EDITORIAL

Diagnostic testing in cardiac sarcoidosis: what comes first?

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Cardiac sarcoidosis (CS) is a complex disease characterized by granulomatous inflammation and fibrosis that can lead to conduction abnormalities, ventricular arrhythmia (VA), and congestive heart failure and sudden cardiac death (SCD).[1] Presence of non-caseating granulomas is associated with progressive stages of edema, inflammation, and fibrosis on histology however the disease remains patchy and multifocal.[2] Early diagnosis and treatment with immunosuppressants are considered essential to reduce cardiac morbidity and mortality associated with CS.[3] Isolated CS can be difficult to diagnose given its clinical and diagnostic resemblance to other cardiac conditions. Cardiac Magnetic resonance (CMR) is a sensitive tool that can quantify biventricular function and detect myocardial edema, inflammation and fibrosis related to CS.[4] ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) on the other hand can detect active inflammation within the heart and can detect the patients who can benefit from immunosuppressive therapy.[5] A major limitation in the evaluation of CS is absence of gold standard clinical diagnostic criteria. The guidelines recommend using histological diagnosis of extracardiac sarcoid for diagnosing probable CS in patients with suspicious clinical findings, however it still fails to identify the patients with isolated CS which is an increasingly recognized entity[6] Diagnostic utility of endomyocardial biopsy is limited due to patchy nature of the disease which results into limited sensitivity of $\sim 30\%$.[7,8] The current diagnostic criteria (JMHW and HRS) have not been accepted as a gold standard for the diagnosis of CS. Even the research studies focused on diagnostic evaluation of CS show poor agreement among the diagnostic criteria to be used as a reference standard. Thus, there remains significant uncertainty in diagnosis and treatment algorithms for CS.

Evaluation of accuracy for an imaging test often involves comparison with the gold standard to assess sensitivity and specificity. For diseases like CS where the gold standard may not always be performed due to invasive nature, the evaluation of the imaging findings against adverse outcomes can be used as an objective assessment of accuracy of the imaging testing.

In the present issue of the Journal of Nuclear Cardiology, Adhaduk et al performed the metanalysis that evaluates the utility of CMR and FDG-PET for the prediction of adverse outcomes. This analysis included total of four studies with 237 patients with a total of 45 events. The combined results demonstrate high sensitivity for CMR with a modestly improved specificity for FDG-PET in the prediction of adverse events for the included patients with CS. Out of 18 adverse events, five were heart failure admissions and two were atrial fibrillation ablations. Authors conclude that the CMR has a higher sensitivity at predicting adverse outcomes in CS patients; however, FDG-PET was more specific at

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predicting adverse outcomes. Authors also state that depending upon presenting symptoms, clinicians should choose diagnostic tests; CMR or FDG-PET is not superior to others in all CS patients.

While reviewing the findings of the present paper, it is essential to highlight the underlying variability in the patient population, heterogenous methodology of the selected nonrandomized studies and how this affects the overall conclusion. All the studies included were done retrospective, with small number of patients and shorter follow up. Most of the patients were on immunosuppressants and didn't have T2 weighted CMR imaging done to detect inflammation. Furthermore, the diagnostic criteria set for CS was variable amongst the studies included in this analysis. Not every LGE or FDG uptake is CS hence the accuracy of positive read is heavily dependent upon the expertise and experience of reading imager. For example, one of the four study didn't exclude ischemic cardiomyopathy, yet any transmural LGE was classified as positive for CS. Similarly, focal on diffuse uptake on FDG- PET was considered positive in one study, negative in one study, and was not defined in two studies. Even for the adverse event endpoints, one study reported the highest adverse outcomes with CS compared to the rest due to inclusion of hospital admission for decompensated heart failure and other cardiac-related hospital admissions as endpoints. Furthermore, removing each study during sensitivity analysis, authors did not find any significant change in diagnostic parameters for CMR sensitivity, yet FDG-PET sensitivity analysis led to a significant change in diagnostic parameters.

Whilst this study was intended to evaluate the sensitivity and specificity of the imaging findings of two commonly used diagnostic modalities in CS against the adverse outcomes, its conclusions are limited for clinical application. In absence of gold standard imaging evaluation for cardiac sarcoidosis, noninvasive diagnosis of cardiac diagnosis remains challenging given underdiagnosis (no testing) and overdiagnosis (false positive results on advanced imaging). Previous metanalysis comparing the diagnostic accuracy of CMR vs FDG-PET has shown higher sensitivity of CMR compared to FDG-PET for diagnosis of cardiac sarcoidosis but similar specificity. Furthermore, sensitivity for FDG-PET was highest with quantitative versus qualitative evaluation, whereas sensitivity for MRI was highest with inclusion of T2 imaging.[9] These findings are not surprising. The biggest challenges with CS studies included in the present article, is variable diagnostic criteria used to identify patients with CS. Recent CMR data identifying the LGE phenotypes associated with arrhythmic outcomes may help.[10–12] Athwal et al demonstrated that LGE phenotypes of CS derived from the pathology and validated by clinical outcomes are associated with worse outcomes but absence of the pathology frequent LGE phenotype was associated with a low risk of arrhythmic events, even in the presence of other (pathology rare) LGE or abnormal LVEF. Thus, association of any LGE to the clinical outcomes is CS patients may not be strong.[10] Even though edema imaging on CMR has low sensitivity to detect myocardial inflammation compared with FDG-PET,[13] there are no studies of PET positive, LGE negative histology proven CS. In CMR studies, patients with clinically suspected CS and no LGE have extremely low likelihood of developing ventricular arrythmias sudden cardiac death or heart failure.[10] For the patients that have high risk pathology frequent LGE may benefit from FDG-PET for further confirmation of active inflammation to evaluate eligibility for CS treatment. FDG uptake remains highly dependent on patient preparation and myocardial metabolism, isolated use of FDG-PET in CS diagnostic algorithm remains clinically limited.[14]

Diagnosis of isolated CS remains challenging. Ultimately diagnostic and prognostic evaluation of patient with CS depends on the individual patient, clinical presentation and local expertise at the center doing the testing. Combined CMR and FDG-PET perhaps can be the patient centric approach in patients presenting with suspected CS.[15]

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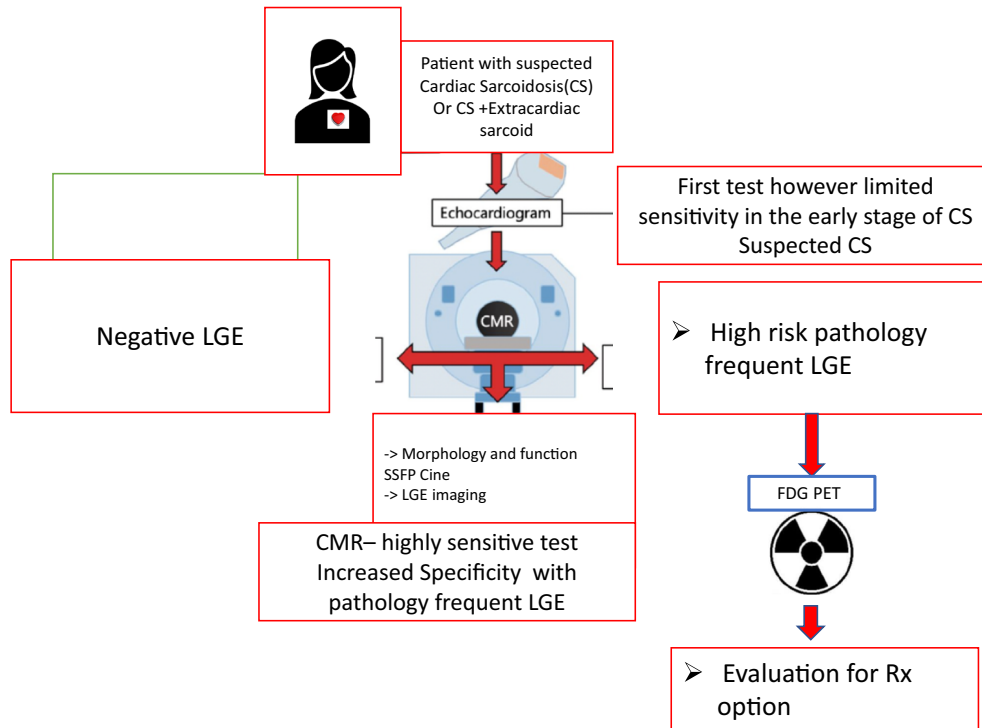
Disclosures

Dr. Parwani has no disclosures.

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