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*Review*

# Advances in Cardiac Imaging of Danon Disease-Associated Cardiomyopathy

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**Abstract**

Danon disease (DD) is a rare X-linked dominant lysosomal storage disorder caused by pathogenic variants in the lysosome-associated membrane protein 2 (LAMP2) gene. DD is characterized by a spectrum of clinical manifestations, including severe cardiomyopathy, skeletal muscle involvement, and variable intellectual disability. Cardiac involvement, particularly severe cardiomyopathy, is the hallmark of DD and the primary determinant of mortality. Early precise diagnosis and meticulous evaluation of cardiac function in Danon disease-associated cardiomyopathy (DDACM) are crucial for guiding appropriate patient management and improving clinical outcomes. Cardiac imaging is a fundamental component in the diagnosis and comprehensive assessment of DDACM. Characteristic imaging features include marked left ventricular hypertrophy (LVH), diffuse impairment of left ventricular wall motion, absent or mild left atrial enlargement, and progressive left ventricular dilatation during advanced disease stages. Recent advances in the understanding of DDACM among cardiac specialists, coupled with the rapid expansion of imaging studies, have provided new knowledge and insights for the accurate identification and comprehensive management of this disease. Therefore, this review aims to summarize current advances in cardiac imaging techniques for DDACM. Moreover, the review explores the clinical value of cardiac imaging for early, precise diagnosis and disease management. This review also provides perspectives on the future roles of multimodal imaging, artificial intelligence-assisted diagnosis, and imaging strategies in the era of gene therapy.

**Keywords:** Danon disease-associated cardiomyopathy; echocardiography; global longitudinal strain; cardiac magnetic resonance; late gadolinium enhancement; multimodality imaging; gene therapy

## 1. Introduction

Danon disease (DD) was first described by Danon et al. in 1981 [1]. It is a rare X-linked dominant lysosomal storage disorder, previously referred to as "glycogen storage disease type IIb" or "lysosomal glycogen storage disease with normal acid maltase activity". The actual prevalence of DD remains unknown. In 2000, Nishino et al. [2] identified mutations in the lysosome-associated membrane protein 2 (LAMP2) gene as the underlying cause of DD. DD is characterized by severe cardiomyopathy, skeletal myopathy, and intellectual disability of varying degrees, and is often accompanied by multisystem involvement, including hepatic, gastrointestinal, and pulmonary manifestations [3,4]. Danon disease-associated cardiomyopathy (DDACM) initially presents predominantly as a severe hypertrophic cardiomyopathy (HCM) phenotype, accounting for approximately 1%–6% of patients with an HCM phenotype [5,6]. As the disease progresses, left ventricular dilatation may also develop [7], and a small proportion of patients may exhibit excessive left ventricular myocardial trabeculation [8,9].

While genetic testing represents the gold standard for diagnosing DD, early recognition and clinical suspicion of DDACM remain challenging because of its rarity, phenotypic overlap with other HCM subtypes, and limited awareness among clinicians. In recent years, the increasing number of imaging studies on DDACM has led to a better understanding of the imaging characteristics of this condition. Echocardiography and cardiac magnetic resonance (CMR) are the major noninvasive imaging modalities used to assess DDACM [10]. These techniques play pivotal roles by evaluating cardiac morphology and function, quantifying the extent of myocardial fibrosis, identifying subclinical myocardial injury, and informing clinical decision-making.

This review focuses on the research progress in the application of various imaging modalities in DDACM, explores the value of imaging in the diagnosis and management of this condition, and provides perspectives on multimodal imaging, artificial intelligence-assisted diagnosis, and emerging imaging needs in the era of gene therapy. The overall aim is to provide a reference for accurate diagnosis and appropriate management of DD.

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This narrative review was conducted following a literature search of the PubMed and Web of Science databases, covering the period from database inception to July 2026. The search terms included "Danon disease", "Danon disease-associated cardiomyopathy", "Danon disease cardiomyopathy", "Danon cardiomyopathy", "echocardiography", "speckle-tracking imaging", "cardiac magnetic resonance", "late gadolinium enhancement", "multimodality imaging", and "gene therapy". Priority was given to high-quality original studies, case series, and relevant review articles. Duplicate publications and conference abstracts were excluded. The retrieved literature was subsequently reviewed, synthesized, and organized based on the authors' expertise and understanding of the field.

## 2. Pathophysiological Basis and Clinical Features

DD is known to arise due to pathogenic variants in *LAMP2*, located on chromosome Xq24 [10]. LAMP2 is a highly glycosylated lysosomal membrane glycoprotein that is critically involved in autophagosome–lysosome fusion. It exists in three isoforms: LAMP2A, LAMP2B, and LAMP2C [11]. Although these isoforms share the same luminal domain, they have different transmembrane and cytoplasmic domains [12]. *LAMP2* mutations result in structural abnormalities, loss of expression, or functional impairment of the LAMP2 protein, leading to defective autophagosome–lysosome fusion. In particular, deficiency of the LAMP2B isoform, which is predominantly expressed in cardiac and skeletal muscle, severely disrupts the normal autophagic clearance process. This results in excess accumulation of autophagic vacuoles, glycogen granules, and other cytoplasmic components within cardiomyocytes and skeletal muscle cells, forming the characteristic "autophagic vacuole" phenotype. The pathological changes subsequently induce compensatory cardiomyocyte hypertrophy and disorganized myocardial architecture, which represent the core pathological features of DDACM [13,14]. With disease progression, the apoptosis and necrosis of damaged cardiomyocytes lead to extensive myocardial fibrosis [15]. The consequent impairment of both systolic and diastolic function contributes to the development of refractory heart failure and life-threatening arrhythmias.

Given that LAMP2 is abundantly expressed in cardiac muscle, skeletal muscle, and the brain [10], the major clinical manifestations of DD include severe cardiomyopathy, skeletal myopathy, and cognitive impairment. Among these, cardiomyopathy represents the most severe clinical manifestation and is the leading cause of mortality in patients with DD. DDACM may present with marked left ventricular hypertrophy (LVH), with the maximal left ventricular wall thickness reaching up to 65 mm in some cases [16]. Comparing the markedly thickened left ventricular wall in DDACM with the early age of onset, if the thickness is measured in millimeters and age in years, the left ventricular wall thickness often exceeds the patient's age [13,16,17,18]. Given that DD is an X-linked dominant disorder, male patients generally exhibit earlier onset, accelerated disease progression, and more severe phenotypes. Extracardiac manifestations are common, and severe cardiac dysfunction and malignant arrhythmias often develop during childhood or adolescence [17,19]. Most male DD patients often develop extracardiac symptoms in early childhood, followed rapidly by cardiac involvement, and progress to end-stage disease in the second to third decade of life [19]. In contrast, female DD patients usually demonstrate later onset and a milder, more heterogeneous phenotype owing to random X-chromosome inactivation. Paediatric DD predominantly manifests as the HCM phenotype, and affected boys may have an easily overlooked asymptomatic phase characterised by elevated serum creatine kinase (CK) and transaminases [20]. Boucek et al. [21] analyzed 145 patients with DDACM and reported that mean ages at first symptom onset, heart transplantation, and death in male patients were 12.1, 17.9, and 19.0 years, respectively, compared with 27.9, 33.7, and 34.6 years in female patients. A small proportion of patients with DDACM may also present with severe myocarditis [22], eosinophilic myocarditis [23], or transient stroke-like episodes as the initial clinical manifestation [24]. Patients with DDACM may develop various types of arrhythmias, with Wolff–Parkinson–White (WPW) syndrome being one of the most common arrhythmic manifestations [25,26,27]. Other electrical abnormalities include atrial fibrillation, complete atrioventricular block (AVB), supraventricular tachycardia, and left ventricular high voltage on electrocardiography [28,29]. Lotan et al. [30] reported elevated serum CK levels in 80% of male patients, whereas most female patients showed no significant CK abnormalities. Similarly, increased alanine aminotransferase/aspartate aminotransferase (ALT/AST) levels were detected in 83% of male patients, but in only 6% of female patients.

## 3. Advances in Echocardiography

### *3.1 Findings on Conventional Two-Dimensional and Doppler Echocardiography*

Two-dimensional echocardiography typically reveals severe LVH in patients with DDACM. The left ventricular wall thickness commonly exceeds 20–30 mm and may reach 40–60 mm or greater in some cases; the hypertrophy pattern is predominantly symmetric, with asymmetric hypertrophy reported in only a minority of patients [16,31,32]. Approximately one-quarter of patients with DDACM may develop left ventricular outflow tract (LVOT) obstruction [10], which results from the combined effects of severe myocardial hypertrophy narrowing the LVOT and systolic anterior motion (SAM) of the mitral valve. The initial clinical presentation or early stage of DDACM may be characterized by marked LVH without significant impairment of wall

motion. As the disease progresses, diffuse hypokinesis of the hypertrophied left ventricular wall may develop. In a cohort of 116 patients with DDACM, Hong et al. [19] reported progressive declines in left ventricular ejection fraction (LVEF) and increases in left ventricular end-diastolic dimension (LVEDD) with advancing disease. These longitudinal changes were independent of sex and heart failure status, with male patients demonstrating a more rapid deterioration of cardiac function. In the end-stage of the disease, female patients may exhibit progressive thinning of the previously hypertrophied ventricular wall alongside gradual enlargement of the cardiac chamber, with the cardiac phenotype transitioning from hypertrophic to dilated. In contrast, male patients less frequently undergo such remodeling changes [19,33].

Left ventricular diastolic dysfunction in patients with DDACM typically presents in the early stage as an impaired relaxation pattern with non-restrictive filling. In advanced stages of the disease, as left ventricular end-diastolic volume (LVEDV) increases, the LVEF decreases, and myocardial fibrosis worsens. Restrictive filling impairment may develop, characterized by an increased E wave, decreased A wave, and an E/A ratio >2 on the mitral inflow Doppler spectrum [8]. Tissue Doppler imaging revealed significantly reduced e' velocities at the lateral and septal mitral annulus, with a mean E/e' ratio >14 [8]. These abnormal parameters indicate a marked elevation in left ventricular filling pressure and significant impairment of diastolic function, often suggestive of a poor prognosis. In contrast to the pronounced LVH characteristic of DDACM, the left atrial diameter may be normal or only mildly enlarged [16]. Pulmonary hypertension may occur in a minority of DDACM patients, though a consistent relationship with disease severity has not been established [34,35].

Patients with DDACM generally do not present with thickening of the atrioventricular valves, arterial valves, or pericardium. Significant atrioventricular or arterial valve regurgitation is typically absent in patients without LVOT obstruction or increased LVEDV. However, when LVEDV is increased and LVEF is markedly reduced, significant mitral or tricuspid regurgitation may occur [36,37].

### *3.2 Application of Speckle-Tracking Echocardiography*

Compared to the aforementioned conventional echocardiographic parameters, speckle-tracking imaging is more sensitive in detecting early myocardial abnormalities. Among the various myocardial strain parameters, left ventricular global longitudinal strain (GLS) may serve as an important parameter for the evaluation of left ventricular global systolic function [38].

Miliou et al. [39] and Bui et al. [40,41] reported that patients with DDACM exhibited significantly reduced GLS despite normal LVEF. Bui et al. [40] evaluated left ventricular myocardial strain in 22 patients with DDACM and reported a markedly reduced mean GLS absolute value of 12.2% compared with healthy controls. Segmental analysis revealed mean GLS absolute values of 16.7% in the apical segments, 11.1% in the mid-ventricular segments, and 9.06% in the basal segments. Thus, strain impairment was predominantly observed in the basal and mid-ventricular segments, whereas apical strain was relatively preserved, resulting in an "apical sparing" pattern. However, it should be noted that the "apical sparing" phenomenon is not specific to DDACM, as a similar pattern may also be observed in cardiac amyloidosis (CA). Moreover, given the limited number of cases included in the study by Bui et al. [40], the "apical sparing" phenomenon should be regarded only as a relatively characteristic imaging feature in the diagnosis of DDACM. These authors also reported that impaired GLS was significantly associated with composite adverse outcomes in patients with DDACM and provided superior prognostic value compared with LVEF. Using an absolute GLS cutoff value of 10.0%, GLS achieved a sensitivity of 85.7% and specificity of 86.7% for predicting adverse outcomes, indicating its potential as a sensitive parameter for risk stratification in DDACM. However, the proposed prognostic GLS cutoff value should be considered an exploratory finding due to the small cohort size (n = 22), and further external validation is required.

It is noteworthy that existing speckle-tracking studies on DDACM predominantly employ GLS as the core observational parameter, with a paucity of research focused on global radial strain (GRS) and global circumferential strain (GCS). Currently, key evidence regarding the quantitative characteristics of GRS and GCS in this disease is derived primarily from CMR studies. However, animal experiments conducted by Ma et al. [42] demonstrated that both GRS and GCS values were significantly reduced in rats with *LAMP2* gene deficiency.

### *3.3 Advantages and Limitations of Echocardiography*

Echocardiography offers advantages such as high temporal resolution and the ability to perform real-time dynamic observation. This technique provides a comprehensive assessment of cardiac structure and function and is one of the preferred imaging modalities for the screening and follow-up of DDACM. Echocardiography remains the primary alternative for patients unable to undergo CMR examination due to claustrophobia. However, the myocardial soft tissue resolution of echocardiography is inferior to that of CMR, necessitating the integration of CMR for more accurate quantitative assessment of myocardial fibrosis.

## 4. Advances in Cardiac Magnetic Resonance

### *4.1 Morphological and Functional Imaging Features*

CMR has high spatial resolution, superior soft-tissue contrast, and multiparametric imaging capabilities, enabling comprehensive characterization of myocardial morphology and tissue properties [26,43]. Multiple CMR studies have consistently demonstrated substantial sex-related

heterogeneity in DDACM. Male patients tend to have an earlier disease onset, present more frequently with a severe hypertrophic phenotype, and have a higher prevalence of extracardiac involvement. In contrast, female patients typically develop cardiac disease at a later age, with cardiac involvement more often manifesting as a mixed phenotype characterized by both hypertrophic and dilated features. In a case-series study of 16 patients, Wei et al. [44] reported that all 13 male patients presented a hypertrophic phenotype (median age, 19 years), whereas among the three female patients, two had a hypertrophic phenotype and one had a dilated phenotype (median age, 42 years). Overall, symmetric hypertrophy was observed in 56% of patients, asymmetric hypertrophy in 38%, and a dilated phenotype in only 6%. In a cohort study of 24 patients (15 males and 9 females) by Liu et al. [45], the mean age at disease onset was 17.9 years in males compared with 33.7 years in females. Males were found to predominantly exhibit a hypertrophic phenotype (73.3%), and women mostly a dilated phenotype (88.9%). Impairment of GLS, GRS, and GCS was observed in all patients, with more severe impairment of systolic function in females. Ventricular arrhythmias occurred in 100% of female patients compared with 73.3% of male patients. Male patients had a higher left ventricular mass index (LVMI), whereas female patients had a greater left atrial anteroposterior diameter. In a case series of 12 patients reported by Rigolli et al. [46], eight patients had isolated LVH, two had concomitant left ventricular dilatation, and the remaining two patients had normal CMR findings. Similarly, in a cohort of 27 patients, López-Sainz et al. [47] reported that male patients had a mean age at diagnosis of 14 years and predominantly exhibited a hypertrophic phenotype, with more frequent extracardiac manifestations, including skeletal myopathy, learning difficulties, and visual abnormalities. Female patients had a later mean age at diagnosis of 35 years and were more likely to exhibit reduced LVEF and a dilated cardiac phenotype.

### *4.2 Characteristic Myocardial Late Gadolinium Enhancement Patterns*

Late gadolinium enhancement (LGE) is a relatively common CMR finding in DDACM, and its distribution pattern may provide useful clues for differentiating DD from other cardiomyopathies. CMR in DDACM may show diffuse subendocardial LGE involving the left ventricular free wall and apex, with relative sparing of the basal-to-mid interventricular septum, a pattern referred to as “septal sparing”. As the disease progresses, LGE may extend from the subendocardium toward the mid-myocardial layers, and a “feathery” pattern of transmural enhancement may be observed in some cases [39,48]. In a CMR case-series study by Wei et al. [44], 88% of patients showed no significant LGE in the basal and mid interventricular septum, while apical LGE was observed in all patients, with the extent of enhancement progressively increasing from the base toward the apex. LGE involving the left ventricular free wall was present in 94% of patients, and extensive subendocardial LGE was observed in 88% of patients. However, a study by Liu et al. [45] suggested substantial sex-related heterogeneity in this pattern. Although LGE involving the left ventricular apex and free wall was observed in both males and females, basal-to-mid septal sparing was more frequently observed in male patients, whereas this characteristic pattern was less prevalent among female patients. Given the limited sample sizes of the available studies, “septal sparing” should currently be regarded as a relatively characteristic imaging feature rather than as a specific diagnostic marker of DDACM.

### *4.3 Diagnostic Utility of T1 and T2 Mapping*

Quantitative myocardial tissue characterization using T1 and T2 mapping techniques in CMR enables the assessment of microstructural myocardial alterations. Furthermore, it holds promise for the detection of subclinical myocardial injury that may not be identified by conventional CMR sequences. T1 mapping enables the measurement of myocardial native T1 values and extracellular volume (ECV). Native T1 values increase with edema and expansion of the interstitial space, while ECV reflects the size of the extracellular space [49]. Patients with DDACM may exhibit elevated native T1 and ECV values [45,50]. In septal regions without evident LGE, ECV may remain within the normal range [49]. He et al. [51] investigated six patients with DDACM, three of whom underwent T1 mapping with calculation of the ECV fraction. Both native T1 and ECV were elevated, suggesting these two parameters may have potential value in detecting early myocardial abnormalities.

T2 mapping is a quantitative technique capable of precisely measuring T2 values. Through post-processing, it can generate spatially corresponding pseudo-color maps that reflect the magnitude of T2 values using different colors. The primary pathological basis for increased myocardial T2 values is edema or inflammation, which can provide supplementary information regarding myocardial edema beyond parameters such as T1 and ECV [52]. T2 values may be elevated in patients with DDACM [45], suggesting the presence of myocardial cellular edema or an inflammatory response.

### *4.4 Other CMR Findings of Potential Clinical Significance*

A small number of studies and case reports with CMR perfusion imaging have reported resting first-pass perfusion defects in patients with DDACM [36,44,53]. These defects are predominantly distributed in the subendocardial myocardium and may involve the left ventricular anterior wall, anterolateral wall, and inferolateral wall. Notably, this pattern of perfusion abnormality often does not conform to the anatomical territories supplied by individual coronary arteries. However, given the limited sample sizes of the aforementioned studies, the overall level of evidence supporting

these imaging features remains low. Therefore, the findings should be considered preliminary observations that have yet to be adequately validated. They may serve as an auxiliary warning sign in clinically suspected cases, but should not be considered a core diagnostic criterion.

### *4.5 Prognostic Assessment and Longitudinal Follow-up*

CMR not only contributes to the diagnosis of DD but also enables risk stratification by integrating quantitative myocardial tissue characterization and functional assessment, thereby providing valuable information for clinical decision-making. The extent and severity of LGE may serve as a potential prognostic marker in patients with DD [48,54]. However, compared with sarcomeric hypertrophic cardiomyopathy, prognostic data in DD remain scarce, and larger studies are needed to further validate these associations. In addition to LGE, CMR-derived myocardial strain analysis may provide greater sensitivity for detecting early changes in cardiac function. Such subclinical systolic impairment may represent an early marker of disease progression, and serial monitoring of strain parameters may provide an opportunity for earlier clinical intervention [48]. Cardiac involvement in DD is a dynamic and progressive process, and serial CMR examinations may enable longitudinal assessment of myocardial disease evolution. This would provide objective information to guide treatment adjustments and facilitate periodic reassessment of cardiovascular risk [10].

## 5. Advances in Other Imaging Modalities

Chest radiography in patients with DDACM typically demonstrates cardiomegaly and an increased cardiothoracic ratio, occasionally accompanied by signs of pulmonary venous congestion or pulmonary edema [55,56]. However, these radiographic findings are nonspecific and have limited diagnostic value for DD. They may provide supplementary information, mainly for the evaluation of heart failure-associated complications.

The computed tomography (CT) manifestations of DDACM include non-specific signs such as marked myocardial hypertrophy and cardiac chamber enlargement. However, unlike CMR, cardiac CT has limited capability for myocardial tissue characterization. In clinical practice, cardiac CT is only used as an alternative imaging modality for patients with DDACM who have contraindications to CMR. However, it should be emphasized that cardiac CT can clearly delineate the anatomical configuration of the great cardiac vessels with optimal spatial resolution [57], thereby providing imaging evidence for end-stage DDACM prior to heart transplantation.

A case report by Wang et al. [24] described globally reduced myocardial perfusion on radionuclide myocardial perfusion imaging in a patient with DDACM. Another case report by McLeod et al. [58] used fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) to assess myocardial glucose metabolism. These authors observed abnormal myocardial FDG metabolism, characterized by markedly increased FDG uptake in the interventricular septum and left ventricular lateral wall, suggestive of increased myocardial glucose metabolism. However, reduced myocardial perfusion and abnormal FDG metabolism have been reported only in isolated case reports, and should therefore be considered as preliminary observations. Neither finding is specific to DDACM and may also be observed in other cardiomyopathies. Consequently, their diagnostic value remains limited, and sole reliance on perfusion or metabolic imaging findings for diagnosis may lead to misjudgment. In clinical practice, the results of myocardial nuclear imaging are used only as a supplement to other imaging modalities. Furthermore, Bokhari et al. [59] reported exceptionally high specificity with technetium-99m pyrophosphate ($^{99m}$Tc-PYP) imaging, a valuable non-invasive diagnostic tool for transthyretin amyloid cardiomyopathy. However, it should be noted that case reports by Li et al. [3], Antukh et al. [60], and Xie et al. [61] have shown that patients with DD may also exhibit similarly high radionuclide uptake, reaching Perugini grade 3. This can lead to false-positive results and potential misdiagnosis as transthyretin cardiac amyloidosis (ATTR-CA), highlighting the importance of multimodal imaging in the diagnostic process.

## 6. Differential Diagnosis Based on Imaging Findings

DDACM is primarily characterized by LVH and should be differentiated from a variety of other disorders presenting with similar hypertrophic phenotypes. A summary of the differential diagnostic features is provided in Table 1.

### *6.1 Sarcomeric Hypertrophic Cardiomyopathy*

Sarcomeric hypertrophic cardiomyopathy (sHCM) is the most common inherited cardiac disorder. It is typically inherited in an autosomal dominant pattern due to mutations in genes encoding sarcomere-associated proteins. Although asymmetric septal hypertrophy represents the most common morphological phenotype, other patterns, such as concentric hypertrophy, apical hypertrophy, right and LVH, and isolated papillary muscle hypertrophy, have also been reported [62].

Both sHCM and DDACM present with marked LVH. However, several key differences can help to distinguish these two conditions: (1) sHCM presents as an isolated cardiac phenotype, whereas DD typically manifests with multisystem involvement [10]. (2) The vast majority of sHCM cases present as asymmetric LVH, whereas DDACM predominantly manifests as symmetric LVH. (3) In sHCM, reduced left ventricular wall motion generally occurs only in advanced stages of the disease, whereas patients with DDACM may already exhibit a disproportion between in-

**Table 1. Differentiation of DDACM from other myocardial disorders presenting with LVH.**

| Type of cardiomyopathy | Core pathogenesis and genetic features | Age of onset | Characteristics of myocardial hypertrophy and echocardiographic features | CMR features | ECG | Extracardiac manifestations | Laboratory findings |
|---|---|---|---|---|---|---|---|
| DDACM | *LAMP2* gene mutation, X-linked dominant inheritance | Childhood or adolescence | Severe LVH, mostly symmetric, may progress to dilated cardiomyopathy phenotype in late stages | LGE in the LV free wall and apex (septal sparing), elevated native T1 and ECV | WPW syndrome is the most common | Skeletal myopathy, intellectual disability, retinopathy | Elevated CK and liver enzymes |
| sHCM | Mutations in genes encoding sarcomere-related proteins (MYH7, MYBPC3, etc.), autosomal dominant inheritance | Adolescence to middle-old age | Mostly asymmetric hypertrophy (predominantly septal thickening), prone to SAM and LVOT obstruction | Mid-myocardial LGE at the RV-septal junction and in regions of most severe hypertrophy | Pathological Q waves, ST-T changes, LV high voltage | None | Cardiac troponin may be elevated |
| CA | Misfolding of soluble proteins forming insoluble amyloid fibrils deposited abnormally in the myocardial interstitium; ATTRv-CA is autosomal dominant | Predominantly middle-aged and elderly | Predominantly concentric symmetric hypertrophy; marked biatrial enlargement, thickened interatrial septum and cardiac valves, granular myocardial echotexture; LV GLS shows “apical sparing” pattern | Extensive subendocardial or intermyocardial LGE, elevated native T1 and ECV | Low voltage | Renal insufficiency, peripheral neuropathy, autonomic dysfunction, macroglossia | AL type: positive monoclonal immunoglobulin-related markers |
| FC | *GLA* gene variant causing reduced or absent activity of α-Gal A, X-linked inheritance | Childhood or adulthood | Predominantly concentric symmetric hypertrophy; possible “binary sign”; valvular thickening; reduced longitudinal strain in the inferolateral basal segment | LGE predominantly located in the mid-myocardium of the inferolateral basal segment of the LV, reduced native T1 | LV high voltage, shortened PR interval, ST-segment depression, T-wave inversion | Renal insufficiency, cutaneous angiokeratomas, peripheral neuropathic pain | Reduced α-Gal A activity, elevated plasma Gb3 (mainly in males) |

**Table 1. Continued.**

| Type of cardiomyopathy | Core pathogenesis and genetic features | Age of onset | Characteristics of myocardial hypertrophy and echocardiographic features | CMR features | ECG | Extracardiac manifestations | Laboratory findings |
|---|---|---|---|---|---|---|---|
| MCM | Mitochondrial DNA or nuclear DNA mutations causing dysfunction of oxidative phosphorylation | Any age | Mild LVH | Non-ischemic subepicardial or mid-myocardial LGE, predominantly in the anterolateral or inferolateral basal segments | LV high voltage, repolarization abnormalities, WPW syndrome | Multi-system involvement: diabetes mellitus, ptosis, retinitis pigmentosa/optic atrophy, hearing impairment | Serum lactate levels may be significantly elevated |
| hypertension-induced LVH | Chronic hypertension | Middle-aged and elderly | Symmetric hypertrophy, wall thickness mostly <15 mm, without right ventricle (RV) wall thickening, left atrium often enlarged | LGE was absent or non-specific | LV high voltage with ST-T changes, no pre-excitation syndrome | May have renal insufficiency, cerebrovascular disease | No significant markers |
| Pompe Disease | *GAA* gene mutation causing GAA deficiency, leading to abnormal glycogen accumulation in lysosomes, autosomal recessive inheritance | Infantile, childhood, adult | Infantile type: severe LVH with possible LVOT obstruction | Infantile type: diffuse halo-like LGE in the ventricles | High QRS voltage, repolarization abnormalities, ventricular pre-excitation | Infantile type: severe myasthenia, respiratory insufficiency, feeding difficulties | Reduced GAA activity |
| PRKAG2 Cardiac Syndrome | *PRKAG2* gene mutation causing AMPK dysfunction, autosomal dominant inheritance | Childhood to adulthood; most between 30–49 years of age | LVH, RV may also be hypertrophied | May show extensive subendocardial LGE | Atrial fibrillation, conduction disturbances, repolarization abnormalities | Myopathy rarely reported | CK may be elevated |

Abbreviations: AL, amyloid light-chain; AMPK, adenosine monophosphate-activated protein kinase; CA, cardiac amyloidosis; CK, creatine kinase; DDACM, danon disease-associated cardiomyopathy; ECG, electrocardiogram; ECV, extracellular volume; FC, fabry cardiomyopathy; GAA, acid α-glucosidase; Gb3, globotriaosylceramide; GLA, galactosidase alpha; GLS, global longitudinal strain; LAMP2, lysosome-associated membrane protein 2; LGE, late gadolinium enhancement; LV, left ventricle; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MCM, mitochondrial cardiomyopathy; MYBPC3, myosin-binding protein C3; MYH7, myosin heavy chain 7; PRKAG2, protein kinase AMP-activated non-catalytic subunit gamma 2; RV, right ventricle; SAM, systolic anterior motion; sHCM, sarcomeric hypertrophic cardiomyopathy; ST-T, ST segment and T wave; ATTR-CA, transthyretin-related amyloidosis; WPW, Wolff–Parkinson–White syndrome; ATTRv-CA, variant transthyretin cardiac amyloidosis; CMR, cardiac magnetic resonance; α-Gal A, α-galactosidase A.

creased left ventricular wall thickness and relatively reduced left ventricular wall motion at the initial clinical presentation. (4) The left ventricular cavity diameter is relatively reduced in sHCM, whereas in patients with DDACM, the mismatch between left ventricular wall thickening and left ventricular cavity enlargement often appears in the progressive stage [16]. (5) Left ventricular wall thickening in sHCM is mostly accompanied by significant left atrial enlargement. In patients with DDACM, even with marked left ventricular wall thickening, the left atrium may not be enlarged or only slightly enlarged. Moreover, it is common to observe that the left ventricular wall thickness exceeds the anteroposterior diameter of the left atrium, a phenomenon that is relatively uncommon in other types of hypertrophic cardiomyopathy [16]. (6) LGE is detectable in 60%–80% of patients with sHCM, typically presenting as patchy mid-myocardial enhancement at the right ventricular-septal junction and in regions with the most prominent hypertrophy [63,64]; this differs from the LGE features of DDACM.

### *6.2 Cardiac Amyloidosis*

CA is an infiltrative cardiomyopathy characterized by the deposition of insoluble amyloid fibrils in the myocardial interstitium. This condition arises from the misfolding of soluble proteins associated with genetic, infectious, or other pathological factors. The clinical manifestations of CA include increased myocardial wall thickness and diastolic dysfunction, with progressive disease potentially leading to impaired systolic function. The two predominant clinical forms of CA are immunoglobulin light-chain amyloidosis (AL-CA) and transthyretin-related amyloidosis (ATTR-CA). ATTR-CA may be hereditary and is typically transmitted in an autosomal dominant pattern [63].

The key similarities between CA and DDACM are as follows: (1) All cases mainly manifest as concentric LVH. (2) The absolute values of left ventricular myocardial GLS in both groups are significantly decreased and accompanied by the "apical sparing" sign, which is characterized by markedly reduced strain in the basal and middle segments of the left ventricle, and normal strain in the apical segment [40,41,65]. (3) Both CA and DDACM may demonstrate markedly increased native T1 values and ECV fractions on CMR [63]. (4) Both CA and DDACM may show increased myocardial uptake of $^{99m}$Tc-pyrophosphate on radionuclide imaging.

However, several key differences can help distinguish the two conditions. (1) DD is primarily observed in children and adolescents, the median age at diagnosis for patients with CA is generally in the eighth to ninth decades [66]. (2) AL-CA is characterized by multi-organ involvement, commonly affecting the heart, kidneys, liver, gastrointestinal tract, and peripheral nerves, whereas the central nervous system is typically spared. In addition to cardiac involvement, ATTR-CA primarily affects the peripheral nervous system or tenosynovial structures [67]. In contrast, DDACM is frequently accompanied by skeletal muscle involvement and delayed intellectual development, in addition to cardiac involvement [10]. (3) Pulmonary hypertension is common in patients with CA [68], whereas pulmonary hypertension appears to occur more frequently in the terminal stages of DDACM [34,35]. However, there is still a lack of epidemiological data from large cohorts regarding the prevalence of pulmonary hypertension in DDACM. (4) Electrocardiogram (ECG) findings in CA patients typically present with low voltage or normal voltage, exhibiting a "voltage-mass" mismatch phenomenon [69]. In contrast, patients with DDACM often show high voltage or normal voltage, frequently accompanied by pre-excitation syndrome-like manifestations. (5) Patients with CA commonly exhibit marked bi-atrial enlargement, whereas the left ventricular cavity is generally not significantly dilated; thickening of the interatrial septum and cardiac valves may also be observed, with valvular thickening typically presenting as relatively uniform thickening involving multiple valves [70,71]. Simultaneous involvement of multiple cardiac structures, including the myocardium, pericardium, and cardiac valves, is a prominent feature of CA, although this pattern is not specific to CA. In contrast, DDACM is primarily characterized by marked left ventricular wall thickening, with the left atrium often remaining normal in size or showing only mild enlargement. Significant thickening of the interatrial septum and cardiac valves is generally uncommon. (6) On contrast-enhanced inversion time scout (TI scout) imaging, CA shows a characteristic myocardial nulling pattern, with myocardial signal suppression occurring earlier than that of the ventricular blood pool. This feature may provide useful diagnostic clues for CA [63], although this characteristic nulling phenomenon is absent in DDACM. (7) Typical LGE in CA presents as extensive subendocardial or intramyocardial LGE, which can serve as one of the diagnostic criteria for CA [72]. The extent of LGE in patients with ATTR-CA is generally more widespread than that of patients with AL-CA [73]. In contrast, LGE in DDACM predominantly involves the left ventricular free wall and apex, while the basal and mid portions of the interventricular septum are relatively spared.

In summary, when differentiating CA from DDACM, a comprehensive assessment should integrate their distinct imaging features with age at disease onset, extracardiac involvement, and electrocardiographic manifestations. In atypical cases, genetic testing or histopathological examination may be required to establish a definitive diagnosis.

### *6.3 Anderson–Fabry Cardiomyopathy*

Anderson–Fabry disease (FD) is an X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene, resulting in deficient or absent activity of α-galactosidase A (α-Gal A). Consequently, substrates of α-

Gal A, particularly sphingolipids and their derivatives, accumulate within cardiomyocytes and multiple organs, leading to systemic manifestations. FD comprises two major phenotypes: the classic form, which typically presents in childhood, and the late-onset form, which generally manifests in adulthood [63].

Fabry cardiomyopathy (FC) and DDACM share several common features. Both may present with concentric LVH and mild-to-moderate left atrial enlargement. In addition, electrocardiography may reveal high left ventricular voltage and a WPW syndrome-like pattern in both conditions.

The following features may help to differentiate FC from DDACM: (1) Compared with the early onset characteristic of DDACM, FC generally presents at a relatively later age [10]. In addition, the degree of LVH is typically less pronounced in FC than in DDACM. (2) Diastolic dysfunction is a predominant early manifestation of FC, whereas global wall motion and LVEF may remain preserved for a prolonged period, with global systolic dysfunction generally developing during advanced stages of the disease [74]. In contrast, systolic dysfunction tends to occur earlier and progress more rapidly in DDACM. (3) FC may be associated with thickening and deformation of the cardiac valves, particularly the mitral and aortic valves [75], whereas these valvular abnormalities are relatively uncommon in DDACM. (4) FC is primarily characterized by reduced longitudinal strain in the basal inferolateral wall of the left ventricle [76]. In contrast, DDACM may show reduced longitudinal strain in the basal and mid ventricular segments, with relatively preserved strain at the apex. However, the latter finding is based on observations from a small cohort and requires further validation in larger studies. (5) Reduced native T1 values are a relatively characteristic CMR feature of FC [63]. With disease progression, however, myocardial fibrosis and inflammation may result in pseudonormalization of native T1 values. In contrast, native T1 values are generally markedly elevated in DDACM. This difference may provide a useful imaging clue for differentiating the two conditions. (6) In FC, LGE is predominantly localized to the basal inferolateral myocardial segments of the left ventricle [63]. In contrast, LGE in DDACM primarily involves the left ventricular free wall and apex, with relative sparing of the basal and mid interventricular septum. (7) Although the “binary sign” has occasionally been reported on echocardiography in patients with FC [76], this imaging finding has relatively low specificity and cannot be used as a standalone criterion for definitive diagnosis. It should therefore be considered only as an ancillary finding in the differential diagnosis.

In summary, FC and DDACM exhibit certain differences in imaging findings, as well as different manifestations in systems other than the heart. These differences can be used to distinguish between them. However, in advanced or atypical cases, the phenotypes may overlap, and in such instances genetic testing is required to confirm the diagnosis.

### *6.4 Mitochondrial Cardiomyopathy*

Mitochondrial disease (MD) comprises a group of inherited disorders that are caused by pathogenic variants in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA), resulting in impaired oxidative phosphorylation and subsequent multisystem dysfunction [77]. Tissues with high energy requirements, including the brain, myocardium, and skeletal muscle, are particularly vulnerable to mitochondrial dysfunction and subsequent injury [78]. Cardiac involvement in MD most commonly manifests as myocardial hypertrophy, which can serve as an early and sometimes predominant clinical feature. With disease progression, MD patients may develop cardiac enlargement, impaired cardiac function, and various arrhythmias [79]. In a study of 113 children with MD, Scaglia et al. [80] reported that neuromuscular manifestations were the predominant presentation in 60% of patients, with cardiac involvement occurring in 40% [80]. Among those with cardiac involvement, 58% had a hypertrophic cardiomyopathy phenotype, 29% had a dilated phenotype, and 13% exhibited left ventricular noncompaction.

The most critical differential diagnosis for DDACM is mitochondrial cardiomyopathy (MCM). (1) While there is some overlap in the age of onset between the two conditions, the overall age of onset is younger for DDACM. (2) Both conditions primarily manifest as concentric LVH, but the degree of myocardial hypertrophy is usually more pronounced in DDACM [10]. (3) Although both conditions may present with a mismatch phenomenon involving LVH, reduced wall motion, and left ventricular cavity dilation, MCM is observed more frequently on imaging examinations. (4) Extracardiac manifestations: both conditions may present with intellectual disability and skeletal muscle weakness; patients with MCM are prone to developing diabetes mellitus, ptosis, retinitis pigmentosa, optic atrophy, and hearing impairment [10,81]. However, these complications are relatively uncommon in patients with DDACM. (5) Although both may present with WPW syndrome-like changes on electrocardiography [10], myocardial involvement is more common in DD. (6) MCM is predominantly characterized by non-ischemic subepicardial and mid-myocardial LGE, which may occur in any segment of the left ventricle, most commonly in the basal segments of the anterolateral or inferolateral walls [82]. This differs from the LGE pattern observed in DDACM.

In summary, imaging findings alone cannot reliably distinguish between DDACM and MCM. However, they can be differentiated by combining imaging findings with physical examination, blood biochemical markers, and manifestations involving other organ systems beyond the heart.

### *6.5 Hypertension-Induced Left Ventricular Hypertrophy*

LVH caused by hypertension and DDACM may both present as a uniform pattern. However, there are notable differences in their clinical characteristics and imaging findings. Hypertensive LVH results from long-standing hypertension, is more commonly observed in middle-aged and elderly patients, and manifests as concentric LVH [83]. Its pathological basis is cardiomyocyte hypertrophy and interstitial fibrosis, rather than cardiomyocyte vacuolar degeneration or glycogen accumulation.

In terms of imaging, hypertension-induced LVH is typically symmetric, with wall thickness generally <15 mm. It is frequently accompanied by left atrial enlargement, and right ventricular wall thickening is usually absent. In contrast, DDACM frequently presents with wall thickness >20 mm, minimal left atrial enlargement, and rapid disease progression. Differential diagnosis between the two conditions can be achieved in most cases by considering the patient's age of onset, medical history, and other extracardiac manifestations. Nevertheless, comprehensive assessment remains mandatory for a small subset of atypical patients.

### *6.6 Other Glycogen Storage Disease-Related Cardiomyopathies*

DD, Pompe disease, and PRKAG2 syndrome are all classified as glycogen storage disorders and can each lead to LVH.

Pompe disease is an autosomal recessive glycogen storage disorder caused by mutations in the *GAA* gene, resulting in deficiency of acid α-glucosidase (GAA). The impaired enzyme activity leads to abnormal accumulation of glycogen within the lysosomes of cardiomyocytes and skeletal muscle cells. Pompe disease can be classified into infantile- and late-onset forms [10]. Most patients with infantile-onset Pompe disease exhibit severe cardiac involvement, whereas most patients with late-onset Pompe disease do not exhibit cardiac manifestations. When cardiac involvement does occur in late-onset cases, it is generally milder and progresses more slowly. In typical infantile-onset Pompe disease, the near-complete loss of GAA activity leads to severe clinical manifestations shortly after birth, including progressive myocardial hypertrophy, profound muscle weakness, respiratory insufficiency, and feeding difficulties. The disease progresses rapidly, and in the absence of enzyme replacement therapy, most infants die within the first year of life [84]. Echocardiographic findings include severe LVH, which may be accompanied by LVOT obstruction. Electrocardiographic manifestations include high QRS voltage, repolarization abnormalities, and a short PR interval. In some patients, ventricular pre-excitation syndrome may also be present [10]. LGE is more commonly observed in the infantile form, presenting as diffuse halo-like delayed enhancement of the ventricle [84]. Although diagnosis relies on GAA activity assays and analysis of *GAA* gene variants, the prominent features of classic infantile-onset Pompe disease—extremely early onset and early death—are notable clues for distinguishing Pompe cardiomyopathy from other cardiomyopathies.

PRKAG2 cardiac syndrome is an autosomal dominant inherited cardiomyopathy caused by pathogenic variants in the *PRKAG2* gene, which encodes the γ2 regulatory subunit of adenosine monophosphate-activated protein kinase (AMPK). The variant-related dysfunction of AMPK signaling leads to abnormal glycogen accumulation in cardiomyocytes, resulting in a glycogen storage cardiomyopathy phenotype. PRKAG2 cardiac syndrome is primarily characterized by myocardial hypertrophy [85]. In rare cases, it may also present with extracardiac manifestations such as skeletal muscle involvement [85]. Several key features can help to distinguish PRKAG2 cardiac syndrome from DDACM: (1) Compared with DDACM, the mean age of onset of PRKAG2 cardiac syndrome is relatively older, concentrating mostly between 30–49 years [85]. (2) Although PRKAG2 cardiac syndrome may present with extracardiac manifestations, it is predominantly characterized by isolated cardiac involvement. This is different from DDACM, which frequently coexists with extracardiac manifestations. (3) The clinical features of PRKAG2 cardiac syndrome include a predisposition to atrial fibrillation and a potential requirement for permanent pacemaker implantation at a young age [85,86]. In contrast, DDACM is primarily characterized by ventricular pre-excitation syndrome. (4) PRKAG2 cardiac syndrome may present with extensive subendocardial LGE [87], which is different from the LGE characteristics observed in DDACM.

## 7. Current Limitations

Although substantial progress has been made in the field of cardiovascular imaging in DDACM, several important limitations remain. First, DD is a rare inherited cardiomyopathy with a low incidence. Limited awareness of this disease among clinicians and imaging specialists may contribute to missed or incorrect diagnoses. Second, most imaging studies of DD have so far been single-center, retrospective studies with small sample sizes, including cohort studies, case series, and individual case reports. Large prospective cohorts are lacking, and referral and selection biases are common. In addition, some studies may have included overlapping patient populations, thereby limiting the independence and reproducibility of the available evidence. Third, CMR acquisition parameters, imaging sequences, and post-processing protocols are not yet standardized across centers. Moreover, disease-specific standardized diagnostic thresholds for T1, T2, and ECV are lacking in DD. This results in limited cross-study comparability of quantitative mapping measurements, making it difficult to establish high-level evidence.

Furthermore, existing studies have predominantly focused on findings from cross-sectional imaging, and long-term longitudinal imaging data remain scarce. Direct ev-

idence linking imaging parameters with clinical hard endpoints remains limited, making it difficult to accurately determine the prognostic and risk-stratification value of individual imaging biomarkers. Finally, DD exhibits substantial age- and sex-related phenotypic heterogeneity. However, most existing studies have limited sample sizes and insufficiently stratified analyses. Moreover, the patterns of imaging evolution across different patient populations have not yet been fully elucidated. Future studies should therefore focus on large, multicenter, standardized, and prospective cohorts to further strengthen and refine the evidence base for cardiovascular imaging in DDACM.

Major studies that provide the current evidence on cardiovascular imaging in DD are summarized in Table 2 (Ref. [19,24,39,40,41,44,45,46,47,51,58]), including information on study design, sample size, sex distribution, imaging modality, key findings, endpoint and outcome data, and study limitations. This summary provides a comprehensive overview of the existing evidence, while also highlighting the objectively limited strength of the current evidence base.

## 8. Future Perspectives

### *8.1 Future Perspectives Involving Artificial Intelligence, Multimodal Imaging, and Radiomics for the Evaluation of DDACM*

Artificial intelligence (AI) has demonstrated important potential in the diagnosis and management of various cardiovascular diseases [88,89]. However, it should be noted that the aforementioned evidence was derived from cohorts with other cardiovascular diseases, and the application of AI and radiomics specifically in DDACM has yet to be directly investigated. The integration of multimodal imaging through the combination of imaging data from different modalities (e.g., echocardiography, CMR, radionuclide myocardial imaging) may theoretically provide a comprehensive pathophysiological profile of DD [90]. As a high-throughput feature extraction technique, radiomics can identify numerous subtle imaging features that are difficult to detect by visual assessment alone across multimodal imaging datasets. By integrating these features with AI, machine learning, and deep learning algorithms, this technological framework may improve the diagnostic performance for rare cardiomyopathies [91,92]. However, the limited number of patients with DD currently precludes the establishment of large, multicenter datasets. The future accumulation of sufficient radiomics resources may lead to the development of highly accurate automated diagnostic models, potentially enabling early and precise identification of DDACM.

### *8.2 Imaging Applications in the Era of Gene-Targeted Therapy*

Historically, heart transplantation has been the only viable therapeutic option for patients with advanced DDACM [93]. Despite the severity of DDACM, post-transplant outcomes are favorable, with a reported 5-year graft survival rate of 87.1% [94]. Recent studies have indicated that mitochondrial dysfunction and structural fragmentation are key factors in disease progression, leading clinicians to expand their understanding of DD beyond a mere lysosomal defect. The discovery of these mechanisms has opened new avenues for therapeutic strategies [15,95]. Gene therapy has emerged as one of the most promising strategies, with RP-A501 being the most representative approach. RP-A501 is a recombinant adeno-associated virus serotype 9 (AAV9) vector carrying a *LAMP2B* transgene. The aim of delivering a functional *LAMP2* gene into DD patients is to restore LAMP2 protein expression in cardiac tissue and improve myocardial function. A phase I clinical trial of RP-A501 gene therapy (NCT03882437) has shown promising outcomes. RP-A501 is currently being evaluated in a phase II clinical trial (NCT06092034) to assess its safety and therapeutic efficacy in male patients with DD aged 8 years or older [96].

In the phase I human gene therapy clinical study of RP-A501, the following imaging-based reference parameters were used to assess the effects of gene therapy: left ventricular mass, LVMI, and interventricular septal and left ventricular posterior wall thickness. Among these, LVMI may serve as an important imaging endpoint, since a reduction in LVMI from baseline following gene therapy potentially reflects reversal of the characteristic myocardial hypertrophy associated with DD [96]. As an important functional safety endpoint, LVEF can be used to monitor the preservation or changes in left ventricular systolic function. Notably, the study also found that not all patients were able to complete CMR examinations incorporating fibrosis assessment, while echocardiographic measurements were more susceptible to measurement variability. These findings suggest that a single imaging modality may be insufficient for comprehensive evaluation of therapeutic efficacy [96]. Although multiparametric imaging biomarkers, including native T1, ECV, and GLS, may detect abnormalities in myocardial tissue characteristics and cardiac function, they have not yet been prespecified as formal efficacy endpoints in gene therapy clinical trials. The efficacy of gene therapy for DD should therefore not be evaluated solely on the basis of imaging parameters. Instead, a comprehensive assessment should integrate myocardial biopsy–based LAMP2 protein expression, biomarkers of myocardial injury, cardiac functional class, and clinical events.

## 9. Conclusion

Compared with the 2023 JACC State-of-the-Art Review/International Consensus on Danon disease, the present review incorporates recently published clinical cohort data and provides several important updates. In particular, we highlight emerging sex-specific CMR findings; provide a preliminary assessment of the diagnostic value

**Table 2. Summary of representative cardiovascular imaging studies in DDACM.**

| Reference | Study design | Sample size (M/F) | Imaging modality | Main results | Outcome endpoint data | Major limitations |
|---|---|---|---|---|---|---|
| Hong et al. [19], 2025 | International multicenter registry study, retrospective longitudinal natural history study | 116 (52/64) | transthoracic echocardiography (TTE) | LVEF decline and LVEDD enlargement observed in both sexes; LV hypertrophy continuously progresses in male patients without heart failure and stabilizes before heart failure; wall thinning occurs in female patients regardless of heart failure status | Male patients: LVEF, LV mass, LVEDD, and LV wall thickness; Female patients: LVEF, LVEDD, and LV wall thickness | Sample size still relatively small; wide time span of data collection; lack of CMR quantitative tissue characterization |
| Miliou et al. [39], 2022 | Single-center case report | 1 (1/0) | TTE, CMR | Severe concentric LVH with RV hypertrophy; extensive diffuse LGE involving all LV walls with relative sparing of the basal-mid interventricular septum; “apical sparing” pattern on strain imaging; GLS absolute value 10%, LVEF 60% | No long-term clinical outcome follow-up; implantable cardioverter-defibrillator (ICD) implanted | Single male case report only; not representative of the population; disease specificity of imaging findings requires validation in larger samples |
| Bui et al. [40], 2021 | International multicenter registry, retrospective cohort study | 22 (14/8) | TTE (speckle-tracking myocardial strain) | Mean GLS absolute value 12.2%, with apical sparing pattern; reduced GLS associated with composite adverse cardiovascular events; proposed GLS absolute value <10% as an exploratory prognostic cutoff | Composite endpoint: death, LVAD implantation, heart transplantation, secondary prevention ICD implantation; 7 cases reached endpoint | Relatively small sample size; based solely on echocardiographic strain analysis; prognostic cutoff not validated in external cohorts |
| Bui et al. [41], 2020 | Retrospective natural history study | 18 (13/5) | TTE (speckle-tracking myocardial strain) | Mean GLS absolute value 12.1%; impaired basal-mid segmental strain with relative apical sparing | No predefined clinical endpoint | Small sample size; only echocardiographic longitudinal strain assessed; no correlation analysis between imaging and prognosis; analysis performed using a single vendor software, limiting generalizability |

**Table 2. Continued.**

| Reference | Study design | Sample size (M/F) | Imaging modality | Main results | Outcome endpoint data | Major limitations |
|---|---|---|---|---|---|---|
| Wei et al. [44], 2021 | Multicenter, retrospective case series | 16 (13/3) | CMR | Symmetric hypertrophic phenotype predominates (56%); typical LGE features: basal-mid septal sparing (88%), apical involvement in all cases (100%), free wall involvement (94%), predominantly subendocardial distribution; resting perfusion defects present in 88% of patients | No long-term prognostic follow-up data, only imaging phenotype description | Small sample size, low proportion of female cases; multicenter but scanning sequences and post-processing protocols not uniform; no correlation analysis between imaging parameters and clinical endpoints; possible retrospective selection bias |
| Liu et al. [45], 2026 | Single-center, retrospective cohort study | 24 (15/9) | CMR | Hypertrophic phenotype predominates in males (73.3%), dilated phenotype predominates in females (88.9%); basal-mid septal sparing sign more common in males; female patients have more severe systolic dysfunction; female patients have higher native T1 values | No predefined clinical endpoint | Single-center study; limited sample size; lack of Danon disease-specific diagnostic cutoff values for mapping |
| Rigolli et al. [46], 2021 | Retrospective case series | 12 (5/7) | CMR | Males predominantly show concentric hypertrophy; females predominantly show asymmetric hypertrophy with RV involvement; all LGE-positive cases showed mid-septal sparing; 2 patients had no significant abnormalities on CMR | No predefined clinical endpoint | Sample size still relatively small; no quantitative mapping or strain analysis |
| López-Sainz et al. [47], 2019 | Multicenter retrospective cohort study | 27 (6/21) | TTE | Significant extracardiac multisystem involvement in males; females predominantly have cardiac involvement with rare multisystem involvement; hypertrophic phenotype is the most common; female patients experience adverse events at an older age | Endpoints: heart failure hospitalization, heart transplantation, all-cause death; 13 cases reached death or heart transplantation (4 males, 9 females) | Retrospective study design; small sample size with few male cases; no CMR tissue characterization data; data collection standards not uniform across centers; referral bias present |

**Table 2. Continued.**

| Reference | Study design | Sample size (M/F) | Imaging modality | Main results | Outcome endpoint data | Major limitations |
|---|---|---|---|---|---|---|
| He et al. [51], 2020 | Single-center retrospective case series | 6 (6/0) | CMR | 5 cases showed hypertrophic phenotype, 1 case showed dilated phenotype; LGE showed diffuse or focal distribution; 3 patients who underwent T1 mapping had mean native T1 of 1313.3 ms and mean ECV of 39.17%, both elevated; global strain and atrial functional strain impaired | Mean follow-up 1.8 years; 1 patient died; some patients received radiofrequency ablation, ICD implantation, etc. | Extremely small sample size, male patients only; mapping performed in only a subset of patients; retrospective design; no Danon disease-specific diagnostic cutoff validation; no external cohort validation |
| Wang et al. [24], 2026 | Single-center case report | 1 (0/1) | TTE, CMR, myocardial perfusion imaging | Presented initially with transient ischemic attack-like episodes; left heart enlargement, reduced LVEF; LGE involved the mid-myocardium of the interventricular septum and LV free wall; reduced myocardial perfusion | No long-term follow-up data | Single female case report only; atypical phenotype; not representative of the population; limited diagnostic specificity of imaging findings |
| McLeod et al. [58], 2019 | Single-center case report | 1 (1/0) | TTE, myocardial metabolic imaging | Severe hypertrophic cardiomyopathy phenotype; radionuclide imaging showed focal increased FDG uptake | ICD implanted | Single case report only; no disease specificity |

Abbreviations: DDACM, danon disease-associated cardiomyopathy; TTE, transthoracic echocardiography; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device; ICD, implantable cardioverter-defibrillator; LVMI, left ventricular mass index; ECV, extracellular volume; M/F, male/female.

and technical limitations of quantitative T1/T2 mapping and ECV parameters; emphasize the importance of an integrated, multimodality imaging approach for comprehensive diagnosis; and provide a brief overview of imaging-based assessment in patients with DD in the era of gene therapy.

DDACM is a rapidly progressive, inherited cardiomyopathy associated with high morbidity and mortality. Imaging plays an essential role in the comprehensive management of this disease, with echocardiography serving as the first-line imaging modality for early diagnosis and longitudinal surveillance. Compared with LVEF, GLS demonstrates superior sensitivity for detecting subclinical myocardial dysfunction, while also providing incremental value for risk stratification. Owing to its excellent soft-tissue characterization, distinctive LGE patterns, and quantitative T1/T2 mapping techniques, CMR provides a more accurate evaluation of myocardial fibrosis and edema, as well as playing an important role in differentiating DDACM from other cardiomyopathies. Chest X-ray and cardiac CT have limited roles in the evaluation of DDACM. In contrast, myocardial nuclear imaging may offer complementary insights into myocardial perfusion and metabolic alterations, although its clinical application remains to be further explored. AI-assisted diagnosis, multimodal imaging, and radiomics have the potential to significantly improve the diagnosis and management of DDACM. The establishment of large-scale, multicenter, and prospective cohort studies is an important direction for future research.

## Abbreviations

DD, Danon disease; LAMP2, lysosome-associated membrane protein 2; DDACM, Danon disease-associated cardiomyopathy; HCM, hypertrophic cardiomyopathy; CMR, cardiac magnetic resonance; LVAD, left ventricular assist device; WPW, Wolff–Parkinson–White; AVB, atrioventricular block; CK, creatine kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LVH, left ventricular hypertrophy; SAM, systolic anterior motion; LVOT, left ventricular outflow tract; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; GLS, global longitudinal strain; GRS, global radial strain; GCS, global circumferential strain; LVMI, left ventricular mass index; LGE, late gadolinium enhancement; ECV, extracellular volume; sHCM, sarcomeric hypertrophic cardiomyopathy; CA, cardiac amyloidosis; AL-CA, immunoglobulin light-chain amyloidosis; ATTR-CA, transthyretin-related amyloidosis; FD, Anderson–Fabry disease; FC, Fabry cardiomyopathy; MD, mitochondrial disease; MCM, mitochondrial cardiomyopathy; GAA, acid α-glucosidase; AMPK, adenosine monophosphate-activated protein kinase; AI, Artificial intelligence; ICD, implantable cardioverter-defibrillator.

## Author Contributions

GS was primarily responsible for the conceptualization and research design of this study. YW, BZ, TL, YT and HH assisted in the conceptualization and research design of this study. GS, YW and BZ prepared the original draft of the manuscript. GS, YW, BZ, TL, YT and HH contributed to the revision and correction of the final manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflicts of Interest

The authors declare no conflicts of interest.

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