

DIAGNOSTIC APPROACH OF MYOCARDITIS

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Summary

Myocarditis diagnosis dates back to 1900 and has evolved significantly. The disease presents with a diverse clinical picture, complex pathophysiology, and various aetiologies, including recent challenges such as the COVID-19 pandemic, making diagnosis difficult. Therefore, an accurate differential diagnosis and newer diagnostic methods are essential. This review aims to analyse and compare diagnostic methods for myocarditis, emphasizing their role in a stepwise diagnostic approach and the relevance of novel techniques. A complete clinical evaluation that includes medical history, physical examination, biomarkers, electrocardiography and echocardiography is recommended in all patients with suspected myocarditis as the initial step in diagnostic assessment. In addition, revolutionary non-invasive imaging techniques have positioned cardiac magnetic resonance (CMR) as the primary tool for diagnosing myocarditis, while the role of endomyocardial biopsy (EMB) has changed. However, no single method is sufficient; instead, a multimodal diagnostic approach integrating clinical, imaging, and histological tools is essential for reliable diagnosis.

Introduction

The diagnosis of myocarditis dates back to 1900, when Carl Ludwig Alfred Fiedler first described “interstitial myocarditis” in autopsy cases as an isolated cardiac inflammation. Later, Schmorl classified Fiedler’s histological sections into lymphocytic and giant-cell subtypes. A major advancement came with the introduction of right heart catheteri-

zation with endomyocardial biopsy (EMB), which, alongside immunohistochemistry and PCR-based virus detection, remains a core diagnostic method. More recently, cardiac MRI (CMR), capable of detecting oedema and inflammation, has emerged as a powerful non-invasive tool. Innovations such as the Lake Louise Criteria and mapping techniques have significantly improved MRI diagnostic accuracy [1,2]. In addition, electroanatomic mapping (EAM) has been developed to enhance EMB sensitivity [3]. Given myocarditis’ complex and variable presentation [4], accurate diagnosis requires continual improvements, especially in light of evolving challenges such as the COVID-19 pandemic.

Objective. This narrative review analyses the stepwise diagnostic approach to myocarditis. It focuses on both established and emerging diagnostic methods, especially imaging, endomyocardial biopsy (EMB), and novel techniques, while emphasizing the importance of differential diagnosis. The aim is to provide a comprehensive understanding of diagnostic advancements in myocarditis.

Research methods

The aim of this narrative literature review is to analyse and compare current data on diagnostic methods for myocarditis, with a focus on their role in a stepwise approach and the relevance of newer diagnostic techniques. To achieve this, a comprehensive search was conducted across databases including PubMed, ClinicalKey, ScienceDirect, Wiley Online Library, Google Scholar, Science.org, the British Journal of Sports Medicine, the European Heart Journal, the American Heart Association Journal, and the WHO database. Only English-language publications from the past five to ten years were included to ensure up-to-date findings. Selected sources included clinical trials, systematic reviews, meta-analyses, cohort studies, randomized trials, national registries, and the

latest ESC and ACC/AHA guidelines. Search terms included: “update on acute myocarditis”, “diagnostic criteria of myocarditis”, “myocardial imaging”, “Immunohistochemistry in myocarditis”, “EMB, when and why?”, “novel diagnostic methods in myocarditis”, combined with “definition and subtypes”, “clinical picture”, “pathophysiology”, “aetiological factors”, “differential diagnosis”, and “COVID-19”. References of relevant publications were also manually reviewed for completeness.

Results

Diagnostic tools. *Criteria for Diagnosing.* Inflammation of the myocardium, triggered by non-infectious or infectious causes and resulting in an immune-mediated inflammation can be challenging to diagnose. A definite diagnosis of myocarditis can be made if a person presents with myocarditis-related clinical symptoms and inflammation of the heart established via cardiac magnetic resonance (CMR) imaging or endomyocardial biopsy (EMB) [5].

General diagnostic techniques. *Electrocardiography (ECG).* The clinical presentation of myocarditis often overlaps with conditions like pericarditis and myopericarditis, complicating diagnosis. Although ECG findings are mostly nonspecific, it remains an essential first-line tool guiding management decisions [6]. PR segment depression, especially in leads II, V5, and V6, is typical in pericarditis and myopericarditis, while PR elevation may appear in aVR and V1 [6,7]. QRS abnormalities, including bundle branch blocks and pathological Q waves in inferior and lateral leads, are common and may indicate fulminant myocarditis [6].

ST segment elevations from subepicardial lesions and subsequent T-wave inversions (seen in 9–48% of cases) are associated with myocardial oedema and necrosis on MRI [6,8]. QT prolongation suggests arrhythmogenic risk and worse prognosis [6]. Brady- and tachyarrhythmias, particularly high-degree AV blocks and ventricular arrhythmias, are linked to increased mortality and sudden cardiac death, especially in fulminant or infiltrative forms [6,9].

Laboratory Investigations. Laboratory diagnosis of myocarditis is challenging due to the nonspecific nature of most biomarkers, which also appear in other cardiac conditions [10]. Inflammatory markers such as CRP, ESR, and leukocytosis are frequently elevated but have limited diagnostic value. Eosinophilia is more specific for eosinophilic myocarditis (75.9%), while novel markers like cytokines and alarmins S100A8/A9 show promise but are not yet standard diagnostics [11].

Myocardial injury markers, including troponins, CK-MB, and LDH, are also nonspecific and time-dependent. Troponin elevations occur in about 50% of biopsy-confirmed

cases but may be missed if sampling is delayed. Troponin I is especially useful in ICI-induced myocarditis. BNP and NT-proBNP can support diagnosis in suspected heart failure or myocarditis. Anti-cardiac autoantibodies, found in up to 60% of chronic cases, are linked to disease progression and poor outcomes in acute cases [11].

Viral serology is of limited value, with <40% positivity, and is not routinely recommended. However, a fourfold rise in antibody titres may support diagnosis when combined with clinical and imaging data [11].

Imaging Modalities. *Echocardiography.* Echocardiography is a standard tool in suspected myocarditis, used to assess cardiac function and exclude other causes of heart failure. It quantifies systolic and diastolic dysfunction, particularly in the left ventricle (LV) [11]. Typical findings in acute myocarditis include transient LV wall thickening, abnormal echogenicity, regional hypokinesia, especially in the inferior or inferolateral wall, and pericardial effusion, helping to distinguish it from ischemic heart disease [2,11]. Right ventricular dysfunction, assessed via tricuspid annular plane systolic excursion (TAPSE), is linked to higher risk of transplant or death. Fulminant myocarditis often shows myocardial oedema with normal cavity size, while acute forms may show dilated LV with preserved wall thickness [11]. Speckle-tracking echocardiography (STE) offers improved sensitivity over standard transthoracic echocardiogram (TTE) by measuring global longitudinal strain (LV-GLS), enabling detection of subtle LV dysfunction, differentiation from myocardial infarction, and monitoring of recovery [11, 12, 13].

Cardiac CT scan. Differentiating acute viral myocarditis from other cardiac conditions can be difficult due to its variable presentation. Multi-detector computed tomography (MDCT) helps exclude differential diagnoses such as heart failure, pulmonary embolism, acute coronary syndrome (ACS), pneumonia, and aortic dissection [2]. In acute myocarditis, increased myocardial permeability leads to greater uptake of iodinated contrast agents, producing delayed enhancement patterns similar to those seen with gadolinium in CMR. MDCT can show midwall or subepicardial enhancement, aiding in distinguishing myocarditis from ACS when coronary artery disease is absent. It also allows assessment of global and regional LV wall motion abnormalities [2].

Although MDCT is not the first-line imaging technique, it remains the gold standard by offering practical advantages such as wider availability, faster acquisition, and suitability for patients with contraindications to CMR (e.g., metallic implants, claustrophobia). One study demonstrated a 95% diagnostic accuracy for acute myocarditis using spectral cardiac CT with late iodine enhancement, compared to CMR [2]. Despite limited data, cardiac CT shows promise as a

supportive diagnostic tool in identifying myocardial inflammation [2].

Cardiac Magnetic Resonance Imaging (MRI). According to the guidelines of European Society of Cardiology (ESC), cardiac magnetic resonance (CMR) is recommended in patients with suspected myocarditis to reach a clinical diagnosis, including assessment of oedema, hyperaemia, necrosis, and fibrosis [4]. The Lake Louise Criteria (LLC), introduced in 2009 and revised in 2018, guide CMR-based diagnosis. The original LLC used T2-weighted imaging, early gadolinium enhancement (EGE), and late gadolinium enhancement (LGE), requiring two of three for diagnosis [15,16]. The updated criteria replaced EGE with T1 and T2 parametric mapping, improving sensitivity (87.5%) while maintaining specificity [2,16,17].

T2-weighted imaging detects oedema but may yield false negatives if skeletal muscle is also inflamed. LGE identifies necrosis or fibrosis in typical non-ischemic patterns but cannot distinguish between active and chronic inflammation, thus it's often paired with T2 imaging [2,14,15]. T1/T2 mapping and extracellular volume (ECV) quantification improve diagnostic accuracy by detecting tissue changes without relying on contrast or subjective interpretation [2,14,18,19]. Their combined use enhances the overall performance of CMR in myocarditis diagnosis [2,14,19].

Nuclear Imaging. Imaging techniques using inflammation-sensitive radioisotopes, such as Ga-67, In-111 antimony, and Tc-99m-MIBI, can support the diagnosis of acute myocarditis, though they are now less commonly used due to the advantages of cardiac MRI (CMR) [2,20]. Ga-67 and In-111 show correlations with histopathology and EMB findings, while Tc-99m-MIBI detects perfusion deficits linked to inflammation [2].

Positron emission tomography (PET), particularly with 18F-FDG, is a more advanced nuclear method that identifies active myocardial inflammation based on uptake patterns [21,22,23]. Specificity improves with proper patient preparation [23]. PET is especially useful in chronic or ambiguous cases, and in cardiac sarcoidosis, where CMR may be limited [21,24,25]. Novel tracers like [11C]-methionine show promise in early studies [24]. PET-CMR hybrid imaging combines metabolic and structural data, aiding in diagnosis, risk stratification, and EMB decisions [21,23]. PET-CT has shown 74% sensitivity and 97% specificity compared to CMR with LGE [26] and should be considered for the diagnostic work-up in patients with suspected myocarditis when echocardiography and CMR are inconclusive for the clinical diagnosis [4].

Endomyocardial Biopsy (EMB) investigation. Indication and Procedure. Although endomyocardial biopsy

(EMB) remains the definitive method for determining the histological subtype of cardiac inflammation, its role in clinical practice has changed. Recent ESC guidelines state that EMB is recommended for patients with high-risk myocarditis or haemodynamic instability, as well as for those with intermediate-risk myocarditis who fail to respond to conventional therapy [4].

Its diagnostic yield is higher in fulminant cases with diffuse inflammation, though negative results cannot definitively rule out disease [3]. EMB use is limited by availability and expertise, with diagnostic success influenced by timing, biopsy site, and myocarditis subtype [27].

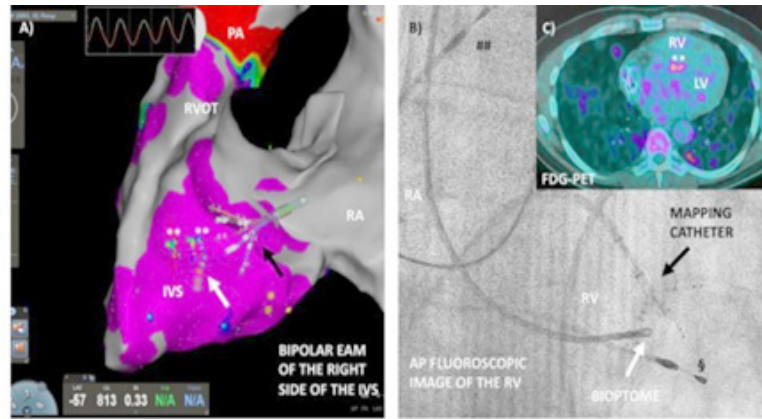
Typically performed via the right internal jugular vein with septal sampling, EMB should be interpreted alongside clinical and imaging data in specific clinical situations [3,4]. Diagnostic accuracy decreases over time, from 89% within four weeks to 38% after three months, underscoring the importance of early sampling. At least 3–4 tissue samples are recommended, and for suspected viral myocarditis, two should be frozen for molecular testing [3].

Histopathology - Dallas Criteria. Accurate diagnosis of acute myocarditis and chronic DCMi relies on both pathogen detection and histological analysis of EMBs. The Dallas criteria, introduced in 1986, define myocarditis by the presence of focal or diffuse inflammatory infiltrates and non-ischemic myocyte necrosis or injury. However, these criteria have limitations due to sampling errors, subjective interpretation, and the absence of necrosis in chronic inflammation. Studies have shown that the Dallas criteria lack sensitivity, specificity, and prognostic value. Despite this, they remain in use today, particularly for assessing myocytolysis in acute myocarditis [28].

Immunohistochemistry. To enhance the sensitivity of EMBs beyond the Dallas criteria, immunohistochemical analysis is essential in diagnosing myocarditis and DCMi. Myocarditis involves infiltration by various immune cells (e.g., monocytes, eosinophils, T and B lymphocytes, NK cells), whereas in DCMi, T lymphocytes and macrophages predominate, with no increase in B or NK cells [28]. Inflammation is classified as acute (e.g., lymphocytic, eosinophilic, giant cell, granulomatous) or chronic, with the acute form, especially lymphocytic myocarditis, being most common [3].

Immunohistochemistry enables identification of cell-specific antigens and markers of active immune responses, thus improving diagnostic accuracy. The 2013 ESC guidelines designate it as the gold standard, recommending thresholds of ≥ 14 leukocytes/mm², including ≥ 7 CD3+ T cells/mm² and up to 4 monocytes/mm². Recent findings suggest including additional cell types and adhesion molecules for better prognostic insight [28].

Figure 1: EAM-guided EMB in a patient with suspected cardiac sarcoidosis (aka granulomatous myocarditis). (3)



Bipolar EAM & high density mapping (black arrow) is shown on the right side of the IVS. In the middle of IVS healthy myocardium (violet areas) and pathology with decreased voltages (green-blue signals) are seen.

The white arrow points to the biopsy forceps. (A) The fluoroscopy (anteroposterior view) from a patient with permanent pacemaker illustrates the atrial pacing wire (##), the ventricular pacing wire (§), biopsy forceps and mapping catheter (black arrow). (B) In the same patient a FDG-PET demonstrated a focal lesion in the middle of IVS, so granuloma was suspected. Additionally, pulmonary lesions consisting sarcoidosis were found.

Electroanatomic mapping (EAM). In order to improve the sensitivity of EMB, electroanatomic mapping (EAM), a new tool for EMB guidance, has been developed. EAM-guided EMB is thereby known to be very sensitive in detecting injured myocardium derived from abnormal electrograms on electroanatomic maps and from low-voltage areas. As a result, the number of performed biopsies is reducing, and the probability of receiving diagnostic samples is increasing [29,30,3].

In fact, a single-centre retrospective study with 162 participants describes EAM as an excellent tool for being very sensitive and specific in detecting pathological substrates in the myocardium. With this study, CMR imaging and EAM shared a similar accuracy and, in both methods, where EAM-guided EMB and CMR imaging accompanied EMB, a positive predictive value of 89% on EMB was achieved. However, CMR imaging is still known to be superior compared to EAM-guided EMB in detecting myocarditis, EAM proves to identify chronic myocarditis with ventricular arrhythmias and abnormalities in a small ratio when CMR imaging was negative [29,3]. As an example, in competitive athletes with an apparently normal heart and known ventricular arrhythmias the EAM-guided EMB investigation detects a pathological substrate in 100% of patients with an inflamed myocardium identified in 53% of cases. Although there are still no trials in the near future, if myocarditis is suspected with known ventricular arrhythmias, EAM-guided EMB reveals to increase EMB diagnostic over conventional

fluoroscopy-guided biopsy. Hence an EAM-guided EMB should be considered either for diagnosis or due to therapeutic reasons, if both EAM and EMB are used for electrical and pathological substrate assessment. Nevertheless, the time needed for EAM performance and the associated costs impede EAM-guided EMB from becoming a routine tool in myocarditis diagnosis. Apart from that, EAM-guided EMB plays an important role as research tool in further defining the importance of myocarditis in the context of inherited or acquired arrhythmic conditions and its pathogenesis. Furthermore, theoretically, an increased diagnostic accuracy of EMB could be achieved if cardiac sarcoidosis or granulomatous myocarditis with the known patchy myocardial disorder is suspected. In summary, EAM-guided EMB is up-and-coming and particularly of great importance where myocarditis linked with a ventricular arrhythmic burden is suspected [3,30] (Figure 1).

Conclusion

1. This narrative review evaluated current guidelines and research on diagnosing myocarditis, a complex and often elusive condition, particularly in younger individuals. Diagnosis begins with clinical assessment, ECG, and laboratory tests, which, despite being nonspecific, are essential. Imaging plays a crucial role: echocardiography and cardiac CT help exclude other causes, while cardiac MRI (CMR), especially with the revised 2018 Lake Louise Criteria and

T1/T2 mapping, is the preferred first-line modality, offering up to 87.5% sensitivity.

2. PET imaging supports differentiation between active and chronic myocarditis but is limited by cost and accessibility. While evolving non-invasive imaging methods have replaced the role of endomyocardial biopsy (EMB), it remains the diagnostic reference standard in specific clinical circumstances with improved yield when using immunohistochemistry and electroanatomic mapping.

3. Ultimately, no single method is sufficient. A multi-modal, context-driven approach integrating clinical, lab, and imaging data is essential for accurate diagnosis and for differentiating myocarditis from other cardiac conditions.

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MIOKARDITO DIAGNOSTIKOS METODAI

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Raktažodžiai: miokarditas, diagnostikos metodai, elektroanatominis žemėlapis, širdies kompiuterinės tomografijos angiografija, širdies magnetinis rezonansas, Dalaso kriterijai, Lake Louise kriterijai, infarkto tipo miokarditas.

Santrauka

Miokardito diagnozė buvo aprašyta 1900 metais ir nuo tada reikšmingai pasikeitė. Įvairi ligos klinikinė išraiška, kompleksinė patofiziologija, skirtingos etiologijos ir tokie iššūkiai kaip COVID-19 viruso pandemija sunkina miokardito nustatymą. Reikalinga tiksli diferencinė diagnostika ir nauji ištyrimo metodai. Šios apžvalgos tikslas – išanalizuoti ir palyginti miokardito diagnostikos metodus, apibrėžiant jų vaidmenį nuosekliame diagnostikos algoritme ir naujų technologijų svarbą. Išsamus klinikinis įvertinimas, apimantis anamnezę, fizinį ištyrimą, biožymenis, elektrokardiografiją ir echokardiografiją, rekomenduojamas kaip pirmasis diagnostikos žingsnis visiems pacientams, kuriems įtariamas miokarditas. Revoliuciniai neinvaziniai instrumentiniai tyrimai leido širdies magnetiniam rezonansui tapti pagrindine miokardito diagnostikos priemone, o endomiokardinės biopsijos reikšmė klinikinėje praktikoje pasikeitė. Vis dėlto nė vienas metodas negali savarankiškai pagrįsti miokardito diagnozės. Todėl, siekiant patikimos miokardito diagnozės, būtinas daugialypis ištyrimas, integruojantis klinikinių, instrumentinių ir histologinių tyrimų rezultatus.

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