European Heart Journal (2024) **00**, 1–3
https://doi.org/10.1093/eurheartj/ehae220

EDITORIAL
Heart failure and cardiomyopathies

Myocarditis diagnosis: harnessing order amongst heterogeneity through collaboration

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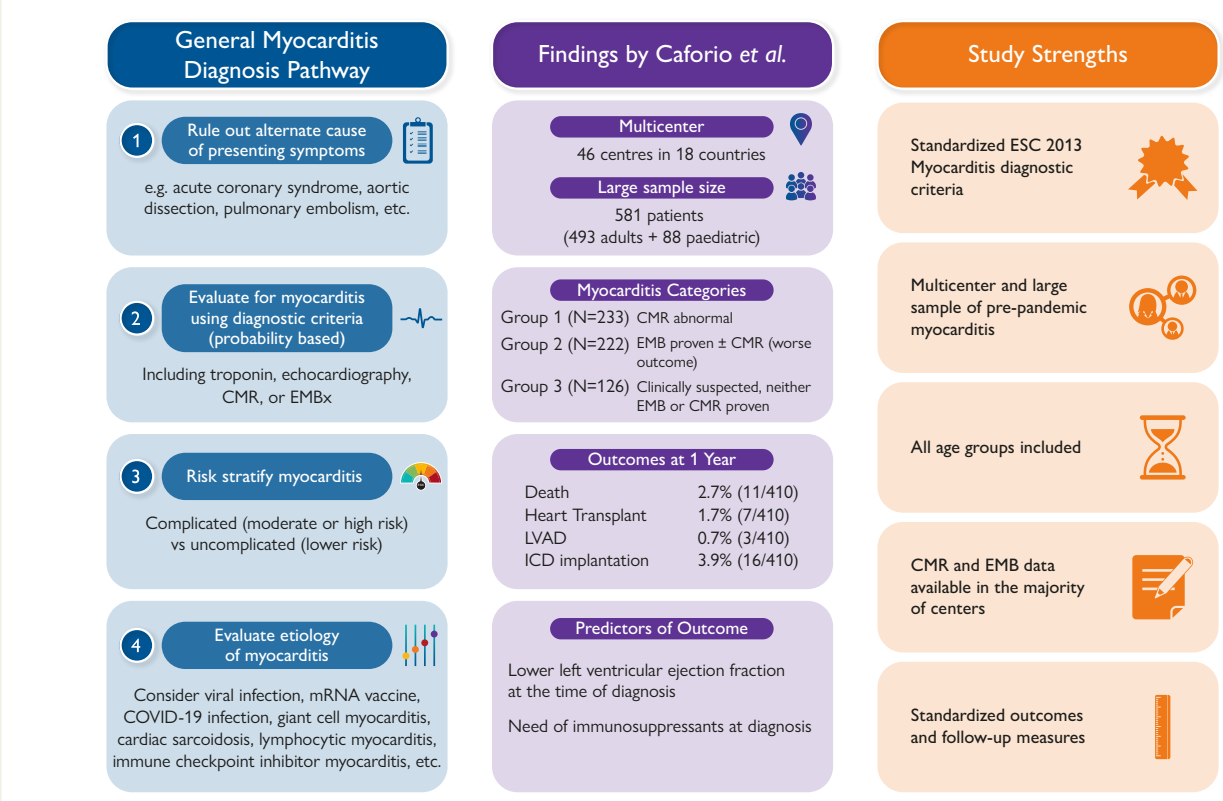
This editorial refers to 'Endomyocardial biopsy: safety and prognostic utility in paediatric and adult myocarditis in the ESC EURObservational Research Programme: Cardiomyopathy and Myocarditis Long-Term Registry', by A.L.P. Caforio *et al.*, https://doi.org/10.1093/eurheartj/ehae169.

Graphical Abstract



A comparative overview of general myocarditis diagnosis pathway, findings by Caforio *et al.*, and study strengths. ECG, electrocardiogram; CMR, cardiac magnetic resonance; EMBx, endomyocardial biopsy; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVAD, left ventricular assist device

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Myocarditis, or inflammation of the myocardium, is a challenging clinical condition to diagnose and treat, due to the diverse aetiology, presentation, and outcomes. Myocarditis can be associated with heart failure/shock, cardiac arrhythmias, or chest pain and other non-specific symptoms. Multiple aetiologies can lead to myocarditis, including viral [the latest being severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)], autoimmune (e.g. sarcoid or eosinophilic), or toxicity related [e.g. immune check point inhibitors (ICIs) for cancer]. The clinical course can also be highly variable, ranging from mildly symptomatic with self resolution (e.g. the majority of mRNA vaccine induced myocarditis), to severe cardiogenic shock requiring circulatory support or cardiac transplantation. Meanwhile, the diagnostic and treatment approaches are also evolving, leading to more uncertainties.

To address this widening gap in knowledge in myocarditis, the European Society of Cardiology (ESC) launched an important EURO/Observational Research Programme: Cardiomyopathy/Myocarditis Long-Term Registry (EORP), following the publication of the 2013 ESC position statement on myocarditis including new diagnostic criteria, incorporating both endomyocardial biopsy (EMB) and non-biopsied cases.[1] This registry aims to determine the performance of the criteria, the contemporary spectrum of aetiology, treatment, and outcomes. In this issue of the *European Heart Journal*, Caforio and colleagues reported on the 1-year outcomes of the EORP myocarditis registry (*Graphical Abstract*).[2] The registry identified 581 patients (of whom 88 were children) who met the strict ESC 2013 clinical criteria for myocarditis, and divided them into three groups: Group 1 = clinical myocarditis that was confirmed by cardiac magnetic resonance (CMR) imaging according to the original Lake Louise criteria;[3] Group 2 = clinical myocarditis diagnosis that was confirmed by EMB ± CMR; and Group 3 = clinically suspected myocarditis, but has neither CMR nor EMB confirmation.

Overall, 50.2% of patient had heart failure or shock, and 31.7% had major cardiac arrhythmias. Myocardial biopsy showed lymphocytic myocarditis to be the most common (82.6%) pathological finding, and positive viral PCR was found in 34.1% of cardiac biopsies. Of the latter, the most common virus found was parvovirus B19 (21.7%), followed by herpes virus 6 (9.5%), and viruses which are more common in children than in adults. There was no SARS-CoV-2 virus in this study as the registry recruitment occurred before the pandemic.

At 1-year follow-up, the event rates were overall low. Death occurred in 2.7%, heart transplant in 1.7%, ventricular assist devices in 0.7%, and implanted defibrillators in 3.9% of the patients. Patients in Group 2 with EMB-proven myocarditis had generally much worse outcomes compared with other groups. Multivariate predictors of adverse clinical outcomes included low left ventricular ejection fraction (LVEF), or the initiation of new immunosuppressive treatment at the time of diagnosis.

The overall results, while not surprising, were very valuable in providing a contemporary overview of the spectrum of myocarditis in Europe. It provided reassurances that diagnosis can be made similarly for children and adults. The registry revealed a risk-based approach in real-world practices, in that EMB was used more in severe cases of myocarditis, and CMR without EMB in milder cases. There was enthusiasm for the use of heart failure therapies particularly for those with heart failure, but much more reticence in the use of immunosuppressive therapy, probably reserved only for the most severe cases. This is likely to be reflected in the prognostic variables, in that lower EF was associated with worse outcomes, as was immunosuppression which was probably a case selection bias.

The study had several strengths, including: (i) the use of standard diagnostic criteria across 46 European centres in 18 countries; (ii) all age groups were included; (iii) prospective enrolment; (iv) standardized outcomes/follow-up measures; and (v) CMR and endomyocardial biopsy data available in the majority of centres. These measures were particularly important in addressing the heterogeneity of myocarditis in a large geographic region. A few findings from the registry warrant further considerations.

Myocarditis diagnostic criteria

The inclusion criteria in early myocarditis studies such as the Myocarditis Treatment Trial depended only on EMB according to the original Dallas criteria.[4] Since the 1990s, the diagnostic criteria shifted towards inclusion of multiple objective findings including CMR imaging and emphasis on the exclusion of alternative diagnoses. While EMB continues to be considered the gold standard, a large meta-analysis of 61 publications found that the mean detection rate of inflammatory cardiomyopathy utilizing EMB alone was only 50.8%.[5] Further, it is often not performed in mild, uncomplicated cases of myocarditis. Hence, the contemporary clinical diagnosis of myocarditis has shifted to a 'level of certainty' approach, as exemplified by the ESC and more recent Brighton Collaboration criteria.

Evolving role of CMR imaging in myocarditis

In stable patients, CMR imaging remains one of the most useful, non-invasive tools for the diagnosis of acute myocarditis. CMR can identify the presence of myocardial inflammation, but not necessarily the specific cause of the inflammation. In the EORP registry, 70.7% of the patients had CMR, which may reflect either access in some, or preference for EMB in very severe cases. Compared with EMB, CMR was less sensitive, particularly in children.

CMR may indeed have temporal- and disease-specific limitations. A study by Zhang *et al.*[6] showed that the presence of late gadolinium enhancement (LGE) increased from 21.6% to 72.0% in those patients that waited until admission day 4 or beyond before receiving CMR. This suggests that inflammation on CMR may evolve over time and there may exist an optimal time window to perform CMR. Interval time from disease onset to CMR may need to be incorporated into future versions of CMR myocarditis criteria.

Furthermore, the aetiology of myocarditis may also affect CMR sensitivity. The study by Zhang *et al.* examined the CMR characteristics of 103 patients clinically diagnosed with ICI-associated myocarditis in an international registry.[6] They found that only 48% had LGE, and 28% had oedema based on elevated T2-weighted images. Another study demonstrated that T1 abnormalities may be more common than T2 abnormalities in patients with ICI-associated myocarditis.[7] Taken together, these findings suggest a 'one-size-fits-all' CMR criterion may not be applicable to all aetiologies of myocarditis.

Endomyocardial biopsy

There is high variation in the rates of EMB use for myocarditis around the world. The EORP registry indicated that EMB is used more often in severe cases, and remains relatively safe even in centres with variable volumes. There was no mortality, and the over complication rate was 4.7%–4.9% in both children and adults. This is consistent with current data on 1368 biopsies in 561 patients over 10 years, and an overall complication rate of 4.1% was found, with serious life-threatening cardiac

complication occurring in <1%.[8] Although EMB is an invasive procedure, it provides a definitive histopathological diagnosis of active myocarditis and can shed light on the aetiology of the inflammation, especially in severe cases. The ability to identify giant cell, sarcoid, or eosinophilic myocarditis can guide therapy, and definitively establish potential viral aetiology. Nevertheless, referral of patients to regional centres with significant EMB experience will further increase the diagnostic yield, while enhancing safety.

Prognostic factors and the role of immunosuppression

The independent prognostic factors in the registry were (i) low LVEF and (ii) the need for new immunosuppressants at the time of diagnosis. The poor ventricular function at the time of diagnosis is a direct indication of the severity of myocarditis, and the impact of inflammation directly on cardiac function. Outside the acute phase, this warrants aggressive heart failure guideline-directed therapies, and careful follow-up to achieve functional recovery if possible.

The need for new immunosuppressants at the time of diagnosis will require a nuanced interpretation in a cross-sectional study. A literal interpretation would be that the introduction of immunosuppression may be harmful. However, this is more likely to be the reflection of the underlying severity of the myocarditis process, and/or the degree of inflammation observed from EMB or CMR. Since there is a general underutilization of immunosuppressive treatments in the entire registry, most patients were undertreated. However, this underscores the importance of rapid and thorough diagnostic workup of patients with severe myocarditis and the identification of potentially more targeted treatment to change the natural history.

Gaps in knowledge and ways forward

As in any well-conducted study, there are more questions and gaps in knowledge identified with the new information than answers. For example, in terms of pathology, intriguingly there were more lymphocytic myocarditis cases observed in Eastern Europe. Was this accidental or due to actual differences in environmental conditions or immunogeography? Could there be more myocarditis-relevant biomarkers emerging to assist in both diagnosis and follow-up? What is the optimal parameter to follow on CMR? Is the persistence of LGE in some patients during follow-up prognostic for only certain aetiologies of myocarditis? What are the predictors of persistent LV dysfunction vs. full recovery?

There are also significant brain–heart linkages in inflammation—are there mental health or cognitive changes during follow-up, as seen in long COVID? How early and frequently should the patients with myocarditis be followed, based on risk and severity? There are indeed better antiviral and more specific immune-modulatory agents today than in any previous era. Could more aetiologically specific or 'personalized' treatment allow faster and more complete recovery?

Unfortunately, this registry closed enrolment before the COVID-19 outbreak. However, the ESC and the multiple myocarditis collaborators should be congratulated on successfully conducting a meaningful registry in this heterogeneous condition, with standardized inclusion criteria, and common process and outcome measures. This should engage the global community to explore follow-up registries to address new questions using state of the art technologies and expert networks involving clinical and methodological expertise.

Acknowledgements

T.S.K. is a Myocarditis Foundation Fellowship Recipient. This work is supported in part by CIHR, Genome Canada, Heart & Stroke Foundation, and Brain–Heart Interconnectome CFREF.

Declarations

Disclosure of Interest

The authors declare no disclosure of interest for this contribution.

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