62 miles) from the coordinating center with a homogeneous population and similar standards of care. The full list of centers is reported in the **Supplemental Appendix**.

Patients were locally identified through the International Classification of Diseases, Ninth Revision (ICD9-CM) diagnostic codes (422.0; 422.91; 422.92; 422.93; 422.99; 429.89) recorded in hospital discharge forms, or through the hospital lists of cases diagnosed with AM by histology or CMR and confirmed by revision of clinical records. The local hospitals were asked to consider only those patients with onset of cardiovascular symptoms within 30 days prior to admission. Patients with previous or current diagnosis of ischemic heart disease or alternative diagnosis at discharge were excluded. Per protocol, only patients with histologically proven myocarditis (from EMB, explanted heart or post-mortem examination) or with positive necrosis biomarkers (troponins or creatine kinase MB) combined with 2 CMR criteria for AM (edema at the dark-blood T2-weighted short tau inversion recovery [STIR] sequence and LGE) and with non-ischemic pattern of LGE were included. It has been previously demonstrated that co-

existence of these 2 "Lake Louise" CMR criteria has a specificity of 91% for the diagnosis of AM compared with histology.[22] In addition, all patients included in the analysis had no evidence of coronary artery disease (patients older than 50 years without available coronary angiography were excluded). Furthermore, patients aged over 70 years were excluded as potential confounders could not be completely ruled out at CMR (i.e. takotsubo or other conditions associated with the ageing heart). Amongst the 684 identified patients, 443 (64.8%) fulfilling the pre-specified criteria were included in the final analysis (**Figure 1** and **Supplemental Table 1**). Myocardial histology was available in 61 out of 443 (13.7%) patients (EMB in 56 cases, post-mortem examination in 4 cases and explanted heart in 1 case). Last data on follow up were acquired in July 2017. A subset of patients enrolled in the present study (170/443; 38.4%) from the Niguarda Hospital in Milan and San Matteo Hospital in Pavia, were also included in our previous report.[14]

Endpoints

Main study endpoint was the overall incidence of cardiac death and HTx. Secondary study endpoints were: i- all cause deaths and HTx; ii- a composite of major AM-related cardiac events that occurred after the acute phase. The latter combined endpoint included cardiac death and HTx (excluding in-hospital events), sustained VA treated with electrical shock or ablation, symptomatic HF needing device implantation. In the patients with follow-up CMR, prevalence of reduced LVEF and evidence of LV dilation (considering the threshold of indexed LV end-diastolic volume [LVEDV-i] of 105 mL/m^2 and 95 mL/m^2, for men and women respectively) were considered.[25]

Statistical analysis

Continuous variables are reported as mean±standard deviation (SD) or as median and Q1-Q3, according to normal or non-normal distribution as per Shapiro-Wilk normality test. Unpaired Student's t test or Mann-Whitney U test were used as appropriate to compare continuous variables. The Wilcoxon matched-paired signed rank test was used to analyze paired data at different time points. Categorical variables were compared with Fisher's exact test and relative-risk (RR) was calculated. The 95% confidential interval (CI) was calculated with the method of Katz.[26] Kaplan–Meier (KM) curves were compared with use of the log-rank statistic. All analyses were two-tailed. Differences with p values <0.05 were considered statistically significant. Software packages used were IBM SPSS Statistics (Version 20) and GraphPad Prism (version 6).

Results

The main characteristics of the study population are reported in **Table 1**. Median age at presentation was 34 years and 19.4% of the patients were females. The most frequent symptom at presentation was chest pain (86.6% of patients) followed by dyspnea (19.2%); 80.5% of patients had prodromal symptoms. An associated autoimmune disorder was observed in up to 7.2% of patients. Eosinophilic granulomatosis with polyangiitis, and mixed connective tissue disease were the most frequently observed autoimmune or systemic inflammatory disorders (**Table 2**).

The 443 patients were sub-divided into two groups based on the clinical presentation at the time of hospital admission. Group 1 (complicated AM) included 118 (26.6%) patients with AM complicated by left ventricular systolic dysfunction (i.e. left ventricular ejection fraction

[LVEF] <50%, at first in hospital echocardiogram), documented sustained ventricular arrhythmias (VA) or with a fulminant presentation (i.e. low cardiac output syndrome requiring inotropes and/or mechanical circulatory support)[15, 16] Group 2 (uncomplicated AM) included the remaining 325 (73.4%) patients. Follow up was completed in all, but 5 patients (1.1%) that were lost after discharge (2 non-European citizens and 3 Italian citizens not resident in Lombardy). Median follow up was 35 months (interquartile range [Q1-Q3]: 15-59 months) with a maximum follow up of 188 months. The median length of follow up did not differ between the 2 groups (p=0.38).

According to the pre-specified criteria, complicated AM was present in 118 out of 443 (26.6%) patients whilst the remaining 325 (73.4%) patients had uncomplicated AM. Females were more prevalent in the group with complicated AM. Symptoms of HF were more frequent in patients with complicated AM who had lower LVEF at first echocardiogram compared with uncomplicated AM.

Right ventricular EMB was performed in 56/443 (12.6%) of patients. EMB was performed in 47/118 (39.8%) of patients with complicated AM compared with 9/325 (2.8%) of those with uncomplicated AM. Histologic evidence of active myocarditis, based on Dallas criteria,[27] was observed in 50 out of the 56 EMB (89.3%). The most common histological sub-type was lymphocytic myocarditis both in complicated and uncomplicated AM (67.3% and 66.7% respectively, **Supplemental Table 2**).

Baseline CMR was performed in 415/443 (93.7%) of the patients and was acquired earlier in patients with uncomplicated AM (median delay from hospitalization was 4 days, Q1-Q3: 3-7 days) compared with those with complicated AM (6 days, Q1-Q3: 3-15 days, p=0.006)

(**Supplemental Table 2**). As per protocol, all 415 patients scanned had evidence of myocardial edema and LGE.

Treatment differed substantially in the two groups (**Supplemental Table 3)**. Immunosuppressive agents, in particular intravenous steroids, were used in up to 37.2% of patients presenting with complicated AM compared with 2.8% in those with uncomplicated presentation ($p<0.0001$). Non-steroidal anti-inflammatory drugs were more frequently used in patients with uncomplicated presentation than in those with complicated presentation (67.6% vs. 44%, $p<0.0001$). Beta adrenoceptor blockers were employed frequently in both groups (61.9% in complicated vs. 53.8% in uncomplicated forms, $p=0.18$) whereas angiotensin converting enzyme inhibitors or angiotensin II receptor blockers were used more frequently in patients with complicated AM (72.4% vs. 49.1%, $p<0.0001$).

Clinical outcome

In-hospital mortality and HTx in the whole study population (n=443) was 3.2% (10 cardiac deaths and 4 HTx) and these events occurred exclusively in patients with complicated AM. Furthermore, a venous-arterial extracorporeal membrane oxygenation (VA-ECMO) or a ventricular assist device (VAD) was used in 23/443 (5.2%) cases, all with complicated AM. Estimated cardiac mortality and HTx at 1, 3 and 5 years of follow up were 3.0%, 3.3% and 4.1%, respectively (**Figure 2A**). As shown in the **Figure 2B**, cardiac mortality and HTx at 1, 3 and 5 years of follow up were 11.3%, 12.5% and 14.7% respectively, in the group with complicated AM compared with 0% in those with uncomplicated AM (Log-rank $p<0.0001$). Death from all causes and HTx in the whole population at 5 years was 5.2% with a higher incidence in complicated vs. uncomplicated cases (18.0% vs. 0.3% respectively, Log-rank $p<0.0001$, **Supplemental Figure 1**). Major AM-related cardiac events after the acute phase occurred in

2.8% at 5-year follow up, with a significantly higher incidence in patients with complicated AM (10.8% vs. 0% in uncomplicated AM, Log-rank p<0.0001, **Figure 3** and **Table 2**).

Changes in left ventricular function at follow up

Of the 415 patients with a baseline CMR scan, 200 (48.2%) had also a follow up CMR scan after a median time of 196 days (Q1-Q3: 126-349 days). The time interval between the two CMR scans did not differ between complicated (n = 55) and uncomplicated (n = 145) AM (228 days; Q1-Q3: 115-464 days vs. 192 days, Q1-Q3: 132-306 days respectively; p=0.68). In the group with complicated AM there was a slight improvement in LVEF at follow up whilst LVEF at follow up was unchanged in uncomplicated AM (**Figure 4A-B**). The proportion of patients with reduced LVEF at follow-up CMR was larger in patients with complicated AM compared with uncomplicated AM (**Figure 4C**). At follow up, only 1 out of 145 patients (0.7%) with uncomplicated AM had a LVEF below 50% compared with 8 out of 55 (14.5%) of those with complicated AM. Similar results were obtained when LVEDV-i was considered (n=190). A larger proportion of patients with complicated AM had LV enlargement at follow up compared with those with uncomplicated AM (17.3% vs. 2.9%; RR: 1.17, 95%CI 1.03-1.33, p=0.003) (**Supplemental Figure 2**).

Discussion

The main finding of the present multicenter study in patients with AM is that cardiac death and HTx occurred in 3.2% of patients during hospitalization and in 4.1% of patients at 5-year follow up. Although these figures are relatively low compared with previous reports, [9, 12, 15, 28] we believe that they are a more realistic reflection of the short and long term outcome of patients with AM currently admitted to hospitals. As supporting independent data, a Finnish study on

childhood myocarditis also demonstrated relative low occurrence of in-hospital death and HTx (1.9%) among all children admitted with AM.[29] Differences in patient cohorts and study design may explain, at least in part, the discrepancies with previous studies that generally included smaller numbers of patients and used non-uniform criteria for diagnosing AM. Some reports included only patients with histologically proven AM whilst others enrolled cases of suspected AM selected only on the basis of CMR criteria. These differences might have affected the estimation of adverse events in the short and long term.[30] The inconsistency of currently available data is evident if one compares two of the largest studies published so far: one carried out in 222 patients where viral AM was diagnosed based on EMB, [15] reported a 15% cardiac mortality rate at 5-year follow up; the second study in 205 patients, where AM was surmised on the basis of CMR, reported no cardiac deaths at 19 month follow up.[31] Two other studies published in 2007 and 2008 reported mortality and HTx rates of 14.9% (median follow up 24 months) and 22% (median follow up 53 months) respectively.[11, 12]

Nevertheless, it must be noted that in the last decade, the diagnosis of AM has been made more frequently due to the introduction of sensitive troponins and CMR imaging. This might have increased the relative proportion of uncomplicated acute myocarditis in our population, resulting in a better outcome compared with older studies, where the diagnosis was mainly based on histology.

The second relevant result of our study is that, cardiac mortality and HTx both in the short (in-hospital, 11.9%) and long term (18.0% at 5 years follow up) occurred exclusively in patients with complicated AM, presenting at admission with LVEF below 50% at first echocardiogram, sustained VA or hemodynamic instability. Patients with uncomplicated AM had more benign short and long-term outcome although all patients had evidence of increased

necrosis biomarkers and LGE at CMR. It must be noted that most of the unfavorable events took place during the initial hospitalization. Furthermore, 14.5% of the patients with complicated AM had evidence of impaired LV function (i.e. LVEF <50%) at follow up CMR. In line with this, evidence of progressive LV dilation at follow up was found in 17.3% of the patients with complicated AM compared to only 2.9% of those with uncomplicated AM. In the uncomplicated group only one patient with preserved LVEF at baseline CMR had a LVEF below 50% at follow up. This patient, despite uncomplicated presentation and LVEF above 55% at baseline CMR, had peripheral eosinophilia, that led to perform an EMB demonstrating an eosinophilic myocarditis. Peripheral eosinophilia in the scenario of a clinically suspected AM represents a class 2A indication for EMB.[17, 18] One important message that can be derived from the present study is that patients can be effectively stratified based on their initial clinical presentation, main vital signs and instrumental findings (ECG and echocardiography) **(Figure 5** and **Supplemental Figure 3**).

Another significant difference compared with previous studies is that median LV end diastolic diameter was in the normal range (49 mm, including those with complicated AM where it was 50 mm) at first echocardiogram, thus confirming a recent onset of the inflammatory damage, without evidence of remodeling. The largest monocentric report on myocarditis (n=670) published so far bears several important differences compared to our study. The diagnosis of myocarditis was based on CMR imaging, 38% of the cases included were outpatients,[20] 48% of the patients had symptoms' onset above 2 weeks and the median LVEDV was 189 mL (LVEDV-i above 98 mL/m^2). Thus, almost half of the patients had LV dilation at the time of evaluation, suggesting an inflammatory damage of longer duration compared with the patients included in our study. Furthermore, the median transplant-free survival at 5 years was 95.7%, and main

predictors of outcome were age (patients were older compared to our study, i.e. 48 vs. 34 years), presence of LGE (in our study all patients had evidence of LGE, thus it could not be considered as potential predictor, but this increased the specificity of the diagnosis of AM in our study) and LVEF<40%. It should be noted that in our study the presence of reduced LVEF was a predictor of high-risk at follow up.

EMB was performed in 12.6% of the patients, primarily in those with complicated AM. This is in line with the current indications of the American Heart Association (AHA) and American College of Cardiology (ACC).[16, 18] Our results demonstrate that the decision not to perform an EMB in uncomplicated patients at admission is not associated with an increased risk of complications both acutely and in the long term. Our findings do not support the idea that performing an EMB can improve prognosis in patients with uncomplicated AM.[4]

On the other hand, our results support the use of CMR both for the diagnosis of AM and for patient stratification. Overall, our patients demonstrated relatively small changes in LVEF between the baseline CMR, performed during hospitalization or early after discharge, and the second CMR scan performed approximately after 200 days from initial admission. It has previously been observed that most changes in LVEF in patients with fulminant presentation and severe LV dysfunction take place in the first 2 weeks after admission.[14] In these patients CMR is generally delayed due to hemodynamic instability.[14] A transition from AM to dilated cardiomyopathy mediated by viral persistence in the myocardium has been suggested in murine models.[1] The stable/improved LVEDV-i found in most of our patients at follow up does not lend support to the hypothesis of progressive LV remodeling late after the acute episode in the absence of persistent or recurrent injury.

The present study has pointed out that autoimmune disorders must be investigated, as they were found in 7.2% of all AM and in particular in those with complicated presentation (15.4%). Therefore, those patients that have systemic autoimmune disorders (such as cardiac sarcoidosis or eosinophilic granulomatosis with polyangiitis), must be followed and considered at risk of further events and potential evolution to inflammatory cardiomyopathy.[1, 16]

In line with this, there is evidence that pharmacological blocking of multiple immune checkpoints by immunotherapy used against cancer (cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] by ipilimumab and programmed death-1 [PD-1] by nivolumab) can lead to fulminant AM suggesting a key role of immune response in the onset of AM.[5] In the setting of AM and in particular in patients with complicated presentation, the use of immunosuppressive agents such as steroids must be further investigated.

Most of the previous studies tested the use of immunosuppressive agents in patients with inflammatory cardiomyopathy during the chronic phase.[32-35] Also in the Myocarditis Treatment Trial (MTT) fewer than 45% of patients were randomized to immunosuppression within 1 month since symptoms' onset.[28] Based on our multicenter experience, physicians still use steroids in AM (11.4%), especially in patients with complicated AM (37.2% versus 2.8% in uncomplicated AM). The current use of immunosuppressive agents is reduced compared with previous series, before the MTT trial, where physician used immunosuppressive agents in up to 63% of cases.[36] Nonsteroidal anti-inflammatory drugs (NSAID) were frequently used, without increased risk particularly in uncomplicated AM at presentation (in 67.6%). This finding does not support the evidence that NSAID worsen the prognosis of viral myocarditis as observed in murine models. [37] Beta-blockers, that have been suggested to be protective in patients with myocarditis,[12] were the most frequently used drug in our patients with AM (up to 55.8%), without significant differences

between uncomplicated and complicated AM at presentation. Most drugs prescribed in uncomplicated AM are not evidence based, in particular the diffuse use of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (in 49.1%). These results remark the need for clinical trials to demonstrate the efficacy of these drugs in the setting of AM, in particular in those with presence of LGE.[20, 21]

Finally, this registry confirms that AM occurs more frequently in male subjects (about 80%),[38] although women more frequently have complicated AM and are therefore at higher risk of complications. The male prevalence observed in our population is consistent with data from the nationwide Finnish study (n=213) which included children hospitalized for AM. They observed that the prevalence of male sex increased with age, and in children aged 11 to 15 years the prevalence of males was 80%.[29] Another study focusing on the outcome of patients with pericarditis, reported the prevalence of male sex was around 80% in those with myocarditis associated with pericarditis (myo-pericarditis or peri-myocarditis) compared with individuals with isolated pericarditis where the prevalence of male sex dropped to 54%.[39] Similarly, in 2 other studies on AM diagnosed by CMR with median LVEF above 55%, the prevalence of male sex was 77% and 76% respectively.[21, 31] The prevalence of male sex can decrease based on the inclusion of high-risk patients, as observed in previous studies where the diagnosis was mainly driven by EMB and the mean LVEF was around 40%, with a male prevalence of approximately 60%.[9-11, 40]

Study Limitations

The retrospective nature of this registry can have introduced potential bias. As the registry spans over a 16-year period, the availability of CMR and even EMB could have changed. Nevertheless, we believed our population reflects the real-world practice more realistically particularly in

regard to the outcome of AM compared with previous monocentric experience of patients with EMB. Furthermore, the clinical practice of our 19 hospitals in Lombardy may not be reflected elsewhere in Europe or United States particularly regarding the relatively high use of steroids and anti-remodeling medications. We cannot exclude that this approach could have impacted on the reported more favorable prognosis. Nevertheless, this point stresses again the need for randomized clinical trials to assess drugs able to reduce the mortality rate in this particular setting of young individuals. Moreover, even if 19 centers participated in this registry, their relative contributions were significantly different, as reported in **Supplemental Table 1**. Finally, there was no centralized review of pathology and CMR data in this registry. It must be noted that even if there was no core facility for the CMR images the identification of areas with positive STIR or LGE, and the calculation of volumes of the LV and LVEF with CMR have high accuracy and inter-observer reproducibility.[25] The absence of a core echocardiography laboratory and the impossibility to retrieve several original echocardiographic images was at the reason why we did not report changes in LVEF at follow up based on echocardiography.

Conclusions

Our study points out that most cardiac deaths and HTx following AM occur during initial hospitalization. We show that integration of clinical data, necrosis biomarkers, CMR and EMB, when indicated, can effectively identify patients at increased risk of major adverse events. By contrast, we feel that collecting data only from histologically proven AM might lead to overestimation of morbidity and mortality. Finally, we provide evidence that when LVEF at first CMR is preserved, the risk of developing an inflammatory cardiomyopathy at follow up is very low. This overall approach might also help identify the most effective allocation of available resources although large multicenter, prospective studies are needed to confirm our findings.

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Disclosures

None

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Table 1. Clinical presentation and initial diagnostic findings in 443 patients admitted with clinically suspected acute myocarditis (AM)

	No. of patients with available data	Acute myocarditis			p
		All	Complicated presentation	Uncomplicated presentation	
No.		443	118	325	
Age–yr *median(Q1-Q3)*	443	34(24-42)	35(22-45)	33(24-42)	0.46
Age <15 yrs-no.(%)		14(3.2)	7(5.9)	7(2.2)	0.06
Female-no.(%)	443	86(19.4)	37(31.4)	49(15.1)	**0.0002**
Caucasian ethnicity –no.(%)	443	407(92.1)	104(88.1)	303(93.2)	0.11
Clinical presentation-no.(%)					
Dyspnea	437	84(19.2)	64(55.7)	20(6.2)	**<0.0001**
Chest pain	437	379(86.7)	68(59.1)	311(96.6)	**<0.0001**
Syncope	437	27(6.2)	19(16.5)	8(2.5)	**<0.0001**
*Fulminant presentation**	443	38(8.6)	38(32.2)	0(0)	**<0.0001**
Fever-no.(%)	437	282(64.5)	73(63.5)	209(64.9)	0.82
Prodromal Symptoms-no.(%)	437	352(80.5)	94(81.7)	258(80.1)	0.78
Sore throat-no.(%)	437	161(36.8)	44(38.3)	117(36.3)	0.74
Respiratory tract infection-no.(%)	437	10(2.3)	6(5.2)	4(1.2)	**0.02**
Gastrointestinal disorders-no.(%)	437	126(28.8)	36(31.3)	90(28.0)	0.55
Patients with Associated Auto-immune disorders†-no.(%)	430	31(7.2)	18(15.4)	13(4.2)	**0.0002**
Previous myocarditis-no.(%)	443	5(1.1)	2(1.7)	3(0.9)	0.61
ECG at admission-no.(%)	426				
Normal		61(14.3)	8(7.6)	53(16.5)	**<0.0001**
ST segment elevation		245(57.5)	45(42.9)	200(62.3)	
Other abnormal ST-T segment		100(23.5)	39(37.1)	61(19.0)	
Bundle branch block		20(4.7)	13(12.4)	7(2.2)	
Any AV block no.(%)	427	13	10(9.6)	3(0.9)	**<0.0001**
Laboratory findings					
Increased CRP at admission-no.(%)	414	333(80.4)	89(84.0)	244(79.2)	0.32
Increased troponin -T/-I/CK-MB at admission-no.(%)	437	434(99.3)	111(99.1)	323(99.4)	1
Echocardiography at admission-no.(%)	431	431(97.3)	112(94.9)	319(98.2)	0.09
LVEF-%(Q1-Q3)	428	55(50-60)	35(20-45)	60(55-60)	**<0.0001**
LVEDD-mm median (Q1-Q3)(only patients ≥15yrs)	246	49(46-52)	50(46-55)	48(46-50)	**0.050**
RV-TAPSE<18 mm or evidence of visual dysfunction no.(%)	259	22(8.5)	19(30.6)	3(1.5)	**<0.0001**
Presence of pericardial effusion-no.(%)	397	102(25.7)	41(38.7)	61(21.0)	**0.0007**
Coronary angiography or CT angiography performed-*no.(%)*	434	203(46.8)	57(50.0)	146(45.6)	0.45
No evidence of CAD -no.(%)	203	203(100)	57(100)	146(100)	-

* Fulminant presentation indicates patients with low cardiac output syndrome requiring inotropes and/or mechanical circulatory support.
† See Table S1 in the Supplementary Appendix for details regarding associated autoimmune disorders.
Yrs indicates years; Q1-Q3, first and third quartile; AV, atrio-ventricular; CRP, C-reactive protein; CK-MB, creatine kinase isoenzyme MB; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; RV-TAPSE, right ventricular tricuspid annular plate systolic excursion; CT, computed tomography; CAD, coronary artery disease.

Table 2. Associated autoimmune or systemic inflammatory disorders in patients with clinically suspected acute myocarditis (available data 430 out of 443; 97.1%)

	All AM	AM with other Autoimmune/ inflammatory disorders	Complicated AM with other Autoimmune/ inflammatory disorders	Uncomplicated AM with other Autoimmune/ inflammatory disorders	p
Patients with Associated autoimmune/ inflammatory disorders-no./total		31/430	18/117	13/313	-
Patients with Multiple autoimmune/ inflammatory disorders-no.(%)	2/430(0.5)	2/31(6.5)	1(5.5)	1(7.7)	-
EGPA-no.(%)	6/430(1.4)	6/31(19.4)	6(33.0)	0(0)	-
Mixed connective tissue disease-no.(%)	5/430(1.2)	5/31(16.1)	3(16.7)	2(15.4)	-
Autoimmune hypothyroidism –no.(%)	4/430(0.9)	4/31(12.9)	2(11.1)	2(15.4)	-
Inflammatory bowel disease-no.(%)	4/430(0.9)	4/31(12.9)	1(5.5)	3(23.1)	-
Sarcoidosis -no.(%)	3/430(0.7)	3/31(9.7)	2(11.1)	1(7.7)	-
Isolated Asthma-no.(%)	3/430(0.7)	3/31(9.7)	1(5.5)	2(15.4)	-
Autoimmune hyperthyroidism-no.(%)	2/430(0.5)	2/31(6.5)	1(5.5)	1(7.7)	-
SLE-no.(%)	1/430(0.2)	1/31(3.2)	1(5.5)	0(0)	-
Antiphospholipid syndrome- no.(%)	1/430(0.2)	1/31(3.2)	1(5.5)	0(0)	-
Psoriasis- no.(%)	1/430(0.2)	1/31(3.2)	0(0)	1(7.7)	-
Celiac disease no.(%)	1/430(0.2)	1/31(3.2)	0(0)	1(7.7)	-
Autoimmune hepatitis no.(%)	1/430(0.2)	1/31(3.2)	1(5.5)	0(0)	-
Multiple sclerosis-no.(%)	1/430(0.2)	1/31(3.2)	1(5.5)	0(0)	-
GVHD-no.(%)	1/430(0.2)	1/31(3.2)	0(0)	1(7.7)	-
Unknown-no.(%)	1/430(0.2)	1/31(3.2)	1(5.5)	0(0)	-

AM indicates acute myocarditis; EGPA, Eosinophilic granulomatosis with polyangiitis; SLE, systemic lupus erythematosus; GVHD, graft-versus-host-disease

Table 3. Events that occurred in 443 patients admitted with clinically suspected acute myocarditis (AM)

	Acute myocarditis			p
	All	Complicated at presentation	Uncomplicated at presentation	
No.	443	118	325	
In-hospital events:				
Overall deaths no.(%)	10(2.3)	10(8.5)	0(0)	**<0.0001**
Cardiac deaths-no.(%)	10(2.3)	10(8.5)	0(0)	**<0.0001**
Non-cardiac deaths-no.(%)	0(0)	0(0)	0(0)	**-**
HTx-no.(%)	4(0.9)	4(3.4)	0(0)	**0.005**
VAD-no.(%)	5(1.1)	5(4.2)	0(0)	**0.001**
Va-ECMO-no.(%)	18(4.1)	18(15.3)	0(0)	**<0.0001**
Lost after discharge no.(%)	5(1.1)	2(0.8)	3(0.9)	
Post-discharge events:				
No.	428	106	322	
Overall deaths –no.(%)	7(1.6)	6(5.7)	1(0.3)	**0.001**
Cardiac deaths-no.(%)	2*(0.5)	2*(1.9)	0(0)	-
Non-cardiac deaths-no.(%)	5(1.2)	4(3.8)†	1(0.3)†	-
HTx-no.(%)	2(0.5)	2(1.9)	0(0)	-
SVT treated with shock/ablation-no.(%)	4(0.9)	4(3.8)	0(0)	0.004
CRT implant-no.(%)	1(0.2)	1(0.8)	0(0)	-
Other events:				
ICD implant-no.(%)	9(2.0)	8(6.8)	1(0.3)‡	**<0.0001**
Recurrence of AM-no.(%)	11(2.6)	1(0.9)	10(3.1)	0.31
STEMI -no.(%)	2(0.5)	0(0)	2(0.6)	-

* On patient died after heart transplantation due to severe graft rejections and graft dysfunction (initial diagnosis: giant cell myocarditis).
† Non cardiac deaths were caused by suicide in 2 patients, cancer in 1 and infection in another one in the complicated AM group and by cancer in 1 patient in the uncomplicated AM group.
‡ The patient was initially admitted for a syncope and diagnosed with a suspected AM. In the follow up an ambulatory ECG monitoring demonstrated a non-sustained asymptomatic ventricular arrhythmia, thus he was implanted. No ventricular arrhythmias were further recorded after ICD implantation.
HTx, heart transplantation; VAD, ventricular assist device; va-ECMO, venoarterial extracorporeal membrane oxygenation; SVT, sustain ventricular tachycardia; CRT cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; AM, acute myocarditis, STEMI, ST-elevation myocardial infarction.

Figure Legends

Figure 1. Flow diagram illustrating screening and inclusion criteria.

Figure 2. **Kaplan-Meier estimates of 5 years cardiac mortality and heart transplantation**

A, events in the whole study population with AM and **B,** events in patients with AM complicated at presentation by left ventricular ejection fraction <50%, sustained ventricular arrhythmias or a low cardiac output syndrome compared with patients without such complications at presentation. Of total cardiac deaths and heart transplantation, 16 patients initially presented with fulminant presentation and 1 with ventricular arrhythmias. One cardiac death occurred after heart transplantation and was omitted.

Figure 3. Kaplan-Meier estimates of 5 years composite of major acute myocarditis-related cardiac events after the acute episode. A, events in the overall patient with AM and **B**, events in patients with AM complicated at presentation by left ventricular ejection fraction <50%, sustained ventricular arrhythmias or a low cardiac output syndrome compared AM patients uncomplicated at presentation. The composite of major acute myocarditis -related cardiac events that occurred after the acute phase included cardiac death and heart transplantation (excluding in-hospital events), sustained ventricular arrhythmias treated with electrical shock or ablation, symptomatic heart failure needing device implantation. Three patients who died in the follow up had initially a fulminant presentation, 2 patients who were transplanted in the follow up had initially a fulminant presentation, 2 patients who had a sustained ventricular arrhythmias treated with shock or ablation in the follow up had initially a sustained ventricular arrhythmias and 2

patients had a fulminant presentation, 1 patient who was implanted with a cardiac resynchronization therapy device due to symptomatic heart failure in the follow up had initially a left ventricular ejection fraction below 50%.

Figure 4. Changes in left ventricular ejection fraction (LVEF) between baseline and follow-up (median time of 196 days) cardiac magnetic resonance. A, Patients with complicated myocarditis at presentation had a significant improvement of left ventricular systolic function, **B,** patients with uncomplicated myocarditis had a similar LVEF at follow up (Wilcoxon matched-pair signed-rank test was used for comparisons). **C,** the proportion of patients with a LVEF below 55%, considering a threshold for impaired left ventricular systolic function at CMR was higher among patients with complicated myocarditis. Categorical variables were compared with Fisher's exact test and relative-risk (RR) was calculated. CI indicates confidential interval.

Figure 5. Risk stratification of patients with acute myocarditis (AM) based on initial clinical presentation, main vital signs and instrumental findings.

Based on the results of the registry, complicated AM based on left ventricular ejection fraction (LVEF) <50% at first echocardiogram (ECHO), presence of ventricular arrhythmias (VA) at ECG or evidence of hemodynamic instability (low cardiac output syndrome [LCOS] at hospital admission can effectively identify patients at risk of death, heart transplantat (HTx) and long-term ventricular assist device (LT-VAD) during hospitalization (increased-risk AM group). Further information of reduced LVEF (<55%) at baseline cardiac magnetic resonance (CMR) associated with the initial clinical presentation can effectively identify those patients at risk of further major AM-related cardiac events (composite of cardiac death, HTx, sustained VA treated

with electrical shock or ablation and symptomatic heart failure needing device implantation) in the follow up or those at risk of having a reduced LVEF at a follow-up CMR. In particular, the prognosis in term of events and risk of LVEF impairment is minimal in patients with uncomplicated AM at presentation and LVEF equal or above 55% at baseline CMR (low-risk AM group). The proportion of AM-related events were significantly higher in the high-risk group compare with low risk group (9.5% vs. 0; p=0.0008, Fisher's exact test was used). Similarly, proportion of patients with LVEF<55% at follow up was significantly high in the high risk-group compared with low-risk group: 21.6% vs. 3.9% (relative risk for LVEF<55% at follow up 5.49 [95%confidence interval] 2.10-14.4; p=0.0002). BP indicated blood pressure.

*The number of patients included in the follow up after discharge was the sum of those with a baseline and a follow-up CMR (N=200) plus one patient (with complicated presentation) who had a baseline CMR and had an event in the follow up who prevented him/her to undergo the follow-up CMR.

Identification

Screening

Eligibility

Included

Patients with clinically suspected acute myocarditis from 19 hospitals in Lombardy region N=684

CRITERIA FOR ACUTE MYOCARDITIS:
Acute symptoms' onset < 4 weeks +
Positive cardiac histology
OR
Positive markers of cardiac necrosis
Positive CMR (LGE+ and STIR+)

Cases assessed for eligibility (n=638)

General exclusion criteria *per protocol*:
- **Age equal or above 70 years (n= 23)**
- **Age between 51 and 69 years without coronary angiograhy (n=13)**
- **Incomplete data or alternative diagnosis (n=10)**

Eligible cases with sufficient diagnostic data (n=522)

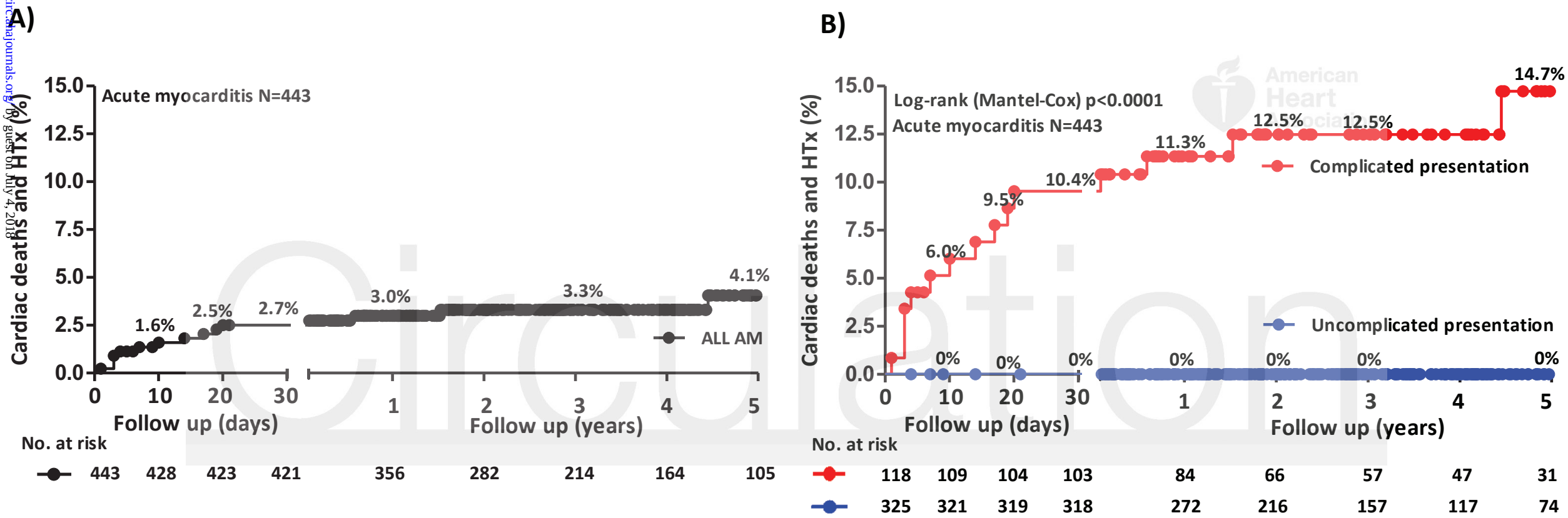
Insufficient diagnostic assessment:
- **Cardiac magnetic resonance/EMB not performed (n=116)**

Not reaching diagnostic criteria *per protocol*:
- **Not meeting cardiac magnetic resonance criteria (n=52)**
- **No elevation of necrosis biomarkers of (n=27)**

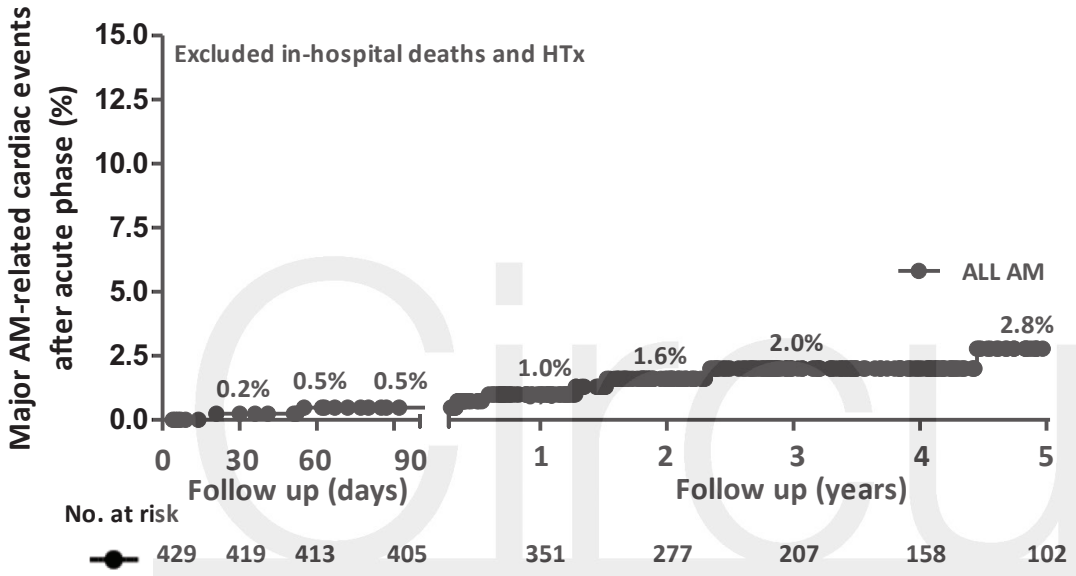
Acute myocarditis included in the analysis (n=443)

118 (26.6%) cases with complicated acute myocarditis at presentation

325 (73.4%) cases with uncomplicated presentation



A)



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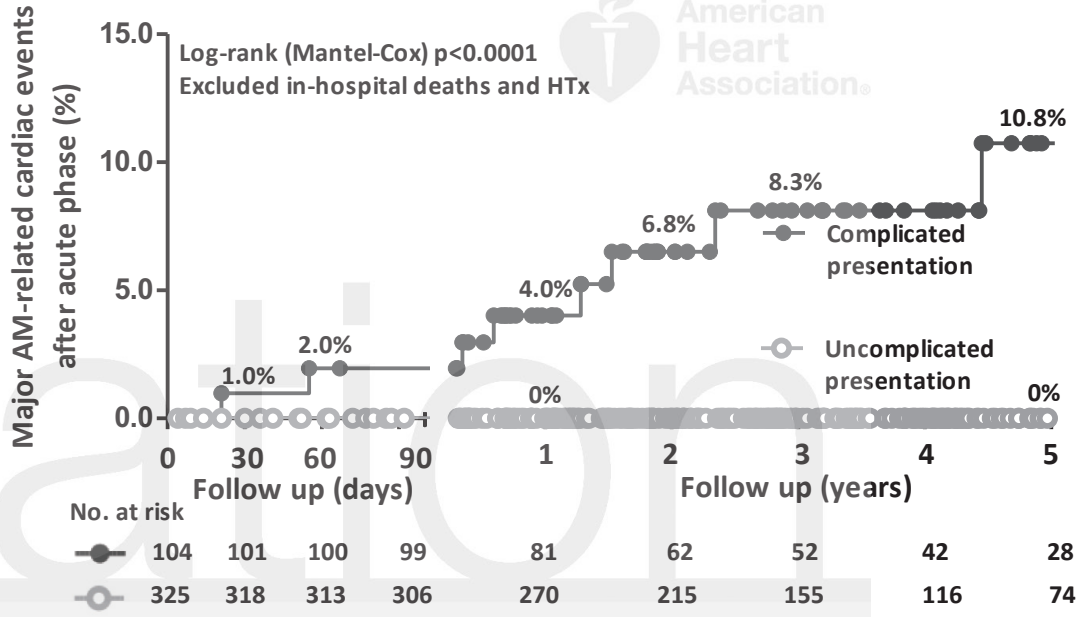

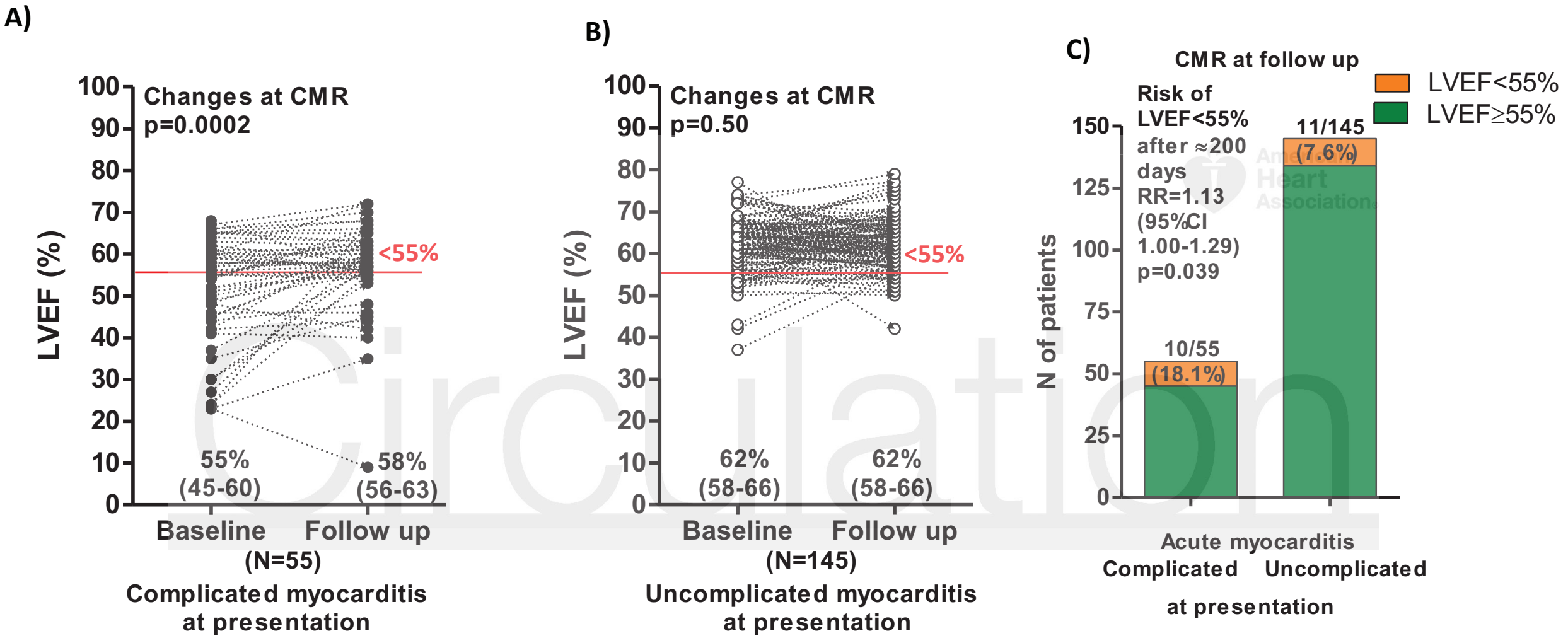

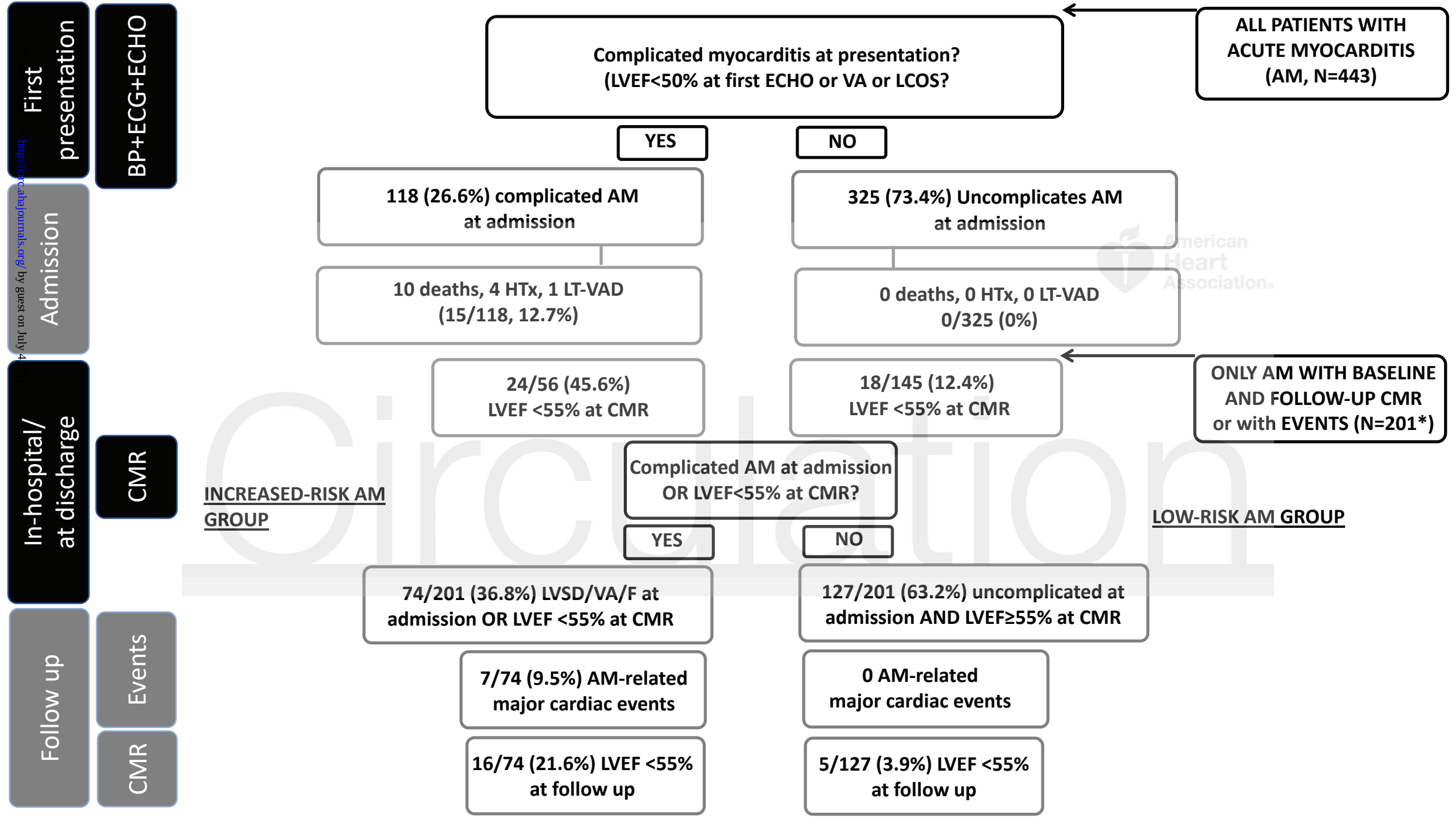

Clinical Presentation and Outcome in a Contemporary Cohort of Patients with Acute Myocarditis: The Multicenter Lombardy Registry

Enrico Ammirati, Manlio Cipriani, Claudio Moro, Claudia Raineri, Daniela Pini, Paola Sormani, Riccardo Mantovani, Marisa Varrenti, Patrizia Pedrotti, Cristina Conca, Antonio Mafrici, Aurelia Grosu, Daniele Briguglia, Silvia Guglielmetto, Giovanni Battista Perego, Stefania Colombo, Salvatore Ivan Caico, Cristina Giannattasio, Alberto Maestroni, Valentina Carubelli, Marco Metra, Carlo Lombardi, Jeness Campodonico, Piergiuseppe Agostoni, Giovanni Peretto, Laura Scelsi, Annalisa Turco, Giuseppe Di Tano, Carlo Campana, Armando Belloni, Fabrizio Morandi, Andrea Mortara, Antonio Cirò, Michele Senni, Antonello Gavazzi, Maria Frigerio, Fabrizio Oliva and Paolo G. Camici

on behalf of the Registro Lombardo delle Miocarditi

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CLINICAL PRESENTATION AND OUTCOME IN A CONTEMPORARY COHORT OF PATIENTS WITH ACUTE MYOCARDITIS: THE MULTICENTER LOMBARDY REGISTRY

Ammirati and Cipriani et al. On behalf of the Registro Lombardo delle Miocarditi **Outcome of acute myocarditis**

SUPPLEMENTAL MATERIALS

SUPPLEMENTAL METHODS

List of participating centers:

In Milano: Niguarda Hospital, coordinating center**;** San Carlo Hospital**;** Humanitas Hospital**;** San Luca Auxologico Hospital**;** Monzino Hospital**;** Sacco Hospital**;** San Raffaele Hospital. **In Monza:** Policlinico Hospital**;** Desio Hospital**;** San Gerardo Hospital. **In Varese:** Mater Domini Humanitas Hospital**;** Gallarate Hospital**;** Fondazione Macchi Hospital**;** Busto Arsizio Hospital. **In Brescia:** Civili Hospital. **In Cremona:** H Spitali. **In Pavia:** San Matteo Hospital. **In Bergamo:** Papa Giovanni XXIII Hospital. **In Como:** Sant'Anna Hospital. All hospitals are in Italy.

Supplemental TABLE 1. Causes of exclusion of patients with clinically suspected myocarditis in each hospital

In bold are reported the name of the provinces/towns where the hospitals are located. CMR indicates cardiac magnetic resonance; N, number; H, hospital.

	Age≥70yrs	Age 51-69yrs without coronary angiography	NO CMR	No CMR criteria	No troponin increase	Unavailable troponin	Others	Excluded (% total)	Total	Included
Milano										
H Niguarda	4	-	10	6	4	1	1	26(17.1)	152	126
H San Carlo	4	-	7	2	-	-	-	13(36.8)	38	25
H Humanitas	3	2	-	6	-	-	4	15(26.3)	57	42
H Auxologico	2	-	6	-	-	-	-	8(30.8)	26	18
H Monzino	3	-	23	2	1	-	1	30(73.2)	41	11
H Sacco	-	-	1	1	1	-	-	3(33.3)	9	6
H San Raffaele	-	-	-	-	12	-	1	13(38.2)	34	21
Monza										
H Policlinico	1	-	3	4	-	-	-	8(100)	8	0
H Desio	-	3	-	-	-	-	-	3(4.8)	62	59
H San Gerardo	-	-	1	-	1	-	-	2(40.0)	5	3
Varese										
H Mater Domini	-	1	-	1	5	-	-	7(41.2)	17	10
H Gallarate	-	-	-	3	-	-	-	3(20.0)	15	12
H Macchi	-	-	33	2	1	-	2	38(90.5)	42	4
H Busto	-	1	-	-	-	-	-	1(8.3)	12	11
Brescia										
H Civili	3	2	2	3	2	-	-	12(50.0)	24	12
Cremona										
H Spitali	3	-	20	3	-	-	-	26(86.7)	30	4
Pavia										

H San Matteo	-	1	7	1	-	-	-	9(15.5)	58	49
Bergamo										
H Papa Giovanni XXIII	-	-	3	12	-	-	-	15(36.6)	41	26
Como										
H Sant'Anna	-	3	-	6				9(69.2)	13	4
N of HOSPITALS (n=19)								241(35.2)	684	443

Supplemental TABLE 2. Pathology and cardiac magnetic resonance findings in 443 patients with clinically suspected acute myocarditis (AM)

	Complicated AM	Uncomplicated AM	P
HISTOLOGY	VALUE	VALUE	
EMB performed *no.(%)*	47/118 (39.8)	9/325 (2.8)	**<0.0001**
Active myocarditis no.(%)	43/47(91.5)	7/9(77.8)	0.24
Borderline/negative for myocarditis no.(%)	4*/47(8.5)	2/9(22.2)	
Post-transplant examination without EMB *no.(%)*	1/118(0.8)	0	-
Post-mortem examination without EMB *no.(%)*	4/118(3.3)	0	-
Overall available histology *no.(%)*	52/118 (44.1)	9/325 (2.8)	**<0.0001**
Specific forms of myocarditis			
Lymphocytic myocarditis no.(%)	35/52(67.3)	6/9(66.7)	1
Giant cell myocarditis no.(%)	7/52(13.4)	0	-
Cardiac sarcoidosis no.(%)	2/52(3.8)	0	-
Eosinophilic myocarditis no.(%)	6/52(11.5)	1/9(11.1)	1
Borderline/Negative no.(%)	2/52(3.8)	2/9(22.2)	0.10
CMR	pts with available data / VALUE	pts with available data /	
CMR performed-*no.(%)*	118 / 90(76.3)	325 / 325(100)	**<0.0001**
Time to CMR since admission-days(Q1-Q3)	81 / 6(3-15)	302 / 4(3-7)	**0.006**
LVEF-%(Q1-Q3)	81 / 54(43-60)	304 / 61(56-66)	**<0.0001**
LVEDV-indexed-mL/m^2 (Q1-Q3)	78 / 80 (70-98)	299 / 80 (72-90)	0.42

CMR indicates cardiac magnetic resonance; EMB, endomyocardial biopsy; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; Q1–Q3, first–third quartiles; and STIR, T2-weighted short tau inversion recovery.

*Three patients had negative endomyocardial biopsy but positive histology at post mortem analysis, and another patient had negative endomyocardial biopsy but positive histology on explanted heart.

Supplemental TABLE 3. Immunosuppressive regimens and heart failure medications in in 443 patients with clinically suspected acute myocarditis

	Complicated AM		**Uncomplicated AM**		**P**
	No. of patients with available data	VALUE	No. of patients with available data	VALUE	
Immunosuppressive therapy- *n(%)*	113	42(37.2)	324	8(2.8)	**<0.0001**
I.v. steroids- *n(%)*	94	30(31.9)	231	2(0.9)	**<0.0001**
Only oral steroids- *n(%)*	94	10(10.6)	231	5(2.2)	**0.002**
IVIG- *n(%)*	86	7(8.1)	229	0(0)	**<0.0001**
Cyclosporine- *n(%)*	75	6(8.0)	160	1(0.6)	**0.005**
Azathioprine- *n(%)*	74	3(4.1)	159	2(1.3)	0.33
Other Immunosuppressive drug- *n(%)*	74	7(9.5)	90	1(1.1)	**0.02**
NSAID- *n(%)*	109	48(44.0)	324	219(67.6)	**<0.0001**
ACEi/ARBs- *n(%)*	105	76(72.4)	324	159(49.1)	**<0.0001**
Beta-blockers- *n(%)*	105	65(61.9)	325	175(53.8)	0.18
MRAs- *n(%)*	105	25(23.8)	320	10(3.1)	**<0.0001**
Amiodarone- *n(%)*	100	7(7.0)	322	0(0)	**<0.0001**
Ivabraidine- *n(%)*	101	8(7.9)	319	3(0.9)	**0.0008**

I.v., intravenous; I.v.Ig, intravenous immunoglobulins; cyA; NSAID, Nonsteroidal anti-inflammatory drug; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; MRAs, mineralocorticoid receptor antagonist.

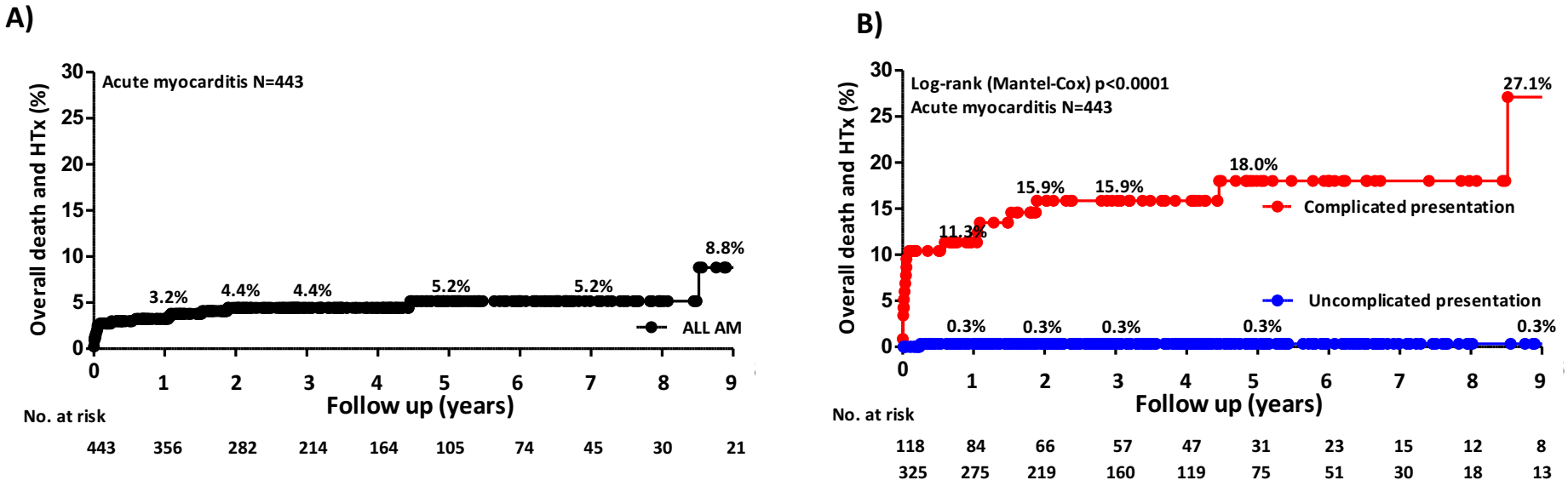
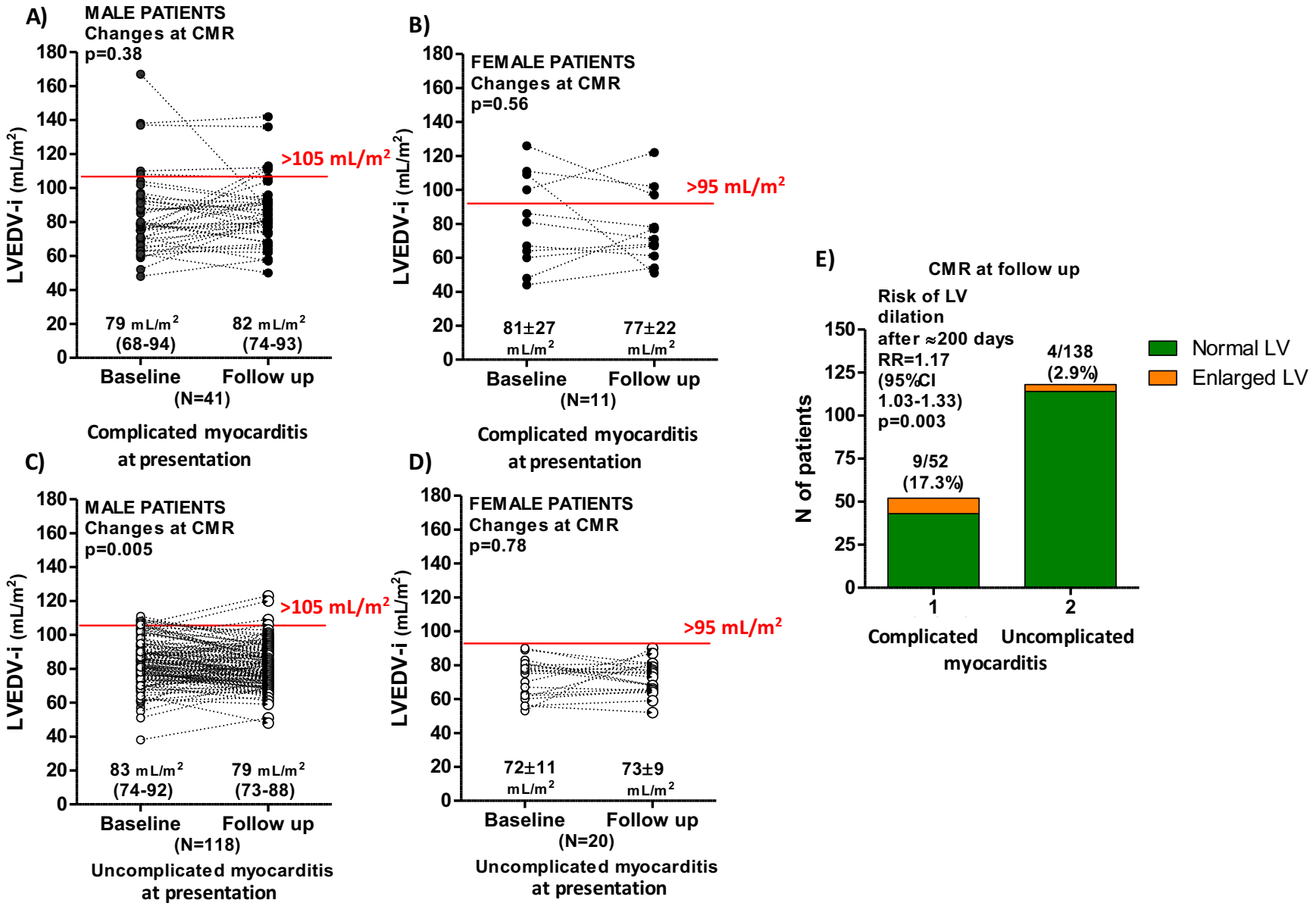


FIGURE S1

Supplemental Figure 1. Kaplan-Meier estimates of 9 years overall mortality and heart transplantation

A, events in the overall patient with AM and **B,** events in patients with AM complicated at presentation by left ventricular ejection fraction <50%, sustained ventricular arrhythmias or a low cardiac output syndrome compared AM patients uncomplicated at presentation.



ONLINE FIGURE 2

Supplemental Figure 2. Changes in indexed left ventricular end-diastolic volume (LVEDV-i) comparing the baseline cardiac magnetic resonance (CMR) with the follow-up CMR at a median time of 196 days in 190 patients with available data.

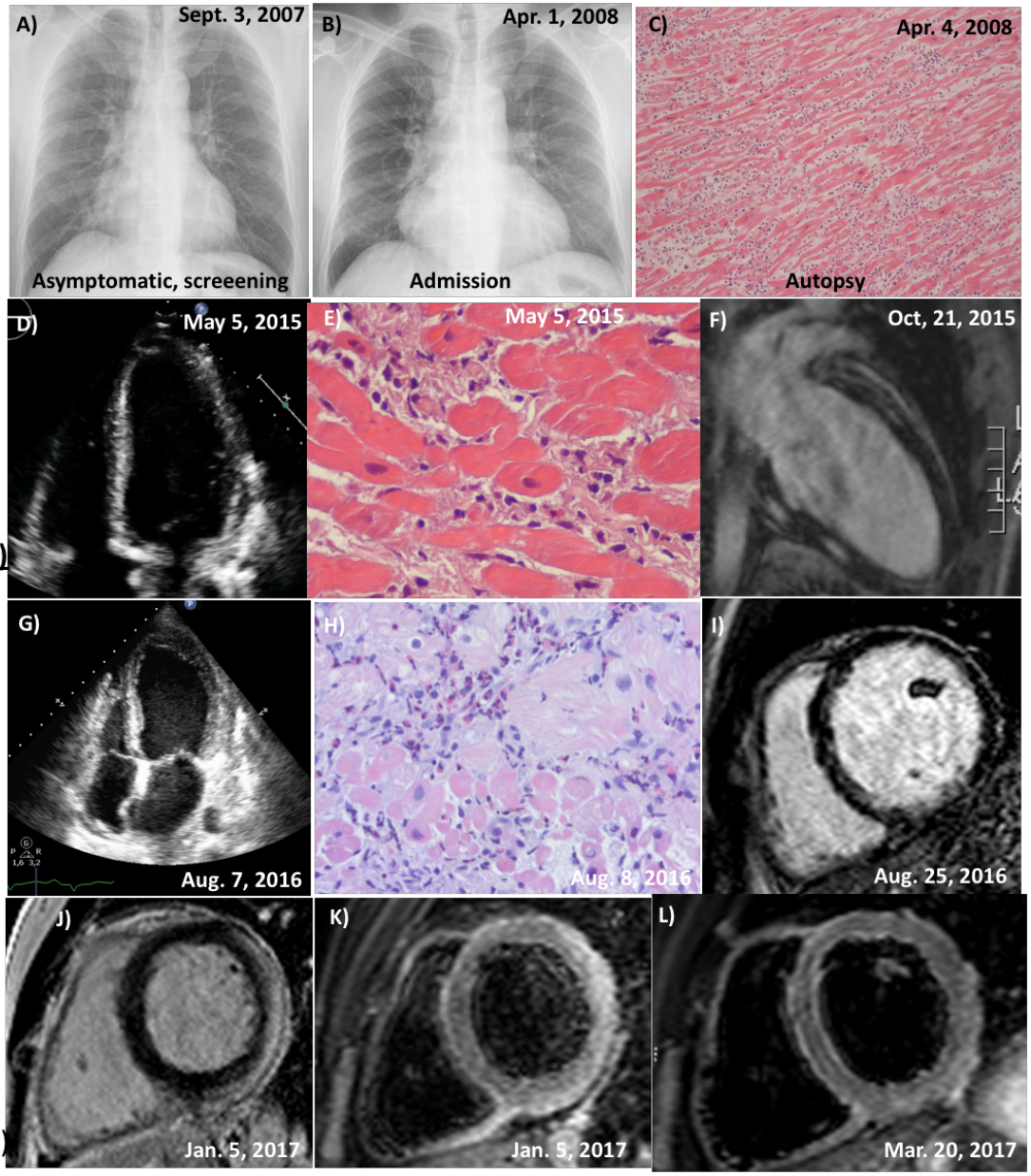
A, Male and **B,** female patients with complicated myocarditis at presentation had a similar LVEDV-I at follow up. **C,** LVEDV-I changes in male and **D,** female patients between baseline and follow-up CMR. **E,** the proportion of patients with a dilated left ventricle, considering a threshold in men of 105 mL/m^2 and in female of 95 mL/m^2 at CMR was higher among patients with complicated myocarditis. Categorical variables were compared with Fisher's exact test and relative-risk (RR) was calculated. CI indicates confidential interval.

CASE 1- COMPLICATED acute myocarditis at presentation.
INCREASED-RISK patient.
At admission: LVEF 47% at echo, rapid development ofLCOS.
D**eath due to VF**.

CASE 2- COMPLICATED acute myocarditis at presentation.
INCREASED-RISK patient.
At admission: LVEF 20% at echo,
No CMR at discharge
Follow up: asymptomatic, NO events
CMR: LVEF 68%, but **LV dilation (128 l/m^2)**

CASE 3- COMPLICATED acute myocarditis at presentation.
INCREASED-RISK patient.
At admission: LVEF 29% at echo, need for IABP. After the acute phase CMR: LVEF 41%, and the same day **cardiac arrest (VT)** successfully shocked.
.

CASE 4- UNCOMPLICATED acute myocarditis at presentation.
LOW-RISK patient.
At admission: chest pain, LVEF 60% at echo, in-hospital CMR: LVEF 62%:
At follow up: asymptomatic, no events,
CMR: LVEF: 60%, no LV dilation (68 ml/m^2)



Supplemental Figure 3. Exemplificative clinical cases of patients with acute myocarditis (AM) at increased-risk presenting with complicated AM and low-risk with uncomplicated AM.

(A-C) Case 1: (A) In 2008, a 46-year-old man from Sri Lanka, with a previous normal chest X ray performed for screening (2007) and without cardiac disorders presented at emergency department with heart failure (HF) symptoms. **(B)** Chest X ray at admission showed signs of pulmonary congestion. First echocardiogram reported left ventricular ejection fraction (LVEF) of 47%. Troponin T was 4.5 ug/L (x150-fold the upper limit [0.03 µg/L]) and CK-MB 56 µg/L. Suddenly he developed low output cardiac syndrome (LCOS) and needed for inotropes. Coronary angiogram was normal; thus, the patient was diagnosed with a clinically suspected complicated acute myocarditis. During hospitalization, he had ventricular fibrillation (VF) and died. **(C)** Autopsy revealed diffuse lymphocytic myocarditis. **(D-F) Case 2:** In 2015, a 16-year-old man was admitted due to chest pain. **(D)** First echocardiogram showed severe systolic dysfunction (LVEF of 20%, **Supplemental Video 1**) with stable hemodynamic (high sensitivity [hs] troponin T was 2293 ng/L [x164-fold the upper limit of 14 ng/L]) with CKMB of 11 µg/L. The diagnosis of complicated acute myocarditis was formulated. **(E)** Endomyocardial biopsy (EMB) showed lymphocytic myocarditis. Systolic function recovered after administration of intravenous pulsed corticosteroid therapy and at discharge he had a complete recovery at echocardiogram (LVEF 57%, **Supplemental Video 2**). No cardiac magnetic resonance (CMR) was performed at discharge. **(F)** At follow-up, the patient was asymptomatic without events for 2 years, and CMR after 5 months (2 chamber view with evidence of mid-wall late gadolinium enhancement in the anterior and inferior walls) confirmed functional recovery (LVEF 68%, **Supplemental Video 3**) but with mild dilation of the left ventricle (LV: indexed LV end-diastolic volume [LVEDV-i] of 128 mL/m^2, considering in male a cut-off for dilation beyond 105 ml/m^2) despite initiation of ramipril, bisoprolol and spironolactone during hospitalization. **(G-I) Case 3:** In 2016, a 35-year-old man was admitted with chest pain and dyspnoea. **(G)** First echocardiogram showed LVEF of 29% (**Supplemental Video 4,** echo-color-Doppler apical 4 chamber view) and hs troponin T was 3195 ng/L (x228 fold the upper limit) and CKMB 102 µg/L thus the patient was admitted with a diagnosis of clinically suspected complicated AM. The same day, due to low cardiac output syndrome, inotropes and intra-aortic balloon pump (IABP) were initiated. **(H)** EMB showed an eosinophilic myocarditis that was treated with intravenous pulsed corticosteroid therapy with significant recovery of the systolic function weaning off IABP at day 4 and inotropes at day 12. After 18 days, the day before discharge (hs troponin 119 ng/L (x8 fold the upper limit) and CKMB 1.8 µg/L (the upper limit was 5 µg/L), he experienced a cardiac arrest due VF that was successfully treated, and the **(I)** CMR performed the same day showed a LVEF of 41% (**Supplemental Video 5**). In the follow up, the patient remained asymptomatic with no further events and no arrhythmias recorded by the defibrillator that was implanted after in-hospital VF. CMR after approximately 4 months showed LVEF of 40% (**Supplemental Video 6**, 2-chamber view, artefacts are due the presence of the device) and dilated LV (LVEDV-i of 136 mL/m^2).

(J-L) Case 4: In 2017, a 19-year-old man presented with chest pain. First hs troponin T was 1688 ng/L (x121-fold the upper limit) and CKMB 11 µg/L with LVEF was above 60%. The patient was admitted with a diagnosis of uncomplicated acute myocarditis. During hospitalization, a CMR was performed with normal LV volumes (LV-EDV-i 81 ml/m^2) and systolic function (LVEF 62%, **Supplemental Video 7**) with positive LGE (**J**) and signs of oedema at T2-weighted short tau inversion recovery (STIR, **K**) involving the anterior, lateral and infero-lateral walls. **(L)** At follow up the patient was asymptomatic without events and CMR showed no more oedema and normal systolic function (LVEF 60%, **Supplemental Video 8**) and volumes LV-EDV-i 68 ml/m^2).

SUPPLEMENTAL VIDEO LEGENDS 1-8

Please refer to the Supplemental figure legend 3.

APPENDIX

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