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Research Progress in Imaging of Cardiac Amyloidosis

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Abstract

Cardiac amyloidosis (CA) is a progressive disease characterized by extracellular deposition of misfolded proteins, leading to myocardial dysfunction and poor prognosis. Early and accurate diagnosis remains challenging due to nonspecific clinical presentations. This review highlights advancements in multimodality imaging for CA: echocardiography, as a noninvasive, accessible, and cost-effective initial screening tool, enhances diagnostic sensitivity through characteristic strain patterns (e.g., "apical sparing"); computed tomography (CT) quantifies amyloid burden via extracellular volume fraction (CT-ECV), particularly valuable for patients with contraindications to MRI; cardiac magnetic resonance (CMR) excels in phenotyping and prognostic stratification using multiparametric techniques (e.g., late gadolinium enhancement and T1 mapping); and nuclear medicine (SPECT/PET) enables noninvasive subtyping and therapy monitoring through targeted tracers (e.g., ^{99m}Tc-PYP and ^{11}C-PiB). The integration of multimodal imaging significantly improves early diagnosis, subtype differentiation, and prognostic evaluation in CA, providing a foundation for personalized treatment strategies.

Keywords

Cardiac Amyloidosis, Echocardiography, CT, MR, Nuclear Medicine

1. Introduction

Cardiac amyloidosis (CA) is a progressive disease caused by the deposition of misfolded proteins outside the cardiac muscle cells. It mainly includes light chain amyloidosis (AL-CA) and transthyretin amyloidosis (ATTR-CA). Its characteristics are the expansion of the extracellular space of cardiac muscle cells and thickening of the ventricular wall, which can lead to diastolic and systolic dysfunction, and has a poor prognosis. Early diagnosis is crucial for treatment decisions and im-

proving prognosis. With the aging of the population, the incidence of CA is increasing year by year. However, its clinical manifestations lack specificity and often present as heart failure, arrhythmia, hypotension, etc., and are easily misdiagnosed as other types of cardiomyopathy. Currently, pathology remains the "gold standard" for CA, but it is an invasive examination with high risks; imaging techniques are particularly important for the early diagnosis and precise assessment of CA. This article reviews the current application status and research progress of various imaging techniques in CA.

2. Ultrasound

Echocardiography, due to its non-invasive, convenient, and cost-effective nature, is the preferred modality for the initial screening of CA. Conventional echocardiography can provide critical diagnostic clues by identifying characteristic structural features of the heart. Typical findings include symmetric left ventricular hypertrophy (septal thickness ≥ 12 mm), myocardial granular sparkling appearance, diastolic dysfunction (elevated E/e' ratio), and bilateral atrial enlargement [1]. Speckle Tracking Echocardiography (STE) enables quantitative assessment of myocardial strain and significantly enhances the sensitivity of CA diagnosis. A hallmark feature in CA patients is the "apical sparing" pattern, characterized by a marked reduction in longitudinal strain (LS) in the basal and mid segments, while LS in the apical segment remains relatively preserved [2]. Liu *et al.* [3] demonstrated that patients with AL-type CA exhibited significantly lower left ventricular global longitudinal strain (GLS) compared to those with hypertrophic cardiomyopathy (−8.71% ± 2.39% vs. −14.2% ± 4.40%), particularly in the basal segments. Among these, the anterior wall base segment (basal-anterior/lateral) showed the highest diagnostic accuracy (AUC = 0.920).

CA patients may exhibit diverse echocardiographic phenotypes. One studies [4] hclassified it into five subtypes: hypertrophic (HP), restrictive (RP), their mixed form (HP + RP), mixed with reduced ejection fraction (HP + RP + EF < 50%), and mild structural change type (MSC), Patients with HP + RP + EF ≤ 50% were found to have significantly increased ventricular wall thickness and relative wall thickness, along with decreased GLS, indicating a poorer prognosis. Chen *et al.* [5] reported that ATTR-type patients exhibited more pronounced left ventricular wall thickening (septal thickness: 15.7 ± 2.2 mm vs. 13.3 ± 2.0 mm), whereas AL-type patients had worse cardiac function (proportion of NYHA III–IV: 48.6% vs. 19.0%). Another study [6] revealed that AL-CA patients were more prone to perivascular amyloid deposition, presenting with less ventricular remodeling (lower left ventricular mass index and better right ventricular function). Fan *et al.* [7] found that ATTR-type CA patients had significantly higher atrial septal thickness (5.83 ± 0.75 mm vs. 3.83 ± 1.12 mm) and E/e' ratio (35.00 ± 6.60 vs. 23.69 ± 9.98) than AL-type patients, with combined diagnostic sensitivity and specificity reaching 100% and 95.24%, respectively. These differences offer valuable insights for clinical classification and differential diagnosis.

Traditional echocardiography evaluates cardiac function and predicts prognosis through parameters such as left ventricular ejection fraction (LVEF) and left ventricular wall thickness. Studies have shown that reduced LVEF and left ventricular end-diastolic volume (LVEDV) are significantly associated with adverse outcomes in AL-CA patients [8]. However, many patients with myocardial amyloidosis maintain normal LVEF in the early stages, and relying solely on conventional parameters may underestimate disease severity. Cao *et al.* [8] demonstrated that combining left ventricular global longitudinal strain (GLS) and global area strain (GAS) yielded an area under the curve (AUC) of 0.929 for predicting prognosis in AL-CA patients, with sensitivity and specificity of 86.84% and 87.80%, respectively. This suggests that GLS and GAS may serve as key prognostic indicators in AL-CA. Furthermore, three-dimensional speckle tracking technology allows for the evaluation of peak left ventricular torsion angle (Ptw) and global radial strain (GRS), thereby enhancing prognostic accuracy [9]. Wassif *et al.* [10] proposed a risk stratification system based on left ventricular global longitudinal strain (LVGLS ≤ 14%) and left atrial volume index (LAVI ≥ 48 mL/m^2), categorizing ATTR-CM patients into low-, intermediate-, and high-risk groups with survival rates of 100%, 81%, and 63%, respectively. Hazaveh *et al.* [11] introduced a multi-parameter scoring system incorporating tricuspid annular systolic displacement (TAPSE), lateral E' velocity (E' lateral), and left ventricular outflow tract velocity-time integral (LVOT-VTI) for AL-CA patients. Patients were classified into high-risk (score ≥ 4) and low-risk (score < 4) groups, with median survival times of 40 months and over 70 months, respectively. These scoring systems offer practical tools for risk stratification in clinical settings.

Echocardiography also plays a crucial role in monitoring therapeutic response. Patel *et al.* [12] evaluated the efficacy of patisiran in patients with ATTR-CA through a combination of cardiopulmonary exercise testing and exercise echocardiography (CPET imaging). The results showed that the peak oxygen consumption (VO_2), stroke volume (SV), and cardiac output (CO) of the treatment group were significantly improved compared to the untreated group, suggesting that disease-modifying treatment can delay the deterioration of cardiac function. Additionally, the ventilation efficiency (VE/VCO_2 slope) of the treatment group improved, which may reflect the reduction of pulmonary amyloid deposition.

However, echocardiography also has its limitations. Image quality is often affected by the patient's body type and the imaging conditions of the window. In patients with obesity or emphysema, it may be difficult to obtain clear images of the heart. The accuracy of speckle tracking technology depends on the operator's experience and the consistency and standardization of the analysis software. Relative apical strain retention was once considered a specific marker, but recent studies have found that this phenomenon can also occur in diseases such as aortic stenosis, suggesting a decrease in its specificity [13]. Therefore, in order to improve the accuracy of diagnosis, it is still necessary to combine multimodal imaging techniques (such as cardiac magnetic resonance imaging, radionuclide imag-

ing) and related biomarkers for comprehensive assessment.

3. CT

Computed tomography (CT) is less commonly applied in the evaluation of cardiac amyloidosis (CA). It primarily enables quantitative calculation of the extracellular volume fraction derived from CT (CT-ECV), by assessing myocardial tissue attenuation before and after contrast administration, and integrating these measurements with hematocrit levels. This approach reflects the extent of amyloid protein deposition or interstitial fibrosis. Deux *et al.* [14] conducted a prospective study involving 84 CA patients, 43 individuals with non-amyloidotic myocardial hypertrophy, and 33 normative controls without hypertrophy. Their findings demonstrated that the mean CT-ECV was significantly elevated in the CA group compared to the non-amyloid group (54.7% ± 9.7% vs. 34.6% ± 9.1%, $P < 0.001$), with an area under the receiver operating characteristic curve (AUC) of 0.93. Furthermore, a CT-ECV threshold exceeding 56% was associated with increased mortality risk (hazard ratio = 4.2). Similarly, Kidoh *et al.* [15] evaluated 552 patients with suspected heart failure and found that using a cutoff value of 37% for CT-ECV yielded high sensitivity (90%) and specificity (92%) for diagnosing CA (AUC = 0.97). Gama *et al.* [16] reported that CT-ECV values were higher in patients with ATTR amyloidosis compared to those with AL amyloidosis (56% ± 11% vs. 43% ± 13%, $P < 0.001$), and these values correlated with Perugini grades obtained via radionuclide imaging. Hayashi *et al.* [17] compared CT and cardiovascular magnetic resonance (CMR) data in 31 CA patients and observed no significant difference in global ECV between modalities (51.3% vs. 50.0%, $P = 0.172$), with strong segment-wise correlations ($r = 0.77$ - 0.88). Collectively, these studies indicate that CT-ECV demonstrates robust diagnostic performance in distinguishing CA from other forms of myocardial hypertrophy, such as hypertensive cardiomyopathy, and in differentiating disease subtypes. Moreover, CT-ECV shows strong agreement with CMR-ECV. Given its widespread availability, rapid acquisition time, insensitivity to cardiac implantable electronic devices, and high test-retest reliability (intraclass correlation coefficient = 0.852 [18]), CT may serve as a viable alternative to MRI for patients with contraindications to magnetic resonance imaging.

Beyond ECV, CT offers additional diagnostic insights into CA. For example, microvascular dysfunction is commonly observed in CA patients, and CT perfusion imaging enables quantitative evaluation of myocardial hemodynamic alterations. Deux *et al.* [14] reported that both myocardial blood flow (73.2 ± 25.7 mL/100g/min) and blood volume (4.05 ± 0.80 mL/100g) were significantly reduced in CA patients compared to those without amyloidosis ($P < 0.01$). Furthermore, a gradient pattern was observed from the basal to apical myocardial segments, with lower blood flow in the basal regions ($P < 0.001$). Prolonged perfusion parameters, such as time to peak (TTP) exceeding 20 seconds, were linked to adverse clinical outcomes (HR = 11.6), indicating that CT perfusion imaging not

only aids in diagnosis but also provides independent prognostic value. In addition, ATTR amyloidosis frequently coexists with aortic valve stenosis, particularly in elderly patients, making differential diagnosis challenging. Alexios *et al.* [19] applied standard CT angiography (CTA) to extract myocardial radiomic features and achieved high accuracy in identifying ATTR among patients with severe aortic stenosis (AUC = 0.925, 95% CI: 0.825 - 1.000, P = 0.0002). Similarly, Benedikt Bernhard *et al.* [20] utilized conventional 4D cardiac CT to evaluate left ventricular (LV) mass index, global longitudinal strain (GLS) of the LV and left atrium (LA), and relative apical longitudinal strain, demonstrating high diagnostic accuracy for detecting ATTR-CA in this population. Collectively, these findings support CT as a promising non-invasive modality for the screening and auxiliary diagnosis of CA.

Radiation exposure from conventional CT scans has historically been a major concern. However, recent technological advancements offer promising solutions to mitigate this limitation. Dual-energy CT and photon-counting detector CT (PCCT) have streamlined the ECV measurement process by enabling direct calculation of ECV through iodine density mapping without the need for non-contrast acquisitions. This innovation effectively reduces both radiation dose and contrast agent requirements. Furthermore, PCCT improves the accuracy of CT-derived ECV by reducing calcium-related artifacts through high spatial resolution and spectral imaging capabilities. It also allows for concurrent assessment of coronary artery disease (CAD), offering a comprehensive one-stop imaging solution for patients with cardiac amyloidosis (CA) [21]. In addition, a simplified CT-derived biomarker—the myocardium-to-lumen signal ratio—does not require non-contrast CT scans or hematocrit measurements and demonstrates diagnostic performance comparable to CT-ECV (AUC = 0.96 vs. 0.97, P = 0.27) [15]. This index provides a more practical and accessible alternative for clinical applications.

In addition to radiation exposure, the use of iodine-based contrast agents in CT examinations poses potential risks for patients with renal dysfunction and is contraindicated in individuals with known hypersensitivity to contrast media. Although photon-counting computed tomography (PCCT) demonstrates improved capability in reducing calcium-related artifacts, its widespread adoption remains limited by high costs. Moreover, the influence of calcification on diagnostic accuracy cannot be overlooked, highlighting the necessity for further technological optimization.

4. MRI

Cardiac magnetic resonance imaging (CMR), owing to its non-invasive nature, multi-parametric capabilities, and high spatial resolution, not only enables high-resolution soft tissue visualization but also facilitates comprehensive functional assessment. As a result, it has become an essential tool in the diagnosis, subtype differentiation, and prognostic evaluation of CA.

Late gadolinium enhancement (LGE) is currently recognized as the optimal MR

technique for evaluating CA. It generates characteristic enhancement patterns based on differences in the distribution and washout kinetics of gadolinium-based contrast agents between normal and pathological myocardium, thereby reflecting the extent of amyloid deposition and the degree of myocardial fibrosis [22]. The typical LGE pattern includes diffuse subendocardial or transmural enhancement, often accompanied by reduced blood pool signal intensity—a phenomenon referred to as "blood pool washout"—which results from rapid extravasation of contrast into the expanded extracellular space [23]. The LGE pattern varies across disease stages: early-stage disease typically presents with isolated subendocardial enhancement due to subendocardial amyloid deposition, whereas transmural enhancement may indicate more advanced disease, where extensive amyloid infiltration leads to widespread myocardial fiber encasement and irreversible injury [24]. Importantly, LGE findings are strongly associated with clinical outcomes. Patients with positive LGE demonstrate higher mortality rates compared to those without LGE, and individuals exhibiting transmural enhancement have significantly worse survival than those with subendocardial enhancement [25]. Nevertheless, the use of LGE is limited by its reliance on gadolinium-based contrast agents, which pose risks for patients with renal impairment.

LGE provides characteristic morphological information, whereas T1 mapping and extracellular volume (ECV) enable early detection and quantitative assessment of amyloid burden by measuring the longitudinal relaxation time of myocardial tissue and the extent of extracellular matrix expansion. In the study by Daniel Lavall *et al.* [26], native T1 times were significantly prolonged in patients with cardiac amyloidosis (CA) compared to healthy controls. At a cutoff value of 1341 ms, native T1 demonstrated excellent diagnostic performance with 100% sensitivity and 97% specificity, yielding positive and negative predictive values of 88.9% and 100%, respectively. The area under the receiver operating characteristic curve (AUC) was 0.9938 ($P < 0.0001$), indicating high diagnostic accuracy.

ECV is calculated based on changes in myocardial and blood pool T1 values before and after contrast administration using the formula: ECV = (1 − hematocrit) × [Δ(1/T1) myocardium/Δ(1/T1) blood pool]. This parameter directly quantifies the degree of extracellular space expansion and correlates positively with myocardial amyloid load. A meta-analysis of 955 patients showed that each 60 ms increase in native T1 was associated with a 33% higher risk of mortality, while each 3% increase in ECV corresponded to a 16% greater risk [27]. Furthermore, a follow-up study of AL-CA patients undergoing chemotherapy revealed that those with favorable treatment responses exhibited reductions in ECV, suggesting regression of amyloid deposition [23]. These findings collectively highlight the significant role of T1 mapping and ECV in the diagnosis, prognostic stratification, and monitoring of therapeutic response in CA.

Notably, ECV measurements in extracardiac organs such as the spleen and liver show strong correlations with myocardial ECV [28], suggesting their potential utility as non-invasive markers for systemic amyloid involvement. However, ECV

has limitations, including its inability to capture short-term treatment effects in patients with ATTR-related CA and susceptibility to confounding factors such as myocardial edema [29]. T2 mapping, which assesses myocardial edema and inflammation by detecting changes in myocardial water content, has shown elevated T2 values in AL-CA patients, potentially reflecting light chain toxicity [30]. When combined with LGE, T2 mapping can facilitate rapid and accurate differentiation between AL and ATTR subtypes [31] [32].

CMR-FT technology enables quantitative assessment of myocardial strain, including radial strain (RS), circumferential strain (CS), and longitudinal strain (LS), through analysis of steady-state free precession (SSFP) sequence images. According to the study by You *et al.* [33], global and segmental strain parameters (RS, CS, LS) in patients with cardiac amyloidosis (CA) were significantly lower compared to those in patients with hypertrophic cardiomyopathy (HCM) and healthy controls ($P < 0.05$). Notably, reduced longitudinal strain (LS) represents an early manifestation of CA, reflecting subendocardial myocardial fiber injury. Additionally, a decrease in peak diastolic strain rate (PDSR) indicates impaired diastolic function, which aligns with the increased myocardial stiffness resulting from amyloid protein deposition.

Beyond strain analysis, other CMR techniques also offer valuable diagnostic insights in CA. For example, diffusion tensor imaging (DTI) can characterize the microstructural impact of amyloid infiltration and quantify the extent of myocardial amyloid deposition [34]; 4D flow MRI provides comprehensive evaluation of cardiac hemodynamics, reflecting alterations in myocardial function among CA patients [35]; myocardial perfusion reserve (MPR) demonstrates that myocardial ischemia in CA correlates with the degree of amyloid deposition, thereby reflecting underlying microcirculatory dysfunction [36].

The cost of MRI examinations is high, and some patients are unable to undergo the examination due to implanted devices (such as pacemakers); some early CA patients may not exhibit the typical LGE pattern, resulting in missed diagnoses; MRI also cannot directly distinguish between amyloid protein subtypes (such as ATTR and AL), and still requires combined with biopsy or nuclear medicine imaging.

5. Nuclear Medicine

Nuclear medicine imaging techniques are primarily categorized into single-photon emission computed tomography (SPECT) and positron emission tomography (PET). SPECT utilizes gamma-ray emitting isotopes, predominantly technetium-99m (^{99m}Tc), labeled tracers to acquire functional images. During the procedure, detectors rotate around the patient to collect multi-angle projection data, which is then reconstructed into three-dimensional images using computational algorithms. In the context of cardiac amyloidosis, SPECT employs bone-targeting radiotracers such as ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanedicarboxylic acid (^{99m}Tc-DPD), and ^{99m}Tc-hydroxymethylene di-

phosphonate (^{99m}Tc-HMDP). Among these, ^{99m}Tc-PYP imaging has been widely accepted as an effective diagnostic tool for transthyretin-related cardiac amyloidosis (ATTR-CA) [37], with several studies incorporating tracer uptake patterns from bone scintigraphy into diagnostic criteria for ATTR-CA [38].

Currently, multiple clinical guidelines and expert consensus statements recommend bone scintigraphy as a key diagnostic modality for ATTR-CA [39] and recognize it as the non-invasive "gold standard" for diagnosing ATTR-CA [40]. Image interpretation of ^{99m}Tc-PYP scans typically involves a combination of visual grading and quantitative analysis to ensure comprehensive evaluation. To minimize inter-observer variability, both planar imaging and SPECT/CT tomography are recommended: planar imaging provides an overview of global tracer distribution, while SPECT/CT enhances spatial localization accuracy and reduces interference from overlapping anatomical structures. Quantitative metrics further enhance the diagnostic utility of SPECT bone imaging. Commonly used parameters include the heart-to-lung uptake ratio (H/CL) and the heart-to-mediastinum uptake ratio (H/M), with an H/CL ratio ≥ 1.5 considered diagnostically significant [41]. Recent studies have demonstrated that in patients with comparable clinical profiles, ^{99m}Tc-HMDP exhibits a positive scan rate similar to that of ^{99m}Tc-PYP, along with a higher myocardial retention index (MRU) at 3-hour post-injection [42]. These findings suggest that ^{99m}Tc-HMDP offers comparable diagnostic sensitivity to ^{99m}Tc-PYP within the same time frame, combined with improved myocardial-to-blood pool contrast, thereby facilitating more straightforward image interpretation.

A non-invasive diagnosis of ATTR-CA can be established when characteristic imaging findings are present and there is no evidence of clonal plasma cell proliferation, particularly through the use of bone-affinity tracers. However, myocardial biopsy remains indispensable in certain clinical scenarios [43]. A study [44] has demonstrated that the ^{99m}Tc-PYP scan exhibits a markedly high false-negative rate in ATTR patients harboring the Leu58His genetic variant, potentially leading to diagnostic omission. Furthermore, tafamidis therapy has been shown to significantly reduce ^{99m}Tc-DPD myocardial uptake in patients with wild-type ATTR-related cardiomyopathy (ATTRwt-CM) [45], suggesting that SPECT may serve as a valuable tool for monitoring therapeutic response.

Positron emission tomography (PET) utilizes positron-emitting isotopes, such as ^{18}F and ^{11}C, labeled with specific compounds to achieve high-sensitivity and high-resolution imaging by detecting paired gamma photons generated during positron annihilation. In the context of cardiac amyloidosis, PET imaging predominantly relies on amyloid-specific tracers, including ^{11}C-Pittsburgh Compound B (^{11}C-PiB) and ^{18}F-florbetapir. Originally developed for the detection of amyloid plaques in Alzheimer's disease, these tracers have been subsequently validated for their utility in systemic amyloidosis affecting the heart [46]. Notably, 11C-PiB demonstrates particular promise in both the detection and differentiation of ATTR-CA from AL-CA [47]. Unlike SPECT-based bone tracers, PiB has a

molecular structure derived from thioflavin T—a dye widely used in histopathological staining. Studies have demonstrated that PiB PET/CT enables direct and quantitative assessment of myocardial amyloid deposition, offering an objective imaging biomarker for disease monitoring. This capability is particularly valuable in evaluating the therapeutic efficacy of tafamidis [48]. The ^{18}F-labeled tracer, with its longer half-life, is more readily applicable in clinical settings and demonstrates significant potential in the detection and assessment of cardiac amyloidosis. However, inconsistencies in findings have been reported, necessitating further investigation [47] [49]. Accumulating evidence indicates that ^{18}F-florbetapir specifically binds to both AL- and ATTR-type amyloid deposits in the myocardium, exhibiting increased tracer uptake upon repeat imaging. This characteristic offers a promising strategy for distinguishing between these two predominant forms of cardiac amyloidosis [50] [51].

Furthermore, a recent study [52] employing ^{68}Ga-FAPI-04 PET/CT targeting fibroblast activation protein (FAP) revealed significantly elevated myocardial FAP expression in patients with AL-CA. Notably, this increased uptake was strongly correlated with established clinical parameters, including Mayo staging, NT-proBNP levels, and left ventricular ejection fraction (LVEF), highlighting its potential as a breakthrough tool for early diagnosis, risk stratification, and prognostic evaluation in AL-CA.

The advantages of PET technology include superior spatial resolution, robust quantitative capabilities, and the ability to perform whole-body imaging. Ongoing advancements in PET instrumentation and the development of novel amyloid-targeting radiotracers are paving the way for earlier disease detection, precise quantification, and longitudinal monitoring of therapeutic response.

Although ^{99m}Tc-PYP imaging demonstrates high sensitivity for detecting transthyretin-related cardiac amyloidosis (ATTR-CA), it may produce false-positive results in AL-type cardiac amyloidosis (AL-CA). Furthermore, certain hereditary ATTR gene mutations (e.g., Phe64Leu, Thr59Lys) have been associated with false-negative findings. In addition, the high cost and technical complexity of the procedure partially limit its utility in longitudinal disease monitoring.

6. Conclusion

In recent years, substantial advancements have been achieved in the diagnosis and evaluation of CA through imaging modalities. The integration of multimodal imaging has not only enhanced the accuracy of disease subtyping but also provided a robust foundation for monitoring therapeutic responses and prognostic assessment. Looking ahead, the implementation of artificial intelligence (AI)-assisted image analysis, the development of novel molecular probes, and the application of multi-parameter quantitative models are poised to further refine the precision medicine framework for CA. For example, deep learning algorithms can enable automated segmentation and quantitative analysis of medical images; integrating multiple biomarkers—such as echocardiographic strain parameters, MRI-derived

extracellular volume (ECV), and PET-based metabolic activity—can facilitate the construction of machine learning-driven risk stratification models. Ongoing innovations in imaging technologies hold great promise for significantly improving the clinical management of this challenging disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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