Review Article

Exploring the latest advances in ^{18}F-FDG PET/CT and cardiac magnetic resonance for imaging for cardiac sarcoidosis diagnosis

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Abstract: Sarcoidosis is a systemic inflammatory disease that affects multiple organs. Various clinical signs are associated with cardiac sarcoidosis (CS), and the diagnosis process is complicated because any organ could be involved. Despite the critical clinical importance of early and precise diagnosis of CS, there is currently no gold-standard method for CS evaluation. The non-invasive imaging modalities of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and cardiac magnetic resonance (CMR) imaging have demonstrated the potential for identifying various histological characteristics of CS. Recently, the development of hybrid FDG-PET/CMR scanners has enabled the simultaneous acquisition of these attributes. Compared to just one imaging modality, these scanners detect CS and stratify risk more accurately and with higher sensitivity. Analyzing the potential role of concurrent FDG-PET/CMR in enhancing the diagnosis of CS, the present review concentrates on the advantages of this technique in light of recent technological developments.

Keywords: Cardiac sarcoidosis, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, cardiac magnetic resonance imaging

Introduction

Sarcoidosis is an inflammatory, multi-systemic disease with non-caseating granulomas in the affected organs. However, the disease's underlying cause is unknown [1]. Sarcoidosis mainly affects the lungs. This disease develops in the lungs in almost 90% of cases. However, it can harm extrapulmonary organs like the heart. Cardiovascular involvement is rare, affecting only ~5% of sarcoid individuals, yet it can occur without symptoms. At least 25% of sarcoidosis patients have cardiac involvement [2].

The potential involvement of any organ complicates the diagnostic process for cardiac sarcoidosis (CS), which results in a wide range of clinical manifestations. Furthermore, the lack of dependable biomarkers or diagnostic tools makes diagnosing CS difficult. The lack of a trustworthy reference standard to validate the diagnosis presents a problem [3]. Although the sensitivity of endomyocardial biopsy is limited, it can confirm cardiac involvement [4]. Several expert consensus criteria have been established; however, their diagnostic accuracy is likewise restricted [3, 5]. Recently, research has shown that the use of advanced imaging techniques, such as ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE), can enhance the diagnosis and care of patients with CS [6]. These imaging technologies are essential for early diagnosis, illness prediction and progression, and therapy response monitoring.

While FDG-PET can identify myocardial inflammation, its specificity is diminished, particularly in instances where FDG uptake from healthy myocardium is not well suppressed. Integrating FDG-PET and CMR scanners has just been introduced, and they show promise for a full evaluation of CS in a single scan [7, 8]. Our investigation focuses on the advantages of such an approach in relation to recent technological advances as well as the potential role of combined FDG-PET and CMR in enhancing CS diagnosis.

Materials and methods

Search strategy

We have conducted a literature review of an update on using ^{18}F-FDG PET/CT and CMR imaging of diagnose CS. The research was performed in compliance with the PRISMA criteria, Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the Flow Diagram is shown in **Figure 1**. The research was conducted in the PubMed, MEDLINE, Scopus, Web of Science, DOAJ, Science Direct, and Google Scholar databases between January 2020 and October 2023. It used the Advanced
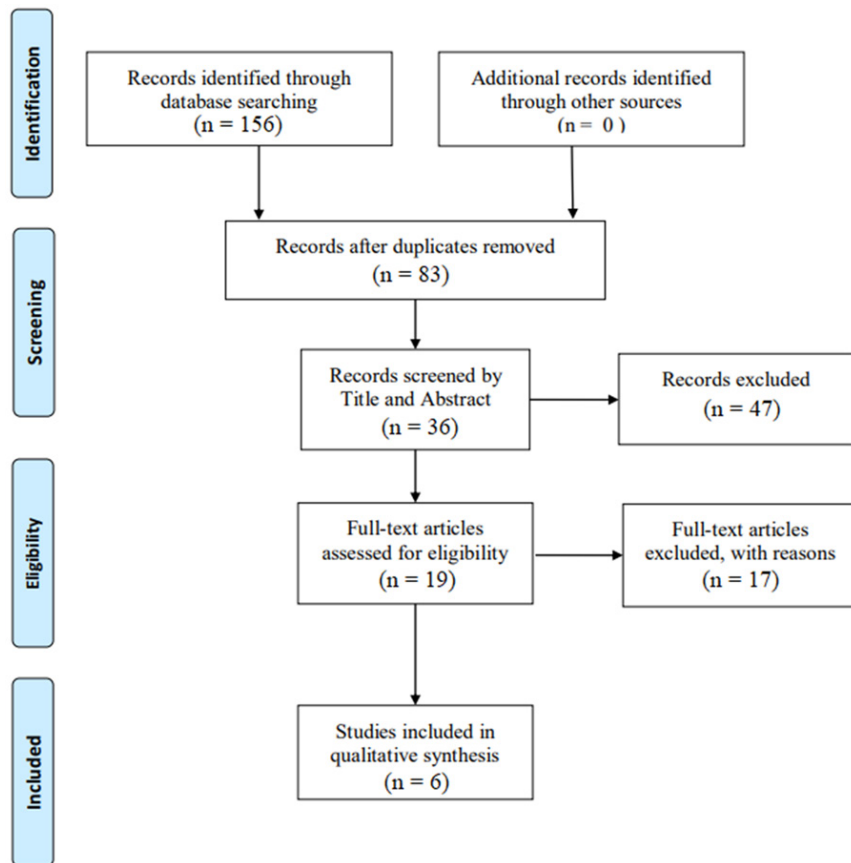
Figure 1. PRISMA flow diagram for enrollment of studies.

Search Builder, and the keywords were searched in [Title OR Abstract]. We have filtered only research articles published in English language and using the terms '(^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography [Mesh] OR FDG-PET/CT [Mesh]) AND (Magnetic resonance imaging [Mesh] OR MRI [Mesh] OR Cardiac magnetic resonance imaging [Mesh] OR CMR [Mesh]) AND (Cardiac sarcoidosis [Mesh])'.

Inclusion and exclusion criteria

In the systematic review, articles that assessed the use of ^{18}F-FDG PET/CT and cardiac magnetic resonance imaging for the diagnosis of CS were included. In the final evaluation of articles, we included articles that included both imaging methods of FDG-PET/CT and CMR for CS diagnosis. References in selected research were reviewed for other relevant literature. There were both retrospective and prospective investigations and blinded and non-blinded research. Case reports and series involving a limited number of patients, review articles lacking original data, editorials, letters, and conference papers were all excluded.

Data extraction and quality evaluation

Titles and abstracts were reviewed by two authors (F.R. and A.M.). After implementing inclusion and exclusion cri-

teria, data from studies were extracted based on the requirements of the survey.

Any relevant studies were included after scanning the references in previously published review articles. We obtained 17 eligible published research articles in their final version. For some of them, we chose to include only the main findings that fit the purpose of this review (**Table 1**).

Results

Epidemiology, pathogenesis, clinical features of cardiac sarcoidosis

Research has indicated that populations of northern European and African American descent have a significantly higher incidence of sarcoidosis than other regions. Scandinavian countries have had the highest incidence, with an estimated 11.5 occurrences per 100,000 people. The United States (US) has a rate of 8-11 per 100,000 people, but other regions of the globe have recorded lower rates [9]. It is estimated that approximately 5% of patients with sarcoidosis who experience extra-cardiac symptoms may develop CS. Research on autopsies has revealed that subclinical (silent) CS affects 20-25 percent of patients exhibiting extra-CS symptoms. It is estimated that 27-54% of CS patients have isolated CS; however, the absence of extracardiac manifestations of sarcoidosis makes the clinical identification of isolated CS difficult [10].

In organs afflicted with sarcoidosis, non-caseating epithelioid granulomas emerge as the histological hallmark of the disease. Sarcoid granuloma is composed primarily of CD4+ T lymphocytes encircling its central nucleus. Components comprising the core comprise both multinucleate giant cells and macrophages, the latter of which are fusions of large macrophage epithelioid cells [11, 12]. Initially, there is a discernible presence of lymphocytes; however, as the disease advances, their quantity diminishes. The sub-epicardial part of the left ventricular (LV) free wall is the first part that granulomas damage. This is followed by the right ventricle (RV) and the basal interventricular septum. In most cases of sudden cardiac death due to undetected CS, autopsies revealed extensive fibrosis and lymphocytic infiltration [13, 14].

CS manifests differently depending on the location and extent of the granulomas; however, the most prevalent initial symptoms are high-grade atrioventricular block and ventricular arrhythmias. Re-entry circuits in inflamed and

Table 1. Characteristics of the included articles evaluating FDG-PET/CT and CMR for CS diagnosis

Study (year)	Study type	Study population	Total number of patients	Mean of age, year ± SD (IQR)	Gender, male (%)	LVEF (%)	Conclusion
Greulich et al. (2022)	Prospective cohort study	Known extra CS and suspected CS	43 (36 cases with CS)	48 (37-57)	28 (65%)	64 ± 6	Results from the hybrid FDG-PET/CMR showed that out of 36 individuals, 13 (36%) had active CS, 5 (14%) had chronic CS, and 18 (50%) had no CS at all. In summary, the findings of this study showed that the hybrid FDG-PET/CMR improves the diagnosis of individuals with active CS.
Cheung et al. (2021)	Prospective cohort study	Known or suspected CS	42	53 ± 13	28 (67%)	52 ± 11	This investigation found that the diagnostic specificity of co-localizing focal FDG uptake with elevated T2, elevated T2, co-localizing focal FDG uptake with LGE or higher T1, and focal FDG uptake for CS were 83%, 79%, 76%, and 69%, respectively.
Mathijssen et al. (2021)	Retrospective cohort study	Known or suspected CS	35	52.5 ± 12.7	26 (74.3%)	60	Overall, they discovered that repeated CMR and FDG PET/CT scans may be useful in confirming or refuting the initial diagnosis of CS when it is unclear.
Kebed et al. (2021)	Retrospective cohort study	Known VT that suspected for CS	67	60 ± 12	50 (75%)	44 ± 14	The LGE demonstrated a negative predictive value of 100% in relation to ventricular arrhythmia, whereas the FDG demonstrated a negative predictive value of 79% in the same regard. There was no correlation between FDG uptake and an increased incidence of ventricular arrhythmia in FDG-PET evaluations of CS patients who tested positive for LGE.
Okune et al. (2020)	Retrospective cohort study	Known or suspected CS	74	63.8 ± 12.8	39 (52.8%)	43.3 ± 14.9	Fusion PET/CMR imaging demonstrated an overall accuracy of 87.8% in diagnosing CS, superior to the diagnostic accuracy achieved with PET alone (82.4%). Even after analyzing the diffuse and focal patterns versus diffuse patterns alone, fusion PET/CMR imaging maintained superior accuracy (81.8%).
Gowani et al. (2020)	Retrospective cohort study	Known CS	50	53 ± 14	29 (58%)	53 ± 14	The LGE demonstrated a negative predictive value of 100% in relation to ventricular arrhythmia, whereas the FDG demonstrated a negative predictive value of 79% in the same regard. There was no correlation between FDG uptake and an increased incidence of ventricular arrhythmia in FDG-PET evaluations of CS patients who tested positive for LGE. Overall, they found that CMR may be the recommended initial clinical risk classification technique for CS patients.

IQR: Interquartile range, CS: Cardiac sarcoidosis, LVEF: Left ventricular ejection fraction, CMR: Cardiac magnetic resonance, FDG-PET: Fluorodeoxyglucose positron emission tomography, CMR: cardiac magnetic resonance, LGE: Late gadolinium enhancement.

scarred cardiac regions cause sustained ventricular tachycardia, but automatic and triggered arrhythmias are also possible [15]. There are numerous ventricular tachycardia morphologies. Heart failure is characterized by extensive LV infiltration and systolic dysfunction; however, restricted filling caused by edematous or fibrotic LV walls can also play a role. Mitral regurgitation can be caused by scarred LV wall restriction impeding valve closure, LV or mitral annular dilatation, or granulomas invading the leaflets of the valve. RV infiltration can be mistaken for arrhythmogenic right ventricular cardiomyopathy [16]. Although atrial fibrillation is uncommon at the onset, its incidence significantly increases over time [17]. Angina-like chest pain can arise and is mainly attributable to decreased coronary flow reserve due to myocardial microvasculature compression [18]. Nevertheless, granulomatous coronary arteritis may also manifest, and in uncommon cases, CS may precisely resemble an acute myocardial infarction, manifesting as dissection or total occlusion of a single coronary artery or normal findings on angiography. Extraordinary manifestations include effusive and constrictive pericarditis [19, 20].

Diagnostic approach

Embryomyocardial biopsy (EMB) has a low diagnostic yield overall. EMB is also unsuitable for therapeutic monitoring. Consequently, ^{18}F-FDG-PET/CT and CMR have emerged as potential new "gold standard" approaches to CS diagnosis [3]. It is recommended that every person with extra-CS have an electrocardiogram (ECG) and a transthoracic echocardiography (TTE) with a longitudinal strain study [21]. Conduction disorders are linked to an increased risk of sudden cardiac death. Furthermore, ambulatory ECG monitoring and high-sensitivity cardiac troponin T (hs-cTnT), serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), CMR, and ^{18}F-FDG PET/CT are recommended for patients who present with cardiac symptoms (including palpitations, pre-syncope, and syncope) or exhibit aberrant ECGs [22]. Limited evidence suggests that early immunosuppressive medication may be beneficial. Other TTE features that may indicate CS include anomalies in regional wall motion, the presence of wall aneurysms, thinning of the basal septum wall, and a decreased left ventricular ejection percentage (LVEF) [23].

CMR imaging

CMR is regarded as the primary approach in CS evaluation owing to its exceptional spatial resolution, capacity to characterize tissues, and ability to assess the structure and function of the heart. The main advantage of CMR in detecting CS is the ability to identify patchy foci of LGE in the myocardium. LGE foci are typically distributed along the insertion sites of the RV and sub-epicardial or mid-myocardial regions (non-ischemic pattern). Furthermore, LGE is linked to a higher risk of all-cause death and ventricular arrhythmia in CS [24].

Gadolinium is classified as an extracellular contrast agent due to its ability to be extensively removed from healthy regions of the myocardium [25]. Nevertheless, the presence of scarring or inflammation-induced extracellular expansion may result in the dilation of the extracellular space, which subsequently inhibits the gadolinium's removal and enhances the T1 signal. A widespread misconception is that LGE always implies an irreparable scar [26]. As a result, LGE alone is insufficient for distinguishing between active and dormant illnesses. Although T2-weighted imaging has the capability to identify edema and inflammation, its sensitivity is compromised by artifacts and a low signal-to-noise ratio [27, 28]. According to a study by Zhang et al., CMR-LGE had an overall sensitivity and specificity of 93% and 85% for diagnosing CS [29].

^{18}F-FDG-PET/CT scanning

FDG-PET is now frequently used to assess sarcoidosis infiltration in the myocardium. FDG is a glucose analog whose absorption is linked to the expression of glucose transporters (GLUTs) [30]. The elevated levels of GLUT in inflammatory cells, including macrophages, lymphocytes, and granulocytes, are responsible for the enhanced uptake of FDG in inflammatory diseases such as sarcoidosis [31].

In order to better observe FDG uptake in the afflicted myocardium and decrease myocardial glucose absorption, patients must be properly prepared. A high-protein, high-fat diet is recommended for patients preparing for ^{18}F-FDG PET/CT in cases of cardiac sarcoidosis the day before the procedure. The last meal before the scan should be consumed by 5 pm the night before. Additionally, patients can fast for 18 hours before their appointment. Enhanced image quality, improved patient adherence, and blood pool glucose suppression were all outcomes of this protocol. It is recommended that communication with the patient be established 48 hours before the imaging procedure and that written instructions be provided to ensure adequate preparation. In addition to fasting and receiving heparin before ^{18}F-FDG administration, research has shown that a low-carbohydrate or no-carbohydrate meal can effectively limit the normal myocardium's uptake of ^{18}F-FDG. It is critical to minimize the number of patients whose appointments must be rescheduled due to non-compliance with the preparation protocol, as this may burden the patients impacted [32, 33]. **Figure 2** demonstrates a 22-year-old man, a known case of sarcoidosis, who underwent a whole body ^{18}F-FDG PET/CT for idiopathic sustained ventricular tachycardia with suspected cardiac involvement.

Overall, ^{18}F-FDG PET/CT sensitivity and specificity were 84% and 83%, respectively; however, there was a lot of variation throughout the included trials, which was probably caused by the preparation techniques employed. A prolonged risk of serious adverse cardiovascular events (MACE) was linked to an abnormal ^{18}F-FDG-PET result
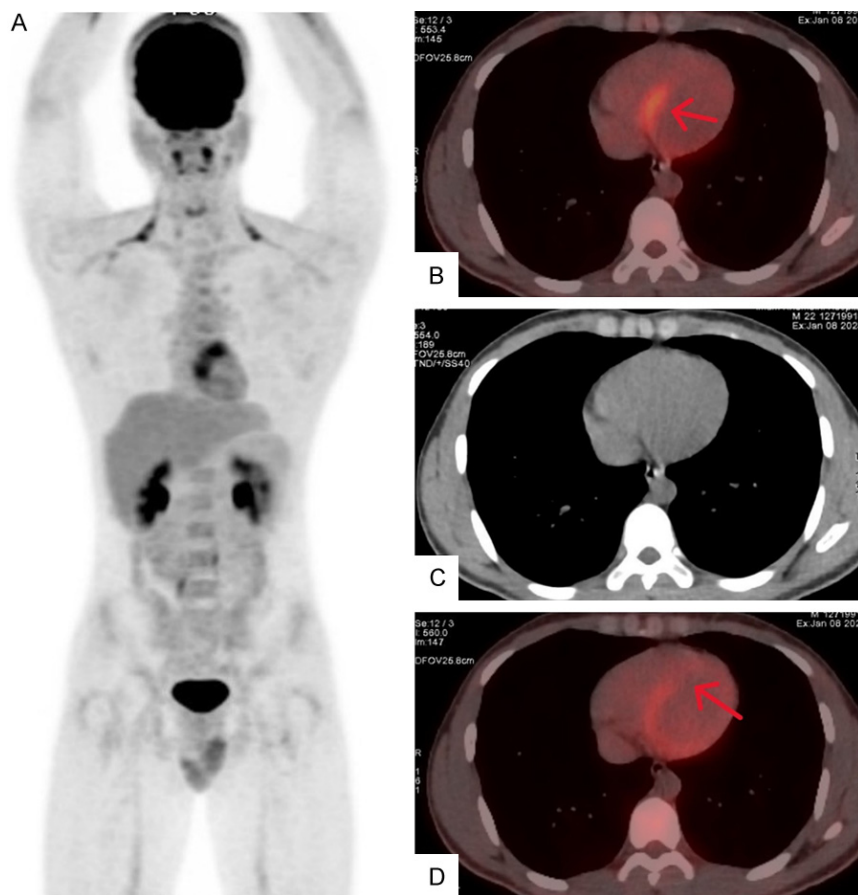
Figure 2. A: A 22-year-old man who was a known case of sarcoidosis underwent a whole body 18F-FDG PET/CT for idiopathic sustained ventricular tachycardia with suspected cardiac involvement. B-D: Patchy increased metabolic activity in the left ventricle middle to basal segment of septum extending to anteroseptal and inferoseptal segments (SUVmax up to 5.9); considering 18 hours fasting, the PET/CT scan is suggestive of the active inflammatory process (sarcoidosis).

[33]. In addition, serial surveillance of patients during therapy employs 18F-FDG-PET to distinguish between responders and non-responders, thereby excluding those who might benefit from intensification or tapering of immunosuppressive therapy. Furthermore, a decrease in 18F-FDG uptake at long-term follow-up was substantially linked with fewer MACE [34]. In 2022, Nakata et al. studied 231 individuals with FDG PET data, including 150 with sarcoidosis histology in any organ and 37 with CS-compatible myocardial histology. The higher percentages of positive cardiac FDG uptake results (89% and 83% for the histological CS and the clinical CS, respectively) demonstrated the high diagnostic accuracy of this technique and the revised recommendations, even in the absence of cardiac histology. In another investigation, Kim et al. [35] conducted a study that analyzed 17 other studies involving 891 patients. They found that the pooled sensitivity of these studies was 84%, while the specificity was 83%. However, the results of sensitivity and specificity varied considerably due to methodological differences among the studies.

Information regarding the time of serial follow-up in patients whose 18F-FDG PET/CT scans are positive is lim-

ited. However, a limited number of case reports and studies indicated that an initial response could be detected three months following the beginning of immunosuppressive therapy. As a result, serial imaging at three, six, and twelve months is feasible. Ten to fifteen percent of 18F-FDG PET/CT scans are inconclusive, and the primary drawbacks are the relatively high cost and radiation exposure [33, 36].

Evaluating the utilization of CMR and 18F-FDG PET/CT for CS

Advanced imaging techniques influence prognosis, assist in therapy direction, and improve diagnostic yield. CMR and FDG-PET/CT imaging have complementary roles in the diagnosis and therapy of CS because they assess somewhat distinct features of the disease. CMR is an ideal initial screening test due to its enhanced specificity, negative predictive value, and capacity to assist in the exclusion of alternative diagnoses. FDG-PET/CT imaging is recommended when the CMR is ambiguous or negative and there is a strong clinical suspicion, or when the CMR indicates a high probability of CS, in order to detect active inflammation and consider additional treatment. It is useful to assess therapy response using FDG-PET/CT imaging and indices such as the Standard Uptake Value, which reflect a decrease in the severity and extent of myocardial inflammation.

In 2021, Cheung et al. [37] conducted a study with the aim of assessing the diagnostic and prognostic value of integrating T1 and T2 mapping of CMR and cardiac FDG-PET/CT when suspected CS was present. This investigation found that the diagnostic specificity of co-localizing focal FDG uptake with elevated T2, elevated T2, co-localizing focal FDG uptake with LGE or higher T1, and focal FDG uptake for CS were 83%, 79%, 76%, and 69%, respectively. The highest diagnostic sensitivity was observed in the presence of LGE, increased T1, and increased extracellular volume. Results showed the best overall diagnostic performance for focal FDG uptake when it was co-localized with LGE or elevated T1.

In 2020, Gowani et al. [38] evaluated the use of FDG-PET and CMR for the prediction of ventricular arrhythmias in CS patients. At 4.1 years of follow-up, the main outcome was ventricular arrhythmia, which was defined as sudden cardiac death, ventricular fibrillation, sustained ventricular tachycardia, or any appropriate device tachytherapy. The LGE demonstrated a negative predictive value of

100% in relation to ventricular arrhythmia, whereas the FDG demonstrated a negative predictive value of 79% in the same regard. There was no correlation between FDG uptake and an increased incidence of ventricular arrhythmia in FDG-PET evaluations of CS patients who tested positive for LGE. Subsequent ventricular arrhythmia was also associated with a significant risk of developing LVEF less than 35% or a history of prior ventricular arrhythmia. They found that CMR may be the recommended initial clinical risk classification technique for CS patients.

In 2020, Okune et al. [39] examined the accuracy of combining FDG-PET/CT and CMR for active CS diagnosis. The study included 74 suspected CS cases. Twenty individuals had active CS mismatch evaluations between PET and fusion PET/CMR imaging; PET alone imaging showed diffuse or focused FDG uptake patterns in the majority of these instances. Fusion PET/CMR imaging demonstrated an overall accuracy of 87.8% in diagnosing CS, superior to the diagnostic accuracy achieved with PET alone (82.4%). Even after analyzing the diffuse and focal patterns versus diffuse patterns alone, fusion PET/CMR imaging maintained superior accuracy (81.8%). In conclusion, the authors discovered that fusion PET/CMR imaging does an excellent job of characterising, differentiating, and visualising the distribution of burnout scars and current inflammation. As a result, it may be able to distinguish between individuals with active CS and those with false-positive FDG uptake, providing a more reliable diagnostic for active CS.

In 2021, Mathijssen et al. [40] assessed 35 individuals with a probable CS diagnosis who underwent subsequent FDG-PET/CT and CMR scans within a year of diagnosis. At baseline, eleven patients (31.4%) showed LGE (CMR+) and 26 (74.3%) patients showed myocardial FDG uptake (PET+). At re-evaluation, nine patients (25.7%) showed LGE, while 16 patients (45.7%) showed myocardial FDG-uptake. When considering both imaging modalities together, 82.6% of patients with CMR-/PET+ at baseline were reclassified as possible or unlikely CS, while 36.4% of patients with CMR+ at baseline were reclassified as probable CS. Three patients with initial CMR-/PET+ showed LGE at re-evaluation. Overall, they discovered that when the initial diagnosis of CS is uncertain, repeated CMR and FDG PET/CT may be beneficial in establishing or rejecting the diagnosis.

In 2022, Greulich et al. [41] examined the diagnostic value of hybrid CMR and FDG-PET for differentiation of active from chronic CS. Results from the hybrid FDG-PET/CMR scans showed that out of 36 individuals, 13 (36%) had active CS, 5 (14%) had chronic CS, and 18 (50%) had no CS at all. LGE was detected in 14 patients (39%); 10 (27%) had abnormal T1 mapping, and 2 (6%) had abnormal T2 mapping. Of the 18 CS patients (22%) who tested negative for LGE, 4 were diagnosed with CS via abnormal T1 mapping. FDG-PET uptake was detected in 17 (47%) of the patients. In summary, the findings of this study

showed that the hybrid FDG-PET/CMR improves the diagnosis of individuals with active CS.

In 2020, Kebed et al. [42] conducted a study on 67 patients with ventricular arrhythmias to evaluate the prevalence of CS in these group by complementary use of CMR and FDG-PET scan. LGE was present in 45 patients (67%), but only 4 (6%) demonstrated myocardial FDG uptake. FDG uptake was observed in 9% of patients with LGE but not in any of those without LGE; 10% of the cohort demonstrated indeterminate FDG uptake, most likely due to inadequate dietary preparation. 3/4 of individuals with both FDG uptake and LGE were eventually diagnosed with CS. According to their findings, 4.5% of cases with ventricular arrhythmias who have no prior history of sarcoidosis or current ischemic heart disease have newly diagnosed CS. As a result, adopting a CMR initial approach and then FDG-PET can improve the identification of CS for patients with non-ischemic LGE.

In a study conducted by Wisenberg et al. [43], they found that the images produced by FDG-PET/CMR exhibited diagnostic quality that was equivalent to or superior to the images obtained using either FDG-PET/CT or CMR images. The ^{18}F-FDG PET/MRI scans showed superior image quality and more excellent uptake definition. It may have been because all FDG-PET/CMR scans were done after the FDG-PET study, when the tracer was cleared from circulation, and because a longer acquisition period was used to correct for decay.

Overall, it is predicted that the preferred imaging modality for CS will soon be combined with FDG-PET imaging rather than standalone CMR or PET imaging. The diagnostic potential of this integrated approach for active CS is substantial, as it offers supplementary insights into the progression of injury and disease. Research has examined the diagnostic use of concurrent hybrid CMR and FDG-PET imaging, and it has been discovered to be an effective means of distinguishing between active and chronic CS [44].

Despite the advantages listed above, hybrid FDG-PET/CMR imaging for CS has several limitations. Some patients may find the cost of combining CMR and FDG-PET imaging prohibitive, as it may be more expensive than the use of either CMR or FDG-PET imaging alone. CMR may be contraindicated in some patients due to the presence of certain pacemakers or other medical devices. As an alternate method for diagnosing CS, FDG-PET with resting cardiac perfusion imaging can be utilized in such instances [45]. Although there is evidence that hybrid FDG-PET/CMR imaging can effectively distinguish between active and chronic CS, its specificity and sensitivity may differ among patients and clinical environments. Hybrid FDG-PET/CMR imaging necessitates access to specialized software and apparatus, in addition to a high level of proficiency in both approaches. This may restrict its availability in specific areas or hospitals.

Ionizing radiation exposure is a part of FDG-PET imaging, which some patients may find concerning [6]. Despite the possible dangers of radiation exposure, the advantages of hybrid FDG-PET/CMR imaging may surpass them when it comes to better diagnosis and treatment planning [8].

Conclusion

The use of hybrid FDG-PET/CMR scans has demonstrated promise in the diagnosis, evaluation of disease activity, monitoring of therapeutic response, and prognosis of CS. The utilization of these two imaging modalities can enhance the sensitivity of the diagnosis during the initial sub-clinical phases of the disease and clarify decisions regarding patient management by providing complementary information. While hybrid FDG-PET/CMR imaging holds promise for the diagnosis and differentiation of CS, there are several limitations that should be considered, including cost, contraindications, sensitivity and specificity, expertise and availability, and radiation exposure. In order to assess the increased usefulness of hybrid FDG-PET/CMR for the thorough evaluation of CS, more research regarding the medical implications of such advancements is still required.

Disclosure of conflict of interest

None.

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