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EDITORIAL COMMENT

# Further Refining the In-Hospital Risk Assessment of Patients Presenting With Uncomplicated Acute Myocarditis

Enrico Ammirati, MD, PhD,[a,b] Leslie T. Cooper, Jr, MD[c]

Male adolescents and young adults are generally more prone to acute myocarditis (AM), a generally transient inflammation of the myocardium mainly triggered by viral infections.[1] Approximately a quarter of patients admitted to hospital with suspected AM present with symptoms of heart failure (HF), syncope, and chest or epigastric pain associated with left ventricular systolic dysfunction, symptomatic sustained ventricular arrhythmias (VA), advanced atrioventricular block, aborted sudden cardiac arrest, or overt cardiogenic shock (ie, fulminant myocarditis).[2] The remaining three-quarters of patients, generally complaining of pericardial or anginal type chest pain, have normal or nearly normal left ventricular ejection (LVEF) on echocardiogram (LVEF >50%) without signs of acute HF or evidence of sustained VA or atrioventricular conduction abnormalities.[2] The latter group of patients with an uncomplicated clinical presentation are at low risk of major cardiac events. The Lombardy registry, a retrospective study including 325 uncomplicated patients with definite AM based on cardiac magnetic resonance (CMR) or histology, showed no cardiac deaths or need for heart transplantation (HTx) at a median follow-up of approximately 3 years.[2] Still, confirmatory data from large prospective registries are missing. Thus, collaborative efforts to collect data on patients with AM are welcomed and can enhance our prognostication and overall management.

In this issue of *JACC: Heart Failure,* Bouleti et al[3] report the results of the prospective multicenter MyocarditIRM study that assessed clinical presentation and in-hospital events in 803 adult patients with a confirmed diagnosis of AM based on CMR criteria. Patients with the initially unstable presentation, including cardiogenic shock or unstable heart rhythms directly admitted to the intensive care unit, were excluded. This is a caveat when interpreting the figures derived from this contemporary French registry, including patients between 2016 and 2019. The MyocarditIRM study was focused on clinical presentation, management, and in-hospital events. The reported in-hospital events included: 1) death; 2) LVEF ≤40% on CMR; 3) sustained ventricular or 4) supraventricular arrhythmia; 5) cardiogenic shock; 6) need for mechanical circulatory support; 7) inotropic drugs; 8) temporary cardiac pacing; 9) pacemaker, or 10) cardiac defibrillator implantation.

The proportion of patients with in-hospital events was 8% (64 of 803). Among the overall cohort, 112 (14%) patients had severity criteria (LVEF <50% on first echocardiogram [95 of 112; 84.8%], cardiogenic shock on presentation admitted in cardiac intensive care units [12 of 112; 10.7%], VA [12 of 112; 10.7%], or high degree atrioventricular block [3 of 112; 2.7%]) that were following the definition of complicated presentation, whereas the remaining 691 (86%) did not have these criteria (uncomplicated presentation). In line with the previous observation, 35% (39 of 112) of patients with severity criteria had at least an in-hospital event compared with 3.6% (25 of 691) of patients with uncomplicated presentation. The only patient who died was in the group with the

From the [a]De Gasperis Cardio Center, Transplant Center, Niguarda Hospital, Milano, Italy; [b]Department of Health Sciences, University of Milano-Bicocca, Monza, Italy; and the [c]Department of Cardiovascular Medicine, Mayo Clinic, Jacksonville, Florida, USA.

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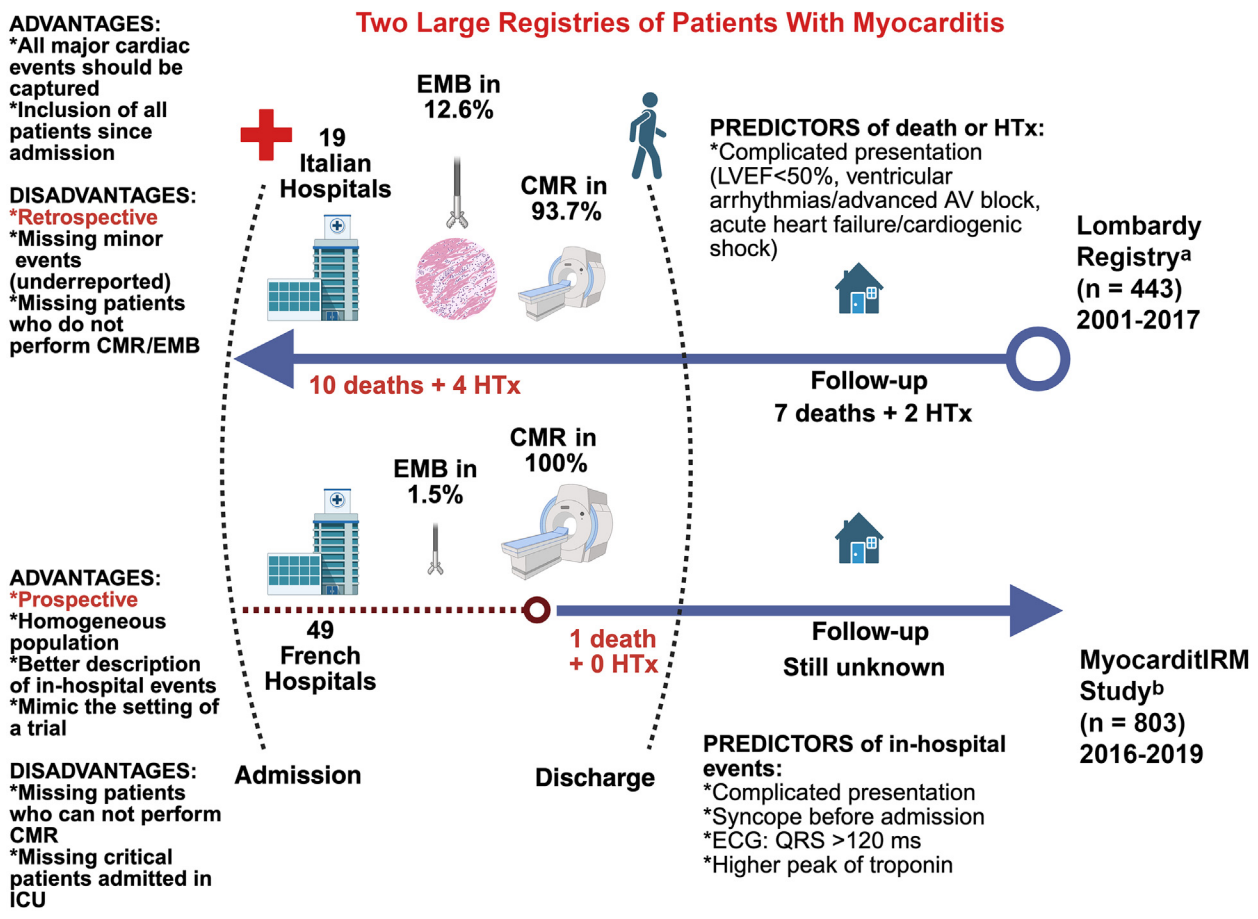
**FIGURE 1** Major Features of the Retrospective Lombardy Registry and the Prospective MyocarditIRM Study




The blue arrows in the figure represent the retrospective and prospective registry designs in the 2 studies. AV = atrioventricular; CMR = cardiac magnetic resonance; ECG = electrocardiogram; EMB = endomyocardial biopsy; HTx = heart transplantation; ICU = intensive care unit; LVEF = left ventricular ejection fraction. [a]Ammirati et al.[2] [b]Bouleti et al.[3]

complicated presentation, but overall, the risk of death in this cohort was extremely low, with a prevalence of 0.12% (1 of 803).[3]

The simple criterion of uncomplicated presentation to identify patients at very low risk of major cardiac events (cardiac death or HTx) proposed in the Lombardy registry has been prospectively validated in this contemporary cohort of definite AM based on CMR.[2] The MyocarditIRM study further refined the risk assessment of patients in this cohort, mainly composed of low-risk patients. The authors identified that beyond the complicated presentation, syncope before admission, bundle branch block (QRS interval >120 ms) on electrocardiogram at admission, and a higher peak of troponin (troponin peak/upper reference limit of the troponin) are associated with the risk of experiencing an in-hospital event as previously defined.[3] Thus, these promising additional risk features must be further externally validated, such as the recently proposed neutrophil-to-lymphocyte ratio ≥4 that has been proposed as an easy-to-use inflammatory biomarker of worse outcomes in a retrospective international registry including 1,150 patients with AM.[4] However, in the MyocarditIRM study, the authors have not yet assessed the ability of tissue features on CMR, such as the extent or pattern of delayed gadolinium enhancement, which have correlated with outcomes in other studies of AM.[5]

Another limitation of the MyocarditIRM study is that subjects who did not survive or were too unstable for CMR would have been excluded from the analysis. Therefore, what appears prospective is more a retrospective design due to the limiting factor of the CMR confirmation to enter the registry (Figure 1). The

absence of information related to patients who rapidly evolved to cardiogenic shock after admission, who could have died or undergone HTx, or any other device implantation (left ventricular assist device or pacemaker) may underestimate the risk of cardiovascular events in all initially nonfulminant patients. Clinical research on patients with AM generally follows the mirage of definite diagnosis, with the risk of losing practical issues that could have a larger impact on the risk stratification and management of patients with AM on admission. Both endomyocardial biopsy and CMR are infrequently seen as emergent/urgent diagnostic tests like coronary angiography is for patients with acute coronary syndromes. Thus, we should focus our attention on the overall population of clinically suspected AM, restricting the population of interest based on rapidly available biomarkers such as high-sensitivity troponin, electrocardiogram, echocardiogram, and the low likelihood of coronary artery disease or ruling out coronary artery disease.

The short duration of this study, an average of 4 days to hospital discharge,[3] would also miss the risk of recurrent myopericarditis, which ranges from 10% to 33% over 2 years.[6] Future prospective registries should start from admission, providing data on: 1) those who die without histologic confirmation or having performed CMR; 2) providing the proportion of patients with clinically suspected AM who reach the definite criteria of AM based on histology or CMR; and 3) reporting the percentage of patients misclassified as AM and what were the alternative diagnoses that were reached. This will impact ongoing and future randomized clinical trials to improve the outcomes of patients admitted with AM.

This registry provides us with a clear message: interventions to reduce mortality in uncomplicated patients with AM are unlikely to be studied in randomized trials because the risk of death or HTx is very low. Specifically, in this prospective series, there was zero death, only 1 patient required a venoarterial extracorporeal membrane oxygenator, and 2 patients needed inotropes before hospital discharge. In an extension of the Lombardy region study, among those without complicated presentation, only 1 of 183 (0.5%) discharged patients who underwent a CMR scan had a major cardiac event (hemodynamically tolerated VA) after a median follow-up of 4.7 years after discharge.[5] Among patients with an initially complicated clinical presentation, 12 of 65 (18.5%) patients had at least 1 event, including cardiac death, HTx, aborted sudden cardiac death, sustained VA, or HF hospitalization. In addition, the optimal duration of abstinence from competitive sports in low-risk individuals remains uncertain.[1] For endpoints such as myocarditis recurrence, studies focusing only on uncomplicated patients will require large cohorts or years of follow-up to demonstrate the efficacy of any intervention. The focus of interventional trials should aim toward complicated cases and specifically with acute HF or VA to improve outcomes by looking for effective treatments.

Finally, among the in-hospital events, VA occurred in 12 (1.7%) patients among those without severity criteria and was the most common in-hospital event. Likely, in the extension of the Lombardy registry, the only patient who had experienced an event in the uncomplicated group had a VA. General cardiologists who can discharge patients with uneventful myocarditis should be aware that a relatively small group of patients with uncomplicated AM can harbor a genetic background for an arrhythmogenic cardiomyopathy that could explain the excess in VA in these low-risk groups of patients.[7] The coexistence of a large extent of fibrosis on CMR, especially if involving the ventricular septum, and a high burden of premature ventricular complexes or nonsustained ventricular tachycardia or a family history of myocarditis beyond myocarditis recurrence can increase the likelihood of positive genetic testing among patients with AM.[7] These characteristics could help to pick the high-risk patient out of the large group of uncomplicated myocarditis.

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**ADDRESS FOR CORRESPONDENCE:** Dr Leslie T. Cooper, Jr, Mayo Clinic, 4500 San Pablo, Jacksonville, Florida 32224, USA. E-mail: cooper.leslie@mayo.edu. OR Dr Enrico Ammirati, De Gasperis Cardio Center, Niguarda Hospital, Piazza Ospedale Maggiore 3, 20162 Milano, Italy. E-mail: enrico.ammirati@ospedaleniguarda.it.

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