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Clinical Research

Rationale and design of the French cohort of acute myocarditis diagnosed by cardiac magnetic resonance imaging (MyocarditIRM)☆

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ABSTRACT

Background: Acute myocarditis usually presents as chest pain with rising troponin and normal coronary arteries. Despite frequent favourable evolution at the acute phase, it is associated with heart failure and ventricular rhythm disorders, and is considered the leading cause of sudden cardiac death in young, apparently healthy, adults. There are no specific recommendations for acute myocarditis diagnosis and management, only expert consensus, given the lack of large databases.
Aim: The main objective is to describe the contemporary presentation of acute myocarditis, its management and in-hospital outcomes. Secondary objectives are to investigate survival and event-free survival for up to 10 years of follow-up, the determinants of prognosis, the modalities of treatment and follow-up and the gaps between expert consensus and real-life management.
Methods: MyocarditIRM is a prospective multicentre cohort that enrolled 803 consecutive patients with acute myocarditis in 49 participating centres in France between 01 May 2016 and 28 February 2019. The diagnosis of acute myocarditis was acknowledged by cardiac magnetic resonance, using the Lake Louise Criteria. Exclusion criteria were age < 18 years, lack of health coverage, contraindication to cardiac magnetic resonance and refusal to participate. Detailed information was collected prospectively, starting at admission. Cardiac magnetic resonance imaging (diagnosis and follow-up) is analysed centrally by the certified core laboratory IHU ICAN. Ten years of follow-up for each patient is ensured by linking with the French National Health Database, and includes information on death, hospital admissions, major clinical events and drug consumption.

☆ Tweet: MyocarditIRM: the largest prospective cohort on acute myocarditis, with 803 patients recruited on 49 centres over 3 years. Proven myocarditis by CMR imaging, with a centralized reading by a certified core laboratory. Long-term follow-up through administrative databases.

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Conclusion: This prospective cohort with long-term follow-up represents the largest database on acute myocarditis worldwide, and will improve knowledge about its presentation, management and outcomes.

1. Abbreviations

AM	acute myocarditis
CMR	cardiac magnetic resonance
CNIL	Commission nationale de l'informatique et des libertés
CoreLab	core laboratory
CCTA	coronary computed tomography angiography
EMB	endomyocardial biopsy
LGE	late gadolinium enhancement
LVEF	left ventricular ejection fraction
SNDS	Système national des données de santé

2. Background

Acute myocarditis (AM) is an inflammatory disease of the myocardium, typically suspected in case of chest pain with increased troponin and normal coronary artery, in young adults (mean age < 40 years) [1,2]. However, there is no specific clinical or biological sign for AM, and patients can present with few or no symptoms or, in contrast, be admitted for cardiogenic shock or arrhythmic storm [3]. A definite diagnosis may be obtained through endomyocardial biopsy (EMB) [4] or by cardiac magnetic resonance (CMR) according to the Lake Louise Criteria [5,6]. Although presented as the cornerstone diagnostic test in the European expert consensus statement, EMB is not performed in current clinical practice in France or most other countries, except in case of fulminant myocarditis [4,7]. In practice, the diagnosis relies mainly on CMR imaging, and additional EMB may be performed in certain cases.

Another issue regarding the diagnosis of AM is the evaluation of coronary arteries to rule out an acute coronary syndrome. The European expert consensus statement recommends that all patients with suspected AM should be considered for selective coronary angiography [4]. Given the profile of young adults with few or no cardiovascular risk factors, invasive examination may seem less indicated than coronary computed tomography angiography (CCTA), when available.

There are still many questions regarding the pathogenesis of AM, its natural evolution, the treatments to offer, their duration and the timing and duration of follow-up. Indeed, given the lack of large databases, there are no guidelines for the management of AM, and our knowledge relies mainly on two expert consensus statements: one European, dating from 2013; and the other international, published in 2020 [4,8].

AM evolution is described in the European Society of Cardiology expert consensus statement as a full recovery in about half of the cases, acute aggravation leading to severe heart failure, heart transplant or death in 12–25% of cases and evolution to chronic inflammatory myocarditis, typically leading to dilated cardiomyopathy, in 20% of cases [4]. However, these data rely on a limited number of old series, and more recent cohorts are not in line with these numbers [9,10]. AM was recently reported as the leading cause of sudden cardiac death in young people serving in the military [11], and its severity should not be underestimated.

Few clinical trials have been conducted in AM [12], and there is currently no specific treatment for it – only optimal care for arrhythmia and heart failure in case of complications. In addition, clinical follow-up and associated investigations are not clearly defined. CMR is suggested at 3–6 months' follow-up to demonstrate resolution of oedema and define the final late gadolinium enhancement (LGE) extent [8], but in the absence of strong consensus, not all centres use CMR for follow-up. Asymptomatic athletes with LGE should remain under annual follow-up [4], but no such recommendation exists for non-athletes.

Based on this lack of data, we initiated the national MyocarditIRM cohort in 2016. The main objective was to provide contemporary and comprehensive data on the epidemiology, clinical presentation and current management of patients with AM in France, as well as their in-hospital and long-term clinical outcomes.

3. Methods

3.1. Study design

MyocarditIRM is a prospective multicentre observational cohort that included consecutive patients with AM diagnosed by CMR. Detailed information was collected prospectively, starting at admission for AM, including demographic data, clinical and paraclinical examination, medical history and treatments, in-hospital management (in particular, CMR and echocardiography), outcomes until hospital discharge, drug prescription at discharge (with dose regimen) and results of imaging examination performed during follow-up. Long-term follow-up is ensured by access to the French national health database Système national des données de santé (SNDS), with a planned observation period of up to 10 years for each patient. The SNDS allows the comprehensive collection of all-cause and cause-specific mortality, all procedures (inpatient or outpatient), hospital admissions, healthcare consumption (including drug reimbursement) and imaging examination performance, as described previously [13,14]. Linkage to the SNDS will also provide valuable information regarding healthcare consumption in the 2 years before the index hospitalization for AM.

MyocarditIRM was conducted in accordance with the principles of the Declaration of Helsinki. All included patients gave their written informed consent, and retain a right to access and rectification of their individual data. The study obtained approval from the Commission Nationale de l'Informatique et des Libertés (CNIL ; n° 915574) and the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (CCTIRS ; n° 15677), as well as specific CNIL authorization for linkage to the SNDS (DR-2020-297). The study is registered on ClinicalTrials.gov (identifier: NCT02717143). The study is observational, and participation was not intended to modify management; sites were instructed to treat patients according to their usual care practices. A list of MyocarditIRM participating centres and investigators is provided in Appendix A.

3.2. Study population

In MyocarditIRM, 803 consecutive patients with AM diagnosed by CMR imaging at 49 French centres were included between 01 May 2016 and 28 February 2019. A total of 821 patients were

included initially, but after careful review of duplicate files and differential diagnosis, the final population comprised 803 patients.

All patients hospitalized for AM were eligible if they met the following inclusion criteria: age > 18 years; affiliated to the French health insurance system (Sécurité Sociale); hospitalized for suspicion of AM based on elevated troponin and at least one of the following: (1) prolonged chest pain > 10 minutes, (2) recent infection (< 7 days) and (3) young patient and/or no cardiovascular risk factor and/or no significant stenosis on coronary angiogram (invasive or CCTA); CMR confirmation of the diagnosis of AM according to the Lake Louise Criteria [5]; and provided written consent. Any symptom compatible with infection and associated with fever in the past 7 days was considered as recent infection. The diagnosis could be made by EMB, but a CMR confirming the AM diagnosis was mandatory for inclusion in the study (Fig. 1). A contraindication to CMR was thus the only non-inclusion criterion other than refusal to participate.

The first patient was enrolled on 01 May 2016 and the last patient on 28 February 2019. During this time period, all patients with AM admitted to the participating institutions and meeting the inclusion criteria were included. No targeted number of inclusions was predetermined.

3.3. Objectives

The first objective of MyocarditIRM is to describe the contemporary presentation of AM, the clinical, biological (including genetic results) and imaging profile of patients, their management, in particular the complementary investigations used during the hospitalization (coronary angiography or CCTA, performance of EMB, prescription of viral serology), their length of stay and their outcomes during the index hospitalization, with the relationship between their baseline characteristics and their outcomes. The outcomes of interest are in-hospital all-cause mortality or cardiovascular complications, defined as the composite of ventricular arrhythmia, supraventricular arrhythmia, need for defibrillator implantation, high-degree conduction disorders, need for a pacemaker or temporary pacing lead implantation, need for dialysis, cardiogenic shock, need for ventricular assistance device, need for inotropic drugs and heart transplantation.

Secondary objectives include: (1) overall survival; (2) event-free survival, defined as survival without major cardiovascular events (namely, rehospitalization for heart failure, heart transplantation, implantation of a ventricular assistance device, recurrence of AM, rehospitalization for ventricular or supraventricular arrhythmia, implantation of a cardiac defibrillator, rehospitalization for severe conduction disorder or implantation of a pacemaker) for up to 10 years of follow-up; (3) the relationship between patient characteristics and management patterns (medications prescribed at discharge with the dose regimen, their changes during follow-up, the complementary tests performed during follow-up) and overall survival and event-free survival, to characterize the determinants of long-term (up to 10 years) prognosis in this population; (4) the identification of gaps between expert consensus statements and management in real-life practice; (5) description of the healthcare pathway and consumption in the 2 years preceding the index hospitalization for AM, in order to identify factors associated with AM before its occurrence; and (6) the identification of patients who had CMR during their follow-up and the CMR prognostic factors associated with long-term outcomes (for up to 10 years for each patient).

3.4. Data collection and evaluation

Data were collected anonymously using a standardized electronic case report form via a dedicated online platform (Clinityx).

Table 1
Baseline demographics.

Age (years)
Male sex
Cardiovascular risk factors
Hypertension
Diabetes
Hypercholesterolaemia
Smoking status
Current
Former
Never
Medical history
Previous acute myocarditis
Previous familial acute myocarditis
Repeated viral infections > 5/year
Previous inflammatory or autoimmune disease
Coronary artery disease
Previous AMI
Previous PCI
Previous CABG
Non-ischaemic cardiomyopathy
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy
Other
Valvular heart disease
Aortic stenosis
Aortic regurgitation
Mitral stenosis
Mitral regurgitation
Tricuspid regurgitation
Atrial arrhythmia
Atrial fibrillation
Flutter
Paroxysmal
Permanent
Ventricular arrhythmia
Ventricular tachycardia
Ventricular fibrillation

AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention.

Data collection quality was optimized by including automated consistency checks of the data when the case report forms were filled in and by centralized data monitoring by the research coordinators of the French Society of Cardiology.

The baseline demographic characteristics collected are detailed in Table 1; they include extensive medical history and cardiovascular risk factors.

Laboratory results were collected at admission and at discharge, and include inflammation profile (C-reactive protein, fibrinogen, white blood cell count and neutrophil blood count) and haemoglobin, platelets, serum creatinine, brain natriuretic peptide, N-terminal prohormone of brain natriuretic peptide, troponin and creatine phosphokinase concentrations. Data collected at hospital admission are detailed in Table 2, including the type of symptoms, a detailed physical examination and a description of the 12-lead electrocardiogram.

Data on hospital management are detailed in Table 3. We specifically detailed the different investigations that could have been used to set the AM diagnosis, namely echocardiography, coronary angiography, CCTA, viral serology testing, EMB and CMR. These investigations are described, with their date of performance, to better assess the management of AM regarding diagnosis. Regarding CMR, image analysis and measurements will be performed by the certified core laboratory (CoreLab; IHU ICAN), and the list of variables analysed by the CoreLab is provided in Table 4.

In-hospital outcomes are investigator reported and not adjudicated; they are detailed in Table 5, and include mortality, left ventricular ejection fraction (LVEF) $\leq$ 40%, ventricular arrhythmia (ventricular tachycardia or fibrillation, non-sustained ventricu-

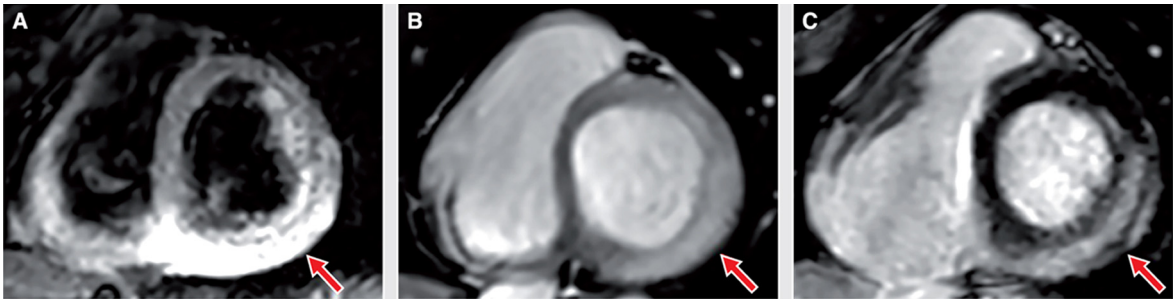


Fig. 1. A–C. Cardiac magnetic resonance images of acute myocarditis with all three positive 2009 Lake Louise Criteria: regional high T2 signal (panel A), early gadolinium enhancement (panel B) and late gadolinium enhancement (panel C) in the inferolateral wall (red arrows).

Table 2
Baseline clinical and biological presentation.

Physical examination
Weight (kg)
Height (cm)
BMI (kg/m^2)
Systolic blood pressure (mmHg)
Diastolic blood pressure (mmHg)
Heart rate (beats/min)
Temperature (°C)
NYHA class
Clinical presentation
Chest pain
Shortness of breath
Palpitations
Syncope
Heart failure
Cardiogenic shock
Ventricular arrhythmia
Conduction disorder
Clinical infectious syndrome
Other
Electrocardiogram
Sinus rhythm
Atrial fibrillation or flutter
Ventricular pacing
ST-segment elevation
ST-segment depression
Negative T wave
Necrosis Q wave
PQ depression
Atrioventricular block
Laboratory results
Troponin (ng/mL)
Creatine phosphokinase (μg/L)
Haemoglobin (g/dL)
Platelets (G/L)
White blood cells (G/L)
Neutrophil leukocytes (G/L)
C-reactive protein (mg/L)
Creatinine (μmol/L)
BNP (ng/L)
NT-proBNP (ng/L)

BMI: body mass index; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; NYHA: New York Heart Association.

Table 3
Data on the initial aetiological work-up.

TTE
Date
LV end-diastolic diameter (mm)
LV end-systolic diameter (mm)
Interventricular septum (mm)
Posterior wall (mm)
LVEF (%)
Subaortic VTI (cm)
Abnormal wall motion
Diastolic dysfunction
Peak mitral E-wave velocity (cm/s)
Peak mitral A-wave velocity (cm/s)
Tissue Doppler imaging peak e′ velocity (cm/s)
RV dysfunction
Systolic pulmonary artery pressure (mmHg)
Pericardial effusion
Coronary angiogram
Date
Degree of maximal coronary lesion
Localization of > 50% stenosis
Coronary CT
Date
Degree of maximal stenosis
Localization of > 50% stenosis
Endomyocardial biopsy
Date
Viral identification
Confirmation of acute myocarditis
Complication of EMB
Viral serologies
Enterovirus
HHV6
EBV
Other
CMR imaging
LVEF (%)
Wall motion abnormalities
Pericardial effusion

CMR: cardiac magnetic resonance; CT: computed tomography, EBV: Ebstein-Barr virus; EMB: endomyocardial biopsy; HHV6: human herpes virus 6; LV: left ventricular; LVEF: left ventricular ejection fraction; RV: right ventricular; TTE: transthoracic echocardiography; VTI: velocity time integral.

lar tachycardia), supraventricular arrhythmia (atrial fibrillation, flutter), implantation of a cardioverter defibrillator, high-grade conduction disorders (second- or third-degree atrioventricular blocks, complete sinoatrial block), need for a pacemaker or temporary cardiac electrical pacing, need for dialysis, cardiogenic shock, need for ventricular assistance device, need for inotropic drugs and heart transplantation.

At discharge, the total length of stay in the intensive cardiac care unit and other sections of the hospital are captured, as are the patient's destination and treatments.

3.5. Long-term follow-up

Detailed postdischarge echocardiography results are completed by the local investigators in each centre, as presented in Table 6. Postdischarge CMR images are analysed by the CoreLab according to the same protocol described previously for the first CMR. We also collect the results of genetic analysis regarding AM (mutation or pathogenic variants).

Postdischarge outcomes are collected using the SNDS linkage; they include vital status, date of death and cause of death, as well as major cardiovascular events (rehospitalization for heart failure, heart transplantation, implantation of a ventricular assistance device, recurrence of AM, rehospitalization for ven-

Table 4
Variables read centrally by the core laboratory for cardiac imaging.

LVEF (%)
LV mass (g)
LV end-diastolic volume (mL)
LV end-systolic volume (mL)
Maximal wall thickness (mm)
RVEF (%)
RV volumes (mL)
Wall motion abnormality
High T2/STIR signal
High signal on first-pass perfusion
Perfusion defect on first-pass perfusion
Early myocardial enhancement on cine-SSFP images
LGE
Volume of LGE (Fuzzy-K-means method) (mL)
Extension of LGE (%)
Topography of LGE
T1 mapping
T2 mapping
Extracellular volume (%)
Pericardial effusion
Pericardial LGE
LV longitudinal strain (%)
LV basal strain (%)
LV radial strain (%)
ARVD criteria
Biplane method LA volume (mL)
LAEF (%)
Presence of LV thrombus
Edge detection

ARVD: arrhythmogenic right ventricular dysplasia; LA: left atrial; LAEF: left atrial ejection fraction; LGE: late gadolinium enhancement; LV: left ventricular; LVEF: left ventricular ejection fraction; RV: right ventricular; RV: right ventricular ejection fraction; SSFP: steady-state free precession; STIR: short-TI inversion recovery.

Table 5
In-hospital management of acute myocarditis.

Complications
Death
Ventricular arrhythmia
Atrial arrhythmia
High-grade conduction disorder
LVEF ≤ 40% (CMR imaging)
Dialysis
Cardiogenic shock
IV inotropic drugs
ECMO or other assistance ventricular device
Transplant list
Implantation of a cardioverter defibrillator
Implantation of a pacemaker
Need for temporary cardiac electrical pacing
Laboratory results
Troponin peak (ng/L)
Creatine phosphokinase peak (μg/L)
C-reactive protein peak (mg/L)
White blood cell peak (G/L)
Discharge
Date
Length of stay in ICCU/ICU
Total length of hospitalization
Mode of discharge
Medications at discharge
Beta-blockers
ACE inhibitors/ARBs
Loop diuretic
Aldosterone receptor antagonist
Aspirin/NSAID
Corticoids
Immunosuppressive medication

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CMR: cardiac magnetic resonance; ECMO: extracorporeal membrane oxygenation; ICCU: intensive cardiac care unit; ICU: intensive care unit; IV: intravenous; LVEF: left ventricular ejection fraction; NSAID: non-steroidal anti-inflammatory drug.

Table 6
Follow-up imaging data.

TTE
Date
LV end-diastolic diameter (mm)
LV end-systolic diameter (mm)
Interventricular septum (mm)
Posterior wall (mm)
LVEF (%)
Subaortic VTI (cm)
Abnormal wall motion
Diastolic dysfunction
Peak mitral E-wave velocity (cm/s)
Peak mitral A-wave velocity (cm/s)
Tissue Doppler imaging peak e′ velocity (cm/s)
RV dysfunction
Systolic pulmonary artery pressure (mmHg)
Pericardial effusion
Follow-up CMR
Date
Abnormal wall motion
LVEF (%)
LV end-systolic volume (mL)
RVEF (%)
High T2/STIR signal
High signal on diffusion sequence
High signal on first-pass perfusion
Perfusion defect on first-pass perfusion
Early myocardial enhancement on cine-SSFP images
Early gadolinium enhancement
LGE
Number of segments
Extension of LGE (%)
Topography of LGE
T1 mapping
T2 mapping
Pericardial effusion

CMR: cardiac magnetic resonance; LGE: late gadolinium enhancement; LV: left ventricular; LVEF: left ventricular ejection fraction; RV: right ventricular; RV: right ventricular ejection fraction; SSFP: steady-state free precession; STIR: short-TI inversion recovery; TTE: transthoracic echocardiography; VTI: velocity time integral.

tricular or supraventricular arrhythmia, implantation of a cardiac defibrillator, rehospitalization for severe conduction disorder and implantation of a pacemaker).

We also collect the use of cardiovascular drugs, with dose regimen, and all additional investigations related to cardiac assessment (radiology examination, CMR, echocardiography, coronary angiography, CCTA, stress test, Holter monitoring, etc.). The data that will be extracted from the SNDS are detailed in Table A.1.

The linkage to SNDS will be performed every year during a 10-year follow-up for each patient.

3.6. Data management

Data are analysed centrally by a senior statistician who is independent from the study (Professor Theodora Bejan Angoulvant, Pharmacology Department, Tours University Hospital).

CMR are analysed centrally by the certified CoreLab (IHU ICAN, La Pitié-Salpêtrière University Hospital, under the supervision of Professor Alban Redheuil), blinded to the clinical results, to ensure high quality data.

Pooled analysis of individual data will be possible for research purposes only.

The cohort is linked to the national hospitalization database, the national death registry and the national insurance database to collect comprehensive clinical outcomes and detailed inpatient and outpatient healthcare consumption information during follow-up and also during the 2 years preceding the index hospitalization.

The 2 years preceding the index AM will allow a complete assessment of care consumption before the index hospitalization for AM.

In accordance with French regulations and the European General Data Protection Regulation (GDPR), the linkage process will employ a probabilistic approach based on matching SNDS data as closely as possible to the profiles in the MyocarditIRM database. The algorithm is developed and executed by the Caisse nationale d'Assurance maladie (CNAM) team to link and match records in the SNDS with patients' data from the electronic case report forms from MyocarditIRM. The algorithm is based on main hospitalization diagnosis (AM) in the SNDS, month and year of birth, sex and hospitalization location. The objective is to achieve 90% linkage, and uses SNDS for follow-up of the MyocarditIRM population.

Data from the SNDS are provided in 1-year batches, and require a substantial curation effort before analysis can be started. Therefore, there is approximately a 2-year lag between the index AM event leading to enrolment in the cohort and access to SNDS data providing information on follow-up after discharge for the same year (Year N). Data available at year X will contain information until year X–2.

Three extractions from the SNDS will be performed: the first in 2025 (analysis for years 2014–2017 for the 2 years preceding the index hospitalization for AM, and analysis for years 2017–2022 for follow-up data), then in 2028 (analysis for years 2023–2025) and the last extraction in 2031 (analysis for years 2026–2029), thus allowing a follow-up of 10 years for each patient.

4. Discussion

Given the lack of large prospective studies on AM, there are currently no strong recommendations regarding its management, treatment or follow-up.

4.1. AM diagnosis

The two expert consensus papers propose very different management strategies for AM, including the diagnosis work-up. For instance, the European expert consensus statement highlights the need for systematic EMB, whereas the more recent international consensus statement proposes CMR imaging as the first-line diagnosis examination in case of non-complicated AM. This latter proposal is more in line with current clinical practice in France and most other countries. As an illustration, < 4% of all cases of myocarditis had an EMB in the USA between 1998 and 2013 [15]. The main reasons advocated for not performing EMB are the inherent risk of complications, the need for expertise of anatomopathologists and the lack of sensitivity as a result of focal lesions [16]. Except in Germany and Italy, where EMBs are common practice, the other European countries rely mostly on CMR for diagnosis, except in case of complicated presentation (in particular, fulminant AM). The MyocarditIRM cohort was designed to reflect the usual clinical practice in France, and EMB was therefore not mandatory for AM diagnosis. It could, however, be performed according to the centre's habits, and the study will thus provide a realistic overview of practices in France.

Another discordant point between the two expert consensus papers is the practice of coronary angiography to rule out acute coronary syndrome [4,8]. The European expert consensus statement suggests a systematic coronary angiography, whereas the more recent international consensus statement suggests that both coronary angiography or CCTA can be performed to rule out an acute coronary syndrome. Once again, this latter approach seems more adequate, given the low-risk profile of patients presenting with suspected AM and the high negative predictive value of CCTA in these patients. The MyocarditIRM cohort will evaluate the proportion of patients undergoing invasive or non-invasive management.

4.2. Outcomes in AM

This is probably the most important goal of the present study: to provide robust and contemporary data regarding in-hospital and long-term outcomes of AM, which are currently limited and mostly conflicting.

AM evolution is generally described as a full recovery in about half of the cases, acute severe heart failure, heart transplant or death in 12–25% of cases, and evolution to chronic inflammatory myocarditis in 20% of cases [4]. However, more recent series have reported conflicting results regarding AM outcomes. A prospective German cohort of 203 patients included between 2002 and 2008 reported a cardiac death rate of 15% at a median of 4.7 years' follow-up [9]. A retrospective Italian cohort of 443 patients included between 2001 and 2017 reported a 27% rate of complicated myocarditis at presentation (LVEF < 50%, sustained ventricular arrhythmias or low cardiac output) and a 14.7% rate of cardiac death or heart transplantation at 5-year follow-up only in these patients, whereas no event occurred in patients with an uncomplicated presentation [10]. The German series included selected patients (203 patients over a 6-year time period, given the single-centre nature of the study), with a median age of 52 years (interquartile range 40–54 years), which is very different from the usual AM population. The Italian series also captured selected patients (443 patients over a 16-year time period), but was more representative of contemporary AM, with a median age of 34 years. However, this latter study was retrospective, with the inherent limitations regarding missing data.

The MyocarditIRM cohort is a large multicentre prospective study of consecutive patients admitted to cardiology wards for AM. We have included 803 patients in less than 3 years, providing good representativeness of the population. The quality of evaluation of long-term outcomes will be ensured by the SNDS linkage, which has never been performed in AM. This study will thus provide robust contemporary data regarding both in-hospital and long-term follow-up.

4.3. Treatments for AM

There are very few data regarding the treatment of patients with AM, and no strong recommendations regarding either the drugs to prescribe or the duration of prescription. Empirically, patients are often prescribed beta-blockers and angiotensin-converting enzyme inhibitors, even in the absence of left ventricular dysfunction. In patients with reduced LVEF, the procedure for weaning of these treatments following recovery of ventricular function is not defined [4]. Drugs, dose regimen and duration of medication are left to each cardiologist's judgment, according to local protocols (if any). Practice is therefore highly heterogenous, and no large series has assessed the impact of beta-blocker or angiotensin-converting enzyme inhibitor prescription on outcomes. On top of the detailed prescription at discharge, the MyocarditIRM cohort will benefit from the linkage to SNDS to assess drug prescription, duration and dose regimen. The MyocarditIRM cohort should help to fill these knowledge gaps.

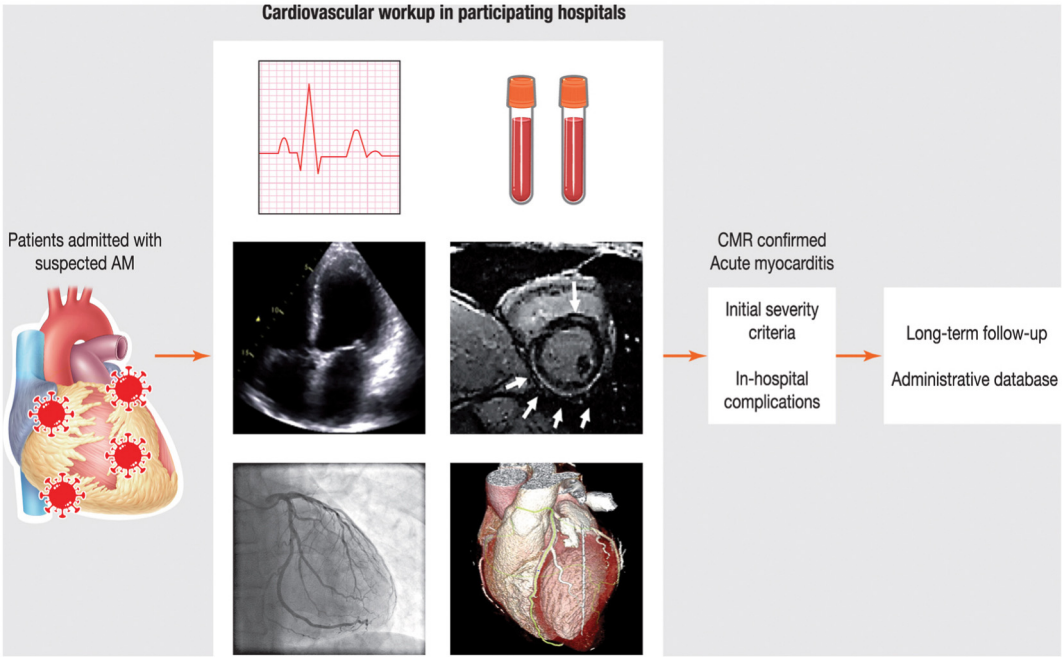
4.4. Limitations

First, this study only involved 49 voluntary institutions, which may represent a skewed sample of French hospitals; this is because of the limited funding associated with such registries. However, general and university hospitals were involved, as well as public

and private institutions, ensuring a wide representativeness of participating centres. Second, patients without health insurance were excluded from this study, but this should not bias the results, as they account for < 0.1% of the French population. Third, outcomes are reported by investigators, and are not adjudicated. However, local investigators were advised to report conscientiously all outcomes of interest and, in case of any doubt, the research coordinators from the French Society of Cardiology did double-check the outcomes.

5. Conclusions

The MyocarditIRM cohort is the largest prospective database on AM, aimed at improving knowledge of the epidemiology and prognostic determinants of AM in contemporary practice. Thanks to its original design, combining comprehensive data collection from the index hospitalization with centralized analysis of CMR by a certified CoreLab and long-term follow-up via a link with the French National Health Database, MyocarditIRM will provide unique data on AM (Central Illustration).



Central Illustration. Design of the MyocarditIRM prospective cohort. AM: acute myocarditis; CMR: cardiac magnetic resonance.

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Disclosure of interest

C. B. reports receiving consulting and lecture fees from AstraZeneca, Novartis, Boehringer-Ingelheim, Sanofi and Janssen, and grants from Pfizer.

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N. G. is the Chief Executive Officer of Clinityx.

J. T. is a consultant for Philips Healthcare and General Electric.

The other authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2024.04.002.

References

[1] Lampejo T, Durkin SM, Bhatt N, Guttmann O. Acute myocarditis: aetiology, diagnosis and management. Clin Med (Lond) 2021;21:e505–10.
[2] Kociol RD, Cooper LT, Fang JC, Moslehi JJ, Pang PS, Sabe MA, et al. Recognition and initial management of fulminant myocarditis: a scientific statement From the American Heart Association. Circulation 2020;141:e69–92.
[3] Ammirati E, Veronese G, Brambatti M, Merlo M, Cipriani M, Potena L, et al. Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2019;74:299–311.
[4] Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636–48 [48a–48d].
[5] Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. J Am Coll Cardiol 2009;53:1475–87.

[6] Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol 2018;72:3158–76.
[7] Heymans S, Eriksson U, Lehtonen J, Cooper Jr LT. The quest for new approaches in myocarditis and inflammatory cardiomyopathy. J Am Coll Cardiol 2016;68:2348–64.
[8] Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. Circ Heart Fail 2020;13:e007405.
[9] Grun S, Schumm J, Greulich S, Wagner A, Schneider S, Bruder O, et al. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. J Am Coll Cardiol 2012;59:1604–15.
[10] Ammirati E, Cipriani M, Moro C, Raineri C, Pini D, Sormani P, et al. Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: Multicenter Lombardy Registry. Circulation 2018;138:1088–99.
[11] Quinn R, Moulson N, Wang J, Isserow S, McKinney J. Sports-related sudden cardiac death attributable to myocarditis: a systematic review and meta-analysis. Can J Cardiol 2022;38:1684–92.
[12] Kerneis M, Cohen F, Combes A, Amoura Z, Pare C, Brugier D, et al. Rationale and design of the ARAMIS trial: Anakinra versus placebo, a double blind randomized controlled trial for the treatment of acute myocarditis. Arch Cardiovasc Dis 2023;116:460–6.
[13] Didier R, Gouysse M, Eltchaninoff H, Le Breton H, Commeau P, Cayla G, et al. Successful linkage of French large-scale national registry populations to national reimbursement data: improved data completeness and minimized loss to follow-up. Arch Cardiovasc Dis 2020;113:534–41.
[14] Logeart D, Damy T, Doublet M, Salvat M, Tribouilloy C, Bauer F, et al. Feasibility and accuracy of linking a heart failure registry to the national claims database using indirect identifiers. Arch Cardiovasc Dis 2023;116:18–24.
[15] Elbadawi A, Elgendy IY, Ha LD, Mentias A, Ogunbayo GO, Tahir MW, et al. National trends and outcomes of endomyocardial biopsy for patients with myocarditis: from the National Inpatient Sample Database. J Card Fail 2018;24:337–41.
[16] Bowles NE, Ni J, Kearney DL, Pauschinger M, Schultheiss HP, McCarthy R, et al. Detection of viruses in myocardial tissues by polymerase chain reaction. Evidence of adenovirus as a common cause of myocarditis in children and adults. J Am Coll Cardiol 2003;42:466–72.