DOI: 10.7860/JCDR/2024/70573.19571

Review Article

Radiology Section

Role of FDG-PET Radiomics in the Diagnosis of Cardiovascular Inflammation: A Narrative Review

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ABSTRACT

Cardiovascular inflammation plays a key role in atherosclerosis and other cardiovascular complications, highlighting the importance of accurate detection methods. While traditional diagnostic tests have limitations in specificity and timing, 18-Fluoro-Deoxyglucose-Positron Emission Tomography (FDG-PET) imaging offers a non invasive approach to visualise inflammation. Radiomics, the extraction of quantitative features from medical images for analysis with machine learning algorithms, presents an opportunity to enhance the diagnostic accuracy of FDG-PET imaging in detecting cardiac inflammation. Studies investigating radiomics in various cardiovascular inflammatory conditions, including Cardiac Sarcoidosis (CS), Infective Endocarditis (IE), and active aortitis, have shown promising results in improving diagnostic performance. The review discusses the challenges and potentials of radiomics in cardiovascular imaging, emphasising the need for standardisation and validation in advancing personalised diagnosis and treatment strategies for cardiovascular inflammation.

Keywords: Active aortitis, Cardiac sarcoidosis, Diagnostic accuracy, 18-Fluoro-Deoxyglucose Positron Emission Tomography, Infective endocarditis

INTRODUCTION

Cardiac inflammation is a crucial factor in the development and progression of atherosclerosis, as well as other cardiovascular complications. It is recognised as a significant contributor to residual cardiovascular risk in individuals with Atherosclerotic Cardiovascular Disease (ASCVD) [1]. Moreover, inflammation plays a role in cardiac and cerebral damage, as well as in the healing process following events like myocardial infarction or stroke [2]. Understanding and effectively targeting inflammation in cardiovascular pathologies is therefore essential for personalised prevention and treatment strategies.

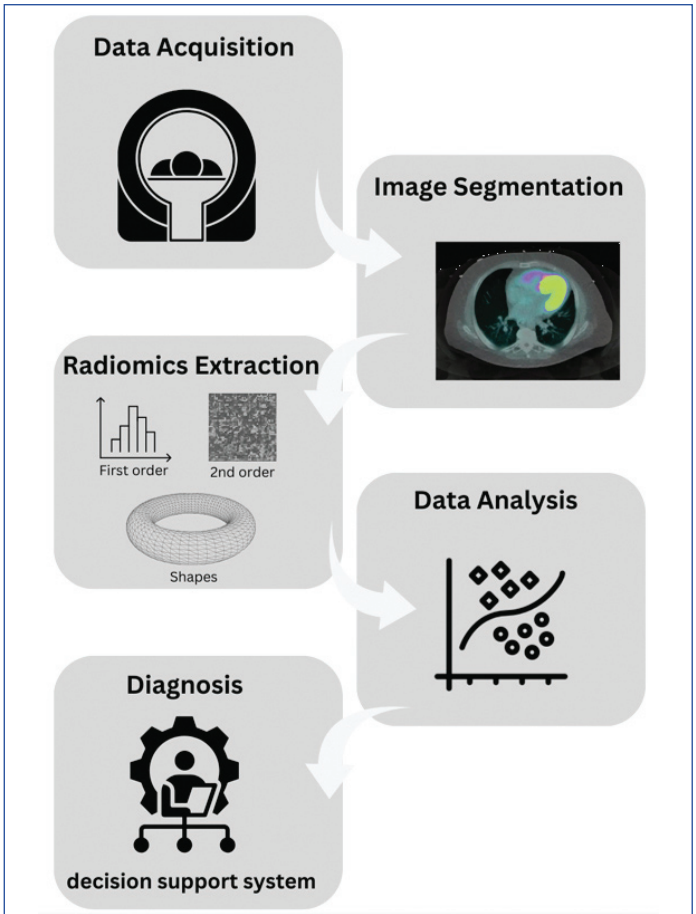
However, current diagnostic methods for cardiac inflammation have their limitations [3]. While several tests such as cardiac troponin I and examination of intracellular cardiac proteins have been utilised, they do not provide a definitive diagnosis with absolute precision [4]. These tests lack specificity, as elevated levels of cardiac troponin I or intracellular proteins can be observed in conditions other than cardiac inflammation, leading to false-positive results [4]. Additionally, the timing of testing can be critical, as these markers may not be immediately elevated after the onset of inflammation, potentially resulting in false-negative results [4]. These methods may be further complicated by the declining proficiency in cardiac auscultation skills, which were once relied upon for diagnosing cardiac conditions [5]. Therefore, it is important to continue developing and improving diagnostic methods to ensure accurate and precise detection of cardiac inflammation.

The utilisation of 18-Fluoro-Deoxyglucose Positron Emission Tomography (FDG-PET) imaging holds significant promise in enhancing the diagnosis of cardiac inflammation [6]. By visualising increased glucose metabolic rates in infarcted segments using PET imaging with FDG, inflammation can be detected non invasively [7]. This imaging technique offers a more comprehensive evaluation of the inflammatory response, providing valuable insights into the extent of inflammation. FDG-PET can also aid in the diagnosis of conditions such as Cardiac Sarcoidosis (CS) and Infective Endocarditis (IE) by identifying active inflammation [8].

The FDG-PET presents several advantages in diagnosing cardiac inflammation; however, it also comes with challenges. The current standard radiotracer, FDG, cannot differentiate between glucose uptake in normal cardiomyocytes and inflammatory cells [7]. However, radiomics offers a potential solution to this issue. Radiomics involves extracting quantitative features from FDG-PET images and analysing them using machine learning algorithms [9]. By studying large sets of data, radiomics enables the identification of meaningful patterns and relationships, which can aid in differentiating between normal and inflamed cardiac tissue [10]. This approach can enhance the diagnostic accuracy of FDG-PET imaging in cardiac inflammation.

Radiomics is a new field in medical imaging that involves the extraction of quantitative features from medical images. It aims to find clinically relevant image-derived biomarkers for lesion characterisation, prognostic stratification, and response prediction. In the context of FDG-PET imaging, radiomics focuses on quantifying radiotracer uptake heterogeneity and other tissue characteristics [11]. FDG-PET imaging with radiomics has the potential to provide valuable information about tissue biology that is not visible to the naked eye [12]. It can contribute to precision medicine by aiding in the detection and staging of cancer or active inflammations, as well as in the diagnosis, treatment, and molecular typing of breast cancer [13]. Radiomic models built using FDG-PET imaging can help to improve the diagnostic accuracy, risk stratification, and follow-up of patients with various cardiovascular diseases, such as coronary heart disease, ischaemic heart disease, hypertrophic cardiomyopathy, and hypertensive heart disease [14].

Radiomic features can be extracted from FDG-PET images using the following steps. First, the images are segmented to identify the Regions of Interest (ROIs) using techniques such as Convolutional Neural Networks (CNN) [15]. Once the ROIs are identified, radiomic features are extracted from the segmented data. These features can include Standardised Uptake Value (SUV) metrics and other quantitative measurements [16]. Various methods can be used to extract these features, including handcrafted features and deep-learning approaches [17]. The extracted features are then harmonised to ensure consistency and comparability across different datasets [18]. Finally, machine learning classifiers can be used to analyse the radiomic features and predict specific outcomes, such as prognosis or treatment response [19]. Overall, the process involves segmentation, feature extraction, harmonisation, and analysis using machine learning techniques [Table/Fig-1].



[Table/Fig-1]: Radiomics framework.

Radiomics in Cardiovascular Inflammation

There have been limited studies conducted to investigate the potential value of radiomics in enhancing the diagnosis of various cardiovascular inflammatory conditions. Summary of the key findings of few recent studies are presented in [Table/Fig-2] [20-24].

Cardiac Sarcoidosis (CS): CS is a rare condition characterised by the infiltration of the heart's myocardium by granulomas [25]. This inflammatory disorder is part of the broader condition known as sarcoidosis, which can affect multiple organs in the body [25]. CS specifically involves inflammation in all layers of the heart, particularly the myocardium [25].

Clinical manifestations of CS can vary from asymptomatic conduction abnormalities to severe heart failure and even sudden cardiac death [26]. Diagnosing CS can be difficult, as there is a lack of definitive diagnostic criteria and the clinical symptoms can be ambiguous [27]. However, PET can help identify and assess the extent of myocardial inflammation [28].

In Mushari NA et al., (2022) study, the researchers aimed to investigate the potential of radiomic feature extraction from PET images for enhancing the diagnostic accuracy of CS using FDG-PET [22]. The study involved 40 sarcoidosis patients and 29 controls who underwent FDG-PET imaging to identify active CS. For analysis, two different segmentations, namely Segmentation A and Segmentation B, were employed. In Segmentation A, the myocardium's ROIs were manually delineated based on regions with SUV exceeding 2.5, indicating heightened metabolic activity. This method aimed to isolate and analyse areas of active disease by distinguishing them from normal myocardial tissue. By focusing on areas with elevated tracer uptake, particularly those with SUV exceeding 2.5, the aim was to evaluate the presence and extent of CS. Elevated SUV values in PET imaging typically signify regions with increased metabolic activity, often associated with inflammatory processes or active disease states such as CS. On the other hand, in Segmentation B, an ROI was drawn on the entire left ventricular myocardium for both study groups [22].

Conventional metrics and radiomic features were extracted from the PET images for each ROI. Subsequently, a Mann-Whitney

Study	Objectives	Study Characteristics	Analysis	Conclusion
Duff L et al., [20], 2022	Develop radiomic imaging biomarkers for assisted diagnosis of active aortitis using FDG-PET images	Radiomic features and SUV metrics were extracted from images of 50 patients with aortitis and 25 controls	The study utilised Sci-kit Learn for machine learning algorithms and PCA to determine the number of components needed to explain 90% of the variance in radiomics signatures	The study proposed a radiomic method for aiding the diagnosis of aortitis with promising results, suggesting further validation for automated and standardised diagnosis
Erba P et al., [21], 2022	Assess the value of FDG-PET radiomics in diagnosing IE, building predictive models, classifying patients, and predicting final diagnosis using radiomics data	- Evaluated FDG-PET scans in 447 patients suspected of IE - Conducted at 3 different centres - Data collected from January 2015 to 2020	- FDG-PET and LIFEx software were used in 447 patients suspected of IE - Texture features and radiomics aided in predicting diagnosis and stratifying disease severity - Multivariate testing with MANOVA and LR improved diagnostic performance	FDG-PET radiomics has a positive impact on classifying IE but more work is needed to refine diagnostic criteria and identify key radiomic signatures
Mushari NA et al., [22], 2022	Evaluate the utility of radiomic features from PET images for detecting CS through comparison with conventional metrics and machine learning techniques	- 40 sarcoid patients, 29 controls had FDG PET-CMR scans	- Two segmentations used for analysis, conventional metrics and radiomic features extracted from each - PCA with five components, testing and training 10 ML classifiers	- PET radiomic analysis may not detect CS effectively - Some radiomic features unrelated to tracer uptake had high AUC and accuracy - TBR max outperformed other features. - More validation needed in normal control subjects with non specific uptake
Duff LM et al., [23], 2023	Develop and validate an automated radiomic pipeline for diagnosing active aortitis	- Training cohort: 43 aortitis patients, 21 control patients - Test cohort: 12 aortitis patients, 5 control patients - Validation cohort: 24 aortitis patients, 14 control patients	An automated radiomic pipeline, using PyRadiomics for feature extraction and Sci-kit Learn for ML classifiers, was developed and validated for diagnosing active aortitis	The findings suggest that the radiomic pipeline can be generalisable and transferable - The pipeline could be used to build an automated clinical decision tool
Godefroy T et al., [24], 2023	Evaluate the performance of a radiomics and machine learning-based analysis of FDG-PET in diagnosing PVE	- Retrospective, single-centre design used - Expert consensus as diagnostic gold standard - Training and hyperparameter tuning with cross-validation - Evaluation on independent test database	- Manual segmentation of each PV and extraction of 31 radiomics features - Training of a ridge logistic regressor to predict PVE	- ML analysis of FDG-PET in PVE diagnosis is feasible and beneficial - ML improves the performance of ESC 2015 criteria for PVE diagnosis - Further developments are needed to optimise the role of FDG-PET in PVE diagnosis

[Table/Fig-2]: Summary of FDG-PET radiomics studies on cardiac inflammation [20-24].
AUC: Area under the curve; CMR: Cardiac magnetic resonance; CS: Cardicac sarcoidosis; IE: Infective endocarditis; ESC: European Society of Cardiology; FDG-PET: 18-Fluoro-deoxyglucose-positron emission tomography; LR: Logistic regression; MANOVA: Multivariate analysis of variance; ML: Machine learning; PCA: Principal component analysis; PVE: Prosthetic valve endocarditis; SUV: Standrised uptake value; TBR: Tissue-to-background ratio

U-test and logistic regression classifier were utilised to compare the extracted features between the study groups. Additionally, Principal Component Analysis (PCA) was employed to identify five components with cumulative variance greater than 90% [22].

The researchers tested and trained ten different machine learning classifiers, calculating the Area Under the Curve (AUC) and accuracy values for each classifier. The PyRadiomics software was used to extract a total of 75 features from the PET image ROIs, adhering to the Image Biomarker Standardisation Initiative (IBSI) feature definitions [22]. The findings indicated that the maximum Target-to-Background Ratio (TBRmax) exhibited superior performance compared to other conventional and radiomic features in both segmentation approaches, demonstrating high AUC and accuracy values [22].

For segmentation A, all classifiers displayed strong performance with AUC and accuracy values ranging from 0.88 to 1.00 (95% CI) and 0.87 to 1.00 (95% CI), respectively. The k-nearest neighbours and neural network classifiers performed exceptionally well, exhibiting AUC and accuracy values of 1.00 [22].

In segmentation B, four classifiers achieved AUCs and accuracies equal to or greater than 0.8. Among these classifiers, the Gaussian process classifier exhibited the highest AUC and accuracy values, namely 0.9 and 0.8, respectively [22].

Overall, these results provide compelling evidence for the effectiveness of TBRmax as a metric for distinguishing between CS patients and controls, showcasing high diagnostic accuracy and performance across different segmentation approaches.

Endocarditis: Infectious Endocarditis (IE) is a heart infection that affects the heart valves and endocardium [29]. It can manifest as acute, subacute, or chronic and is characterised by vague symptoms like fever, malaise, anaemia, and embolic complications [29]. Due to the similarity of symptoms with other diseases, delayed diagnosis is common. IE can lead to serious complications such as heart failure, stroke, nonstroke embolisation, and intracardiac abscess [30]. The diagnosis of IE is primarily based on patient risk assessment, with the modified Duke criteria being the most widely accepted tool [31]. Laboratory tests often yield non specific results, making IE primarily a clinical diagnosis. Procalcitonin can be used as a diagnostic aid, but it lacks specificity for IE [30]. Prosthetic Valve Endocarditis (PVE) is a specific form of IE that occurs in individuals with artificial heart valves. It can be caused by various bacteria, including *Neisseria elongata*, and can have significant consequences for patients [32].

Two studies explored the potential of radiomics and machine learning-based analysis of FDG PET/CT scans in the diagnosis of cardiac inflammation diseases, specifically IE and PVE [21,24]. These studies, collectively suggest that integrating radiomics and machine learning-based analyses with FDG PET/CT scans holds promise for enhancing the diagnosis and management of cardiac inflammation diseases, particularly IE and PVE.

The first study by Erba P et al., assessed the value of radiomics in diagnosing IE. They found that radiomics provided a positive contribution in predicting PET/CT results and IE diagnosis. Specifically, radiomics supported visual imaging assessment in 85% of cases with ambiguous findings. However, its contribution in classifying IE was limited, achieving an accuracy of only 64% [21].

In the second study, conducted by Godefroy T et al., the focus was on PVE diagnosis. They utilised a combination of radiomics and machine learning analysis on FDG PET/CT scans. The findings revealed promising results, demonstrating the feasibility and benefits of this approach. Machine learning analysis improved the specificity of PVE diagnosis from 74% to 90%, and it helped reduce interobserver variability significantly, with an agreement increase from 42% to 85% [24].

Active aortitis: Active aortitis, characterised by inflammation of the aorta in the absence of systemic vasculitis or infection, poses diagnostic challenges, particularly due to its often late detection and non specific routine markers like Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) [33]. Two recent studies investigated the utility of radiomic analysis derived from PET/CT imaging in diagnosing active aortitis [20,23].

In the study by Duff L et al., a methodological framework was developed for assisted diagnosis of active aortitis using radiomic imaging biomarkers from FDG PET-CT images [20]. The study revealed that selected radiomic features and SUV metrics demonstrated high accuracy and performance in identifying active aortitis, comparable to qualitative assessment. Notably, individual radiomic features achieved high accuracy and AUC scores (84% to 86%; 0.83 to 0.97) while radiomic signatures also showed promising AUC scores (0.80 to 1.00). The Grey Level Size Zone Matrix (GLSZM) non-uniformity normalised feature measures heterogeneity in the size of zones within an image. It quantifies the differences in zone sizes, indicating the level of irregularity in their distribution. This feature effectively differentiated active aortitis from controls. The study suggested the potential of a machine learning-based approach using radiomic signatures to develop a clinical decision-making tool for aortitis assessment [20].

In a subsequent study by Duff LM et al., an automated pipeline for diagnosing active aortitis through radiomic analysis was developed [23]. This pipeline incorporated a CNN for automated aorta segmentation and extraction of radiomic features for diagnostic evaluation. Three distinct radiomic fingerprints were constructed, demonstrating high diagnostic performance across multiple datasets and indicating generalisability. The results highlighted the potential of the automated pipeline, including CNN segmentation, radiomic analysis, and ML classifiers, in creating an automated clinical decision tool for standardised assessment of active aortitis.

In conclusion, these studies underscored the potential of radiomic analysis in aiding the diagnosis of active aortitis. The findings suggest that radiomic features and automated pipelines have the capacity to deliver precise and reliable diagnostic information, potentially paving the way for enhanced diagnostic tools for this complex condition.

DISCUSSION

Radiomics has shown its potential in PET/CT imaging by quantifying radiotracer uptake heterogeneity and other tissue characteristics [34]. The studies reviewed herein demonstrate the ability of radiomic features and SUV metrics to provide quantitative analysis that can potentially overcome the subjectivity and variability inherent in traditional imaging interpretation.

However, the findings also point to challenges in translating radiomic and machine learning approaches into clinical practice. For example, while radiomics provided a positive contribution in predicting PET/CT results in IE, its accuracy was limited [21]. Such findings suggest that while radiomic features hold promise, they may not be sufficient alone and should be integrated with clinical and other diagnostic data for optimal results.

In PVE diagnosis, the integration of machine learning analysis improved specificity and reduced interobserver variability significantly [24]. This aspect is particularly important considering that interobserver variability can lead to inconsistent diagnosis and treatment plans. By improving diagnostic specificity and agreement among clinicians, patient care can be substantially improved.

The advancements in diagnosing active aortitis using radiomic imaging biomarkers and machine learning-based approaches indicate a shift toward more objective and reproducible diagnostic tools [20,23]. Such tools could lead to earlier detection and better monitoring of disease progression, which is crucial for conditions like active aortitis, where late detection can have significant consequences for patient outcomes.

Despite these promising developments, it is important to acknowledge the limitations and challenges that must be addressed before widespread adoption in clinical practice can occur. These include the need for standardisation of radiomic feature extraction, robust validation of machine learning models on large and diverse patient populations, and integration with clinical pathways. Additionally, the computational complexity and need for specialised expertise to implement these techniques may limit their accessibility in some healthcare settings.

Future research should focus on multicentre trials to validate these findings and assess the generalisability of radiomic and machine learning models across different populations and imaging equipment. Such studies could also explore the integration of radiomics with other biomarkers and clinical data to develop comprehensive diagnostic models. Furthermore, there is a need to develop user-friendly software and protocols to facilitate the translation of these advanced techniques into routine clinical practice.

CONCLUSION(S)

The reviewed literature underscores the significant potential of radiomics and machine learning in improving the diagnosis of cardiovascular inflammatory conditions. These techniques offer a compelling adjunct to traditional imaging and clinical diagnostics, with the potential to enhance patient care through more accurate and timely diagnosis. However, further research and development are needed to overcome current limitations and fully harness the benefits of these advanced technologies in clinical settings.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 07, 2024
- Manual Googling: May 07, 2024
- iThenticate Software: May 10, 2024 (12%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 07, 2024**
Date of Peer Review: **Apr 30, 2024**
Date of Acceptance: **May 13, 2024**
Date of Publishing: **Jun 01, 2024**