

Review

Cardiac imaging to predict malignant arrhythmias in non-ischemic cardiomyopathy

Toby Paterson^{1,2} · Vivetha Pooranachandran¹ 

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Abstract

Sudden cardiac death (SCD) remains a major contributor to cardiovascular disease mortality, accounting for approximately half of all related deaths. Non-ischemic cardiomyopathy (NICM) presents itself as a common yet challenging cardiac condition. High-risk patients could potentially benefit from implantable cardioverter defibrillators (ICD). However, the limited capacity to accurately identify these individuals results in unnecessary procedures for some and overlooked preventative measures for others, leading to potentially avoidable mortality. The conventional approach to assessing the risk of SCD has primarily involved evaluating the ejection fraction (EF) via echocardiography. However, advanced cardiac imaging techniques, such as cardiac magnetic resonance imaging (CMR), computed tomography (CT), positron emission tomography (PET), and single-photon emission computerised tomography (SPECT) have emerged as promising non-invasive methods for VA and SCD risk assessment. These imaging modalities offer valuable insights into the structural and functional abnormalities that predispose individuals to sudden cardiac death. As a result, these advanced imaging methods have the potential to enhance risk stratification and improve patient outcomes by identifying individuals at high risk of SCD who may benefit from early interventions. This review aims to fill a critical gap in current literature by identifying which imaging features are most strongly associated with malignant arrhythmias in NICM, thus moving beyond traditional risk markers. Each modality provides unique insights into structural, functional, or metabolic changes that may indicate arrhythmogenic potential in NICM. Systematically assessing each imaging method's strengths contributes to a deeper understanding of their individual roles in risk stratification.

Keywords Cardiac imaging · Non-ischaeic cardiomyopathy · Ventricular arrhythmia · Sudden cardiac death

1 Introduction

The significance of utilising cardiac imaging in the realm of clinical decision-making for cardiovascular diseases cannot be emphasised enough. Its pivotal role in assessing and predicting the risk of malignant arrhythmias and sudden cardiac death (SCD) in patients with non-ischemic cardiomyopathy (NICM) has garnered substantial attention and recognition. However, the utilisation of imaging modalities presents its own set of challenges, encompassing the selection of the most appropriate investigative methods and suitability for individual cases. Furthermore, mastering the interpretation of cardiac images is an endeavour that necessitates extensive time and dedication, adding to the complexity of this field. Additionally, the acquisition and operation of various imaging tools contribute significantly to the overall cost of patient

✉ Vivetha Pooranachandran, Vivetha1@mdx.ac.uk | ¹Department of Natural Sciences, Middlesex University, London NW4 4BT, UK. ²Department of Cardiology, North West Anglia, Peterborough, UK.



care. This comprehensive review aims to delineate and explore the array of available imaging tools that play a pivotal role in predicting the risk of SCD in patients with NICM (Table 1).

NICM is a term used to describe a disease of the heart muscle that has causes other than ischemia. This encompasses a wide range of potential causes, including genetic factors, acquired conditions, and secondary aetiologies [1]. Regardless of the specific cause, these conditions often lead to clinical heart failure, which can manifest as either reduced or preserved ejection fraction of the ventricles. In the UK, this condition is a significant concern as cardiomyopathy is associated with an increased risk of ventricular arrhythmia (VA) and SCD [2].

Cardiac imaging has undergone significant developments, emerging as a vital tool for comprehensively assessing cardiac anatomy and gaining insights into the pathophysiology of various conditions. The data derived from these imaging techniques play a crucial role in steering clinicians toward accurate treatment strategies and optimal patient care pathways. The shift towards non-invasive diagnostic approaches in cardiology has not only elevated the quality of patient care but has also reduced associated risks.

These advanced imaging modalities adhere to established gold standards set forth by esteemed organisations such as the British Society of Echocardiography (BSE), the Royal College of Radiologists (CoR), the British Cardiovascular Society (BCS), and the British Society of Cardiovascular Imaging (BSCI). Notably, recent technological advancements have significantly enhanced the accuracy of these imaging techniques, leading to more precise and reliable diagnoses [3].

1.1 Echocardiography

Historically, the use of echocardiography as the primary imaging modality has been crucial in evaluating the risk of VA and SCD in patients, particularly to the patient's left ventricular ejection fraction (LVEF). LVEF has historically been central in assessing SCD risk due to its correlation with heart failure severity. Traditionally, a severe decline in LVEF to 35% or lower has been a key determinant for the implantation of an implantable cardiac defibrillator (ICD), following the guidelines set by the European Society of Cardiology [4]. This approach has been supported by extensive research indicating a reduction in mortality rates.

However, LVEF's limitations are increasingly evident, especially in NICM patients, where SCD events can occur despite preserved or moderately reduced LVEF. Unlike in ischemic cardiomyopathy, where a severely reduced LVEF ($\leq 35\%$) is a reliable predictor of SCD, many NICM patients face arrhythmic risks even with normal or only moderately reduced LVEF. This discrepancy arises because LVEF fails to capture structural abnormalities such as myocardial fibrosis or arrhythmogenic substrates that are common in NICM and are significant contributors to arrhythmia risk. Therefore, relying solely on LVEF can result in high-risk patients being overlooked while potentially low-risk patients undergo unnecessary ICD implantation [5].

Moreover, ICD therapy carries risks and high costs, which are especially concerning if patients do not experience arrhythmic events. ICDs can lead to complications, including infection, lead failure, and inappropriate shocks, which can significantly impact patient quality of life. These factors highlight a critical need for more targeted, accurate selection criteria, particularly for NICM patients, where the unpredictability of arrhythmic events is higher. This review addresses these limitations by investigating alternative imaging markers, such as Global Longitudinal Strain (GLS), Mechanical Dispersion (MD), late gadolinium enhancement (LGE), extracellular volume (ECV), and T1 mapping. These imaging techniques can detect structural and functional abnormalities beyond what LVEF measures, offering a more comprehensive approach to identifying NICM patients at high risk for SCD. By highlighting these alternatives, the review provides a valuable contribution towards improving NICM risk stratification and potentially optimising patient outcomes and resource allocation.

Risk stratification for sudden cardiac death (SCD) evaluates a patient's clinical and functional status to assess their SCD risk. Recent data has demonstrated that a significant proportion of patients who experience SCD do not present with an LVEF below 35% [6]. In light of this, there is a growing need to identify new markers that can enable more precise risk stratification for VA and SCD. Specifically, MD and GLS are emerging as potential indicators for more effective risk assessment. These markers offer the promise of enhancing our ability to predict and manage the risk of adverse cardiac events, especially in cases where LVEF alone may not provide a comprehensive risk assessment.

1.2 Left ventricular ejection fraction

LVEF is a vital measurement used to assess the heart's efficiency in pumping blood. It is calculated by determining the percentage of blood pumped out of the left ventricle with each heartbeat. LVEF values play a key role in classifying the severity of left ventricular dysfunction, with percentages below 35% indicative of severe dysfunction and percentages

Table 1 Key imaging predictors used in stratifying risk for ventricular arrhythmias and sudden cardiac death in patients with non-ischemic cardiomyopathy

Predictor	Population	Hazard Ratio	Confidence Interval	P Value	Clinical Information	Author	Publication Year
Left Ventricular Ejection Fraction (LVEF)	1116 NICM patients with LVEF less than 35%	0.50	0.31–0.82	0.005	Limited predictive value for SCD in NICM	Kober, et al	2016
Mechanical Dispersion (MD)	94 NICM patient	1.28	1.11–1.49	0.001	Increased MD correlates with higher VA risk, independent of LVEF	Haugaa, et al	2012
Global Longitudinal Strain (GLS)	70 NICM and ICM patients	0.84*	-	<0.001	GLS < -10 cm/s predicted VA risk with high specificity, even with preserved LVEF	Niko, et al	2020
Late Gadolinium Enhancement (LGE) Extent	97 NICM patients	60.81	5.14–80.34	0.001	Anterior wall LGE increase VA risk	Tat, et al	2022
Extracellular Volume (ECV)	195 NICM patients	14.1	1.8–111.2	0.01	ECV ≥ 30% linked to higher VA risk; valuable in diffuse fibrosis detection	Di Marco, et al	2023
T2 Mapping	859 HCM patients	22.8**	1.4–361.6	0.026	High T2 signal associated with higher arrhythmic events and adverse outcomes in HCM	Kirshenboim, et al	2023
Cardiac CT (Septal Scar)	33 NICM patients	3.0**	0.9–10.7	0.078	CT offers high-resolution scar detection; septal scars linked to repeat VT ablation risk	John et al	2024
PET (Myocardial Scar)	439 HF patients with LVEF < 35%	1.46	0.99–2.16	0.054	PET identifies non-transmural scar/hibernation burden as a strong predictor of ICD shocks and SCD events	Gupta et al	2018
SPECT (H/M Ratio)	961 HF patients	0.37	0.16–0.85	0.02	Low heart-to-mediastinum ratio predictive of arrhythmic events and SCD risk	Jacobson et al	2010

HF; Heart Failure, NICM; Non-Ischemic Cardiomyopathy, ICM; Ischemic Cardiomyopathy, HCM; Hypertrophic Cardiomyopathy, VA; Ventricular Arrhythmia, SCD; Sudden Cardiac Death, ICD; Implantable Cardioverter-Defibrillator, CT; Computed Tomography, PET; Positron Emission Tomography, SPECT; Single-Photon Emission Computed Tomography, H/M Ratio; Heart-to-Mediastinum Ratio. *Area Under Curve, ** Odds Ratio

above 55% suggesting normal function. However, it's important to understand that even individuals with a normal LVEF can still experience heart failure, particularly in cases of HFpEF (heart failure with preserved ejection fraction). HFpEF occurs when the heart muscle becomes thick and stiff, resulting in inadequate blood pumping despite the LVEF appearing normal. This condition highlights the complexity of heart failure and underscores the importance of considering additional factors beyond LVEF in its diagnosis and management.

Numerous small-scale studies have indicated the limited efficacy of LVEF in predicting VA and SCD. However, the publication of the SCD-HeFT study reformed the approach to managing patients with NICM. The trial included 1308 patients with ischemic cardiomyopathy (ICM) and 1213 patients with dilated cardiomyopathy. SCD-HeFT revealed that supplementing standard therapy with a single-lead, shock-only ICD reduced five-year all-cause mortality by 23% in patients with reduced LVEF (< 35%) and New York Heart Association (NYHA) class II-III symptoms. Nonetheless, the assessment of arrhythmic rates in SCD-HeFT showed only a 5% annual risk of arrhythmia in the studied patient cohort [7].

The reliability of using LVEF as a predictor for SCD has been questioned by several small and large-scale trials. One well-known trial, the DANISH trial, examined the effectiveness of ICDs in patients with non-ischaemic systolic HF on mortality. The trial randomly assigned 1116 patients with NICM, LVEF $\leq$ 35%, and symptomatic HF to receive either ICD $\pm$ Cardiac Resynchronisation Therapy (CRT) along with guideline-directed optimal medical therapy, or to receive optimal medical therapy alone. Over a medium follow-up of 5.6 years, the two groups showed no significant difference in all-cause mortality (21.6% for ICD group vs. 23.4% for medical therapy group, (HR: 0.87 CI 0.68–1.12 P = 0.28). However, a significant reduction (3.8%) in SCD was observed in the ICD group (HR: 0.50, CI 0.31–0.82 P = 0.005). A subgroup analysis also showed an overall survival benefit in patients under 68 years of age (HR: 0.64, CI 0.45–0.90, P = 0.01). A substantial proportion of patients in this trial received CRT (58%), with over 65% of patients being over 70 years of age. Although this may have influenced the final outcome, the results highlight the urgent need to enhance patient selection for risk stratification of NICM patients [8].

1.3 Global longitudinal strain

GLS is a measure that quantifies the percentage of longitudinal shortening in the myocardium, expressed as a change in length relative to baseline length. This measure is obtained using speckle tracking and involves analysing apical images of the LV through post-processing techniques. GLS derived from 2D speckle tracking echocardiography (STE) is an innovative approach used to identify and measure subtle disruptions in global long-axis left ventricular systolic function.

Numerous research studies have been conducted to explore the association between GLS and VA in NICM patients. In a study conducted by Haugaa et al., the predictive value of GLS in patients with dilated cardiomyopathy was assessed. The researchers found that both LVEF and GLS were significantly reduced in patients who experienced arrhythmic events compared to those who did not ($28 \pm 10\%$ vs. $38 \pm 13\%$, P = 0.01, and $-6.4 \pm 3.3\%$ vs. $-12.3 \pm 5.2\%$, P < 0.001, respectively) [9]. Similarly, a study by Nikoo et al., assessed GLS in 70 cases of ischaemic or non-ischaemic cardiomyopathy with an LVEF $\leq$ 40%. The study found a significant difference in GLS between patients with arrhythmic events and those without in both cardiomyopathy groups (-6.97 ± 3.06 vs. -11.82 ± 4.25 ; P < 0.001). Moreover, the study revealed that a GLS value below -10 cm/s could predict the occurrence of a ventricular arrhythmic event with 90% specificity and 72.2% sensitivity (AUC = 0.84, P < 0.001). These findings indicate that a reduced GLS could be indicative of an elevated risk of arrhythmic events in patients with compromised heart function, and may serve as a clinically useful marker for identifying patients at risk of VA, particularly in the context of reduced LVEF [10].

1.4 Mechanical dispersion

MD is a term used to describe the variability in the timing of contractions in different segments of the LV during each heartbeat. It provides insight into the spread of mechanical activation within the LV and is evaluated using speckle-tracking echocardiography, a method that analyses ultrasound images of the heart [11]. This technique measures the longitudinal strain (shortening) in 16 segments of the LV and calculates the standard deviation (SD) of the time from the start of the QRS complex (the electrical signal triggering ventricular contraction) to the point of maximum shortening. An increase in mechanical dispersion has been linked to VA and SCD.

In 2010, Haugaa et al. published a significant report that established the correlation between mechanical dispersion and the risk for VA. Their study involved a 2.3-year follow-up of 85 post-myocardial infarction patients, 38 of whom

experienced VA necessitating ICD therapy. The research revealed that patients with recorded ventricular arrhythmias had greater mechanical dispersion compared to those without (85 ± 29 vs. 56 ± 13 ms, $P < 0.001$), with a 25% increased risk for ventricular arrhythmias for every 10-ms increase in mechanical dispersion [12].

A subsequent study by Haugaa et al., examined 94 patients with non-ischemic dilated cardiomyopathy and found that those with VA exhibited increased MD compared to those without (98 ± 43 vs. 56 ± 18 ms, $P < 0.001$). The study also demonstrated that MD could predict arrhythmias independently of LVEF (hazard ratio, 1.28; 95% confidence interval, 1.11–1.49; $P = 0.001$). Since then, numerous studies have reported a substantial correlation between MD and VA across various types of cardiomyopathies, including ischemic, nonischemic, Chagas disease, hypertrophic cardiomyopathy, mitral valve prolapse, and Brugada syndrome [9].

Comparative studies of LVEF, GLS and MD have additionally been performed to assess individual prediction tools. Mornoş et al., conducted a study involving 340 heart failure (HF) patients, 48 of whom experienced VA/SCD. Their findings demonstrated that GLS/MD served as an independent predictor of SCD/VA, with a hazard ratio (HR) of 3.22 (95% CI 1.72–6.15, $P = 0.03$). The study also identified $-0.2\%/ms$ as the optimal cutoff value for predicting VA and SCD, with a sensitivity of 80% and specificity of 76%. Additionally, individuals with $GLS/MD \leq -0.2\%$ showed significantly better free survival (log-rank test, $p < 0.001$) [13].

In a recent comprehensive study involving 290 patients with NICM and ICM and $LVEF < 40\%$, both MD and GLS were identified as significant markers for VA. Specifically, MD was found to be an independent predictor of VA (HR: 1.19; 95% CI 1.08–1.32, $P = 0.001$), while LVEF did not show significant predictive value ($P = 0.14$) [14]. In comparison to LVEF, MD and GLS provide additional insights into SCD risk by capturing subtleties in myocardial contraction and deformation. These parameters offer predictive value beyond LVEF by identifying early myocardial dysfunction, even in patients with preserved or borderline LVEF. Nevertheless, specific conditions falling within the NICM category have distinct predictive factors. For example, hypertrophic cardiomyopathy and dilated cardiomyopathy are accurately predicted by GLS/MD, whereas Anderson-Fabry disease is better forecasted by MD and fibrosis [15].

1.5 Cardiac magnetic resonance imaging

The prediction of VA and SCD using LVEF has limitations in sensitivity and specificity. In light of this, research has been focused on identifying better predictors in CMR imaging and echocardiography, especially concerning NICM. Current findings suggest that CMR, particularly through the use of LGE, can effectively evaluate myocardial tissue heterogeneity, scar patterns, interstitial fibrosis, LV mass index, wall thickness, and myocardial fibrosis, which are powerful predictors of SCD in NICM. Additionally, CMR has proven to be highly efficient in assessing sarcoidosis, showing twice the sensitivity in detecting cardiac involvement in the condition [16].

1.6 Late gadolinium enhancement

LGE is an intriguing phenomenon observed in cardiac magnetic resonance imaging (MRI), where both contrast and image delay are used in combination to highlight regions of scarring in the myocardium. The mechanism behind LGE is based on the behaviour of the contrast agent gadolinium, which accumulates solely in the extracellular space and not within cells. Consequently, it tends to accumulate to a greater extent and takes longer to dissipate in regions of increased extracellular volume, such as areas affected by fibrosis, compared to healthy myocardial tissue [17]. This phenomenon is notably common in NICM, particularly in patients with dilated cardiomyopathy, with an occurrence rate of approximately 30% among affected individuals. Importantly, research has demonstrated that LGE holds predictive value in forecasting clinical outcomes, including all-cause mortality and SCD [18]. In a comprehensive meta-analysis conducted by Al-Sadawi et al., a total of 46 studies involving 10,548 patients with NICM were reviewed. Out of these patients, 4610 exhibited LGE, while 5938 did not. The analysis revealed a significant association between the presence of LGE and an increased risk of VA and SCD, with an odds ratio of 5.1 (95% CI 3.5–6.0, $p < 0.01$) [19].

The distribution of myocardial scar within the heart provides crucial insights into the underlying pathology and plays a significant role in guiding treatment strategies. The classic subendocardial distribution of scar is frequently observed in cases of ischaemic cardiomyopathy, which is caused by reduced blood flow to the heart. Conversely, the distribution of LGE is typically either subepicardial or midwall, and this pattern is more commonly associated with NICM, a condition not caused by reduced blood flow to the heart. Understanding these different patterns of scar distribution is essential for risk stratification by revealing disease specific fibrosis locations, which can affect arrhythmia risk [20].

Studies in recent years have delved into the significance of LGE in risk stratification. In a study by Tat et al., 97 patients with NICM were examined to identify LGE predictors of outcomes. The findings revealed that the extent, location, and pattern of LGE all independently predicted worse outcomes for the patients [21]. The presence of LGE in the anterior wall of the heart emerged as the strongest predictor of ventricular tachycardia (VT) with a HR of 60.81 (95% CI 5.14–80.34, $p=0.001$) indicating a high risk. Moreover, LGE involvement in multiple walls was also identified as a significant prognostic factor for VT with a HR of 30.12 (95% CI 4.09–40.93, $p=0.01$). The extent of LGE proved to be predictive of VT. Specifically, LGE mass greater than the 10% median was associated with VT, as evidenced by a HR of 1.20 (95% CI 1.09–2.51, $p=0.01$). Meanwhile, midwall LGE exhibited a strong association with VA (HR 10.22, CI 1.46–17.56, $p=0.02$), whereas subepicardial LGE or the presence of both did not show the same association. This thorough assessment underscores the predictive value of LGE in detecting potential VT. Although LGE was identified as an independent predictor of prognosis in NICM, it was found that the extent, location, and pattern characteristics of LGE were more powerful indicators of worse outcomes in patients with NICM [21].

1.7 Extracellular volume and T1 mapping

In addition to the successful application of LGE in risk prediction, measuring ECV and the longitudinal relaxation time of tissue (T1 mapping), CMR enables consistent and efficient characterisation of diffuse fibrosis. This approach effectively complements the utilisation of LGE, providing a comprehensive assessment of myocardial tissue composition and fibrotic changes [22].

ECV and T1 mapping techniques offer a robust physiological basis for detecting diffusely abnormal myocardium, particularly when such abnormalities cannot be identified using LGE. ECV, in particular, is intriguing as a marker of risk in patients with NICM who do not exhibit identifiable LGE, as it provides the ability to identify diffuse interstitial fibrosis. Unlike LGE, which primarily highlights focal scars, ECV and T1 mapping quantify fibrosis extent across the myocardium, providing insights into global disease burden and VA risk. ECV values above 30% have been linked to increased arrhythmia risk, reinforcing the value of these metrics in identifying high-risk NICM patients. The complementary assessment of diffuse and regional disease through ECV mapping and LGE, respectively, may offer additional benefits for risk stratification in NICM [23].

The T1 relaxation time is a crucial parameter in MRI that measures the rate at which the nuclear spin magnetisation returns to equilibrium following a radiofrequency pulse. T1 mapping is a technique used to visualise these properties, often represented in a colour-coded scheme where pixel values correspond to the T1 values in each voxel. This method allows for the measurement of the ECV, which provides insights into the relative expansion of the extracellular matrix. Notably, even without the use of contrast agents, this process can sensitively detect myocardial oedema, iron overload, and the presence of a scar [20].

In a small-scale study conducted by Barison et al., it was observed that 89 patients with NICM exhibited higher ECV values in comparison to the control group [24]. Furthermore, the study found a positive correlation between ECV values and VA, with a correlation coefficient (R) of 0.21, $P<0.05$. Similarly, in a recent study, it was found that ECV of 30% or higher was the most reliable indicator for the occurrence of VA in patients with NICM. The study involved 703 NICM patients, 2% of whom had VA or SCD. The study also identified that the combination of the presence of LGE, $LVEF \leq 35\%$, and $ECV \geq 30\%$ provided strong predictive capabilities for VA, with a Harrell's C value of 0.82. Interestingly, T1 mapping was not found to be associated with VA or SCD. The findings suggest that when a region of dense scar is surrounded by fibrotic myocardium, the risk of VA is higher compared to when the scar is surrounded by normal myocardium [25].

1.8 T2 mapping

The T2 time, known as the spin–spin or transverse relaxation time, is a crucial measure in magnetic resonance imaging (MRI) that reflects the decay of transverse magnetisation. This decay is tissue-specific and offers valuable insights into differentiating normal from abnormal tissue [26]. Changes in the T2 time are indicative of alterations in tissue composition, and while they are not specific to a single disease, they provide crucial information about disease processes. When considered alongside other parameters or in the context of a specific clinical scenario, T2 time can significantly contribute to the diagnosis of a disease, assessment of disease activity, and evaluation of its repair. T2 values are closely linked to water content in the respective tissue. In the myocardium, T2 maps play a vital role in evaluating myocardial oedema, particularly in the context of myocardial inflammation or myocardial infarction. Moreover, T2 values can also be utilised to assess other pathological conditions within the myocardium [20, 27].

The use of T2 in assessing fibrosis has been suggested, although this area still lacks comprehensive study. T2 mapping is particularly useful in diagnosing myocarditis as a potential cause of VT. In a limited study, the relationship between T2 and VA in 148 patients with HCM was assessed. Patients with elevated T2 signal (> 55 ms) had more non-sustained VT on Holter (26.3 vs 12.5%, $p = 0.05$) [28]. Similarly, a recent study by Kirshenboim et al., who assessed T2 values in septal and apical variants of HCM found the 3rd tertile of T2 values (48 ± 8 ms) were significantly associated with VA 92% vs. 57 and 40% in lower tertiles, $p = 0.02$ [29]. In addition, the T2-weighted short-tau inversion recovery (T2w-STIR) sequence has been employed to evaluate myocardial oedema in survivors of cardiac arrest. The presence of oedema, thought to represent a transient arrhythmogenic substrate, has been linked to a reduction in ICD shocks [30].

Nevertheless, it is important to acknowledge several limitations associated with CMR imaging. Common pitfalls include the long acquisition time, relatively low spatial resolution and high costs associated with CMR. The majority of standard CMR sequences, such as cine and LGE, are a combination of multiple cardiac cycles and require a consistent regular heart rate. However, this can be affected by frequent ectopic heartbeats, which are common in NICM patients. Additionally, CMR images are typically acquired during a 10-s breath-hold, which can be challenging for some patients with cardiomyopathy. Real-time cine imaging, where each image is generated from just one heartbeat, can help mitigate some of these challenges. However, this approach sacrifices temporal and spatial resolution. Lower-resolution single-shot LGE sequences are reliable in the presence of irregular heartbeats, and newer motion-corrected free breathing LGE can be used for patients who are unable to hold their breath. One prevalent limitation is the incompatibility of implantable cardiac defibrillators (ICDs). Although MRI-compatible devices have been developed in recent years, they still generate device-related artifacts that can adversely affect the diagnostic utility of the study. Scar characterisation is particularly susceptible to ICD artifacts, often impacting multiple myocardial segments [20].

1.9 Computed tomography

Computed tomography (CT) is a specialised medical imaging technique that utilises X-rays to create detailed cross-sectional images of the body. The process involves taking a series of X-ray views from different angles and then using a computer to process this information to produce detailed, three-dimensional images of the body's internal structures. This technology is non-invasive and provides valuable information for diagnosing and treating various medical conditions [31]. CT imaging is not typically used to directly detect VA in NICM, however, it has greatly contributed to the accurate diagnosis of NICM subtypes and improved VT ablation strategies.

In a study by Yamashita et al., in which image-integration was used to guide VT ablation in 116 patients (67 ICM, 30 NICM, 19 Arrhythmogenic right ventricular cardiomyopathy (ARVC)), 89% of critical VT isthmuses and 85% of local abnormal ventricular activities (LAVA) sites were identified. However, the efficiency in identifying LAVA with imaging was higher in ICM (90%) and ARVC (90%) than in NICM (72%), $p < 0.0001$ [32].

A recent small-scale study has attempted to evaluate the role of CT in risk prediction. Galand et al., assessed LV wall thickness (LV WT) in 33 NICM cardiac resynchronisation therapy recipients and found that those with a total percentage of LV WT < 6 mm $\geq 40\%$ are at high risk of VA [33]. Similarly John, et al., assessed late iodine-enhanced CT in the characterisation of scar that gives rise to VT, and found that those with septal scar on CT were found to be a better predictor of VT recurrence (OR 3.0, 0.9–10.7, $p = 0.078$). The study determined septal late iodine-enhanced CT have a nearly threefold increased risk of needing a repeat VT ablation [34]. Comparably, another recent study by Xu, et al., assessing lipomatous metaplasia (LM) using contrast enhanced CT found NICM patients with LM extent 2.5 g had a HR of 4.9 for VT recurrence following ablation ($P < 0.001$) [35].

A key benefit of CT over other imaging modalities is its higher spatial resolution and a genuine three-dimensional dataset that can be visualised in any imaging plane. Furthermore, the rapid image acquisition during a cardiac CT takes only seconds, rendering a CT scanner a safer option than an MRI scanner for a patient with VA. Even at 3 T, CMR resolution is confined to a voxel size of 1.4 mm^3 , whereas CT can achieve a voxel resolution of less than 0.4 mm^3 . Due to its exceptional resolution, CT is well-suited for defining anatomical pathologies, such as ventricular aneurysms, vascular anomalies, and congenital abnormalities. However, it is important to take into account several limitations of CT. The lower contrast-to-noise ratio within myocardial tissue of CT compared with CMR leads to poorer tissue characterisation. CT also provides less functional information compared with CMR and carries the additional risks of radiation exposure and iodinated contrast administration [27].

Although CT is not likely to be considered the gold standard over CMR, it can be regarded as a useful alternative through the utilisation of late-enhanced multi-slice formatting to detect fibrosis, thus providing good anatomical detail

and detection of thin-walled scars. This could prove to be highly beneficial if models are developed, particularly for patients who prove to be contraindicated for CMR assessment [36].

1.10 Single photon emission computed tomography and positron emission tomography

Nuclear imaging provides the unique ability to target different pathophysiological aspects of the arrhythmic substrate, depending on the biological pathway of the utilised tracer. Consequently, nuclear techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) allow the evaluation of perfusion, scar, metabolism, and sympathetic innervation [37].

SPECT is a potentially useful imaging technique to evaluate SCD risk in an atypical sense compared to the previously mentioned imaging. Instead, SPECT can be used to identify SCD risk based on autonomic and sympathetic innervation [36].

Assessment of sympathetic innervation involves the use of radiolabeled catecholamines, with 11C-hydroxyephedrine being the most commonly used tracer in PET, and iodine-123-labeled metaiodobenzylguanidine (MIBG) the most commonly used tracer in SPECT. When there is a globally decreased uptake of these tracers, it is indicative of an increased sympathetic tone, which has the potential to precipitate in malignant arrhythmias [27].

The heart-to-mediastinal (H/M) ratio is a commonly used parameter to measure cardiac MIBG uptake, and it is estimated using early and late anterior planar images acquired 15 min and 4 h after MIBG injection, respectively. The washout rate (WR) in SPECT is derived from MIBG scintigraphy and refers to the rate at which a radiopharmaceutical agent clears from the myocardium [38]. A reduced H/M or WR is thought to indicate sympathetic denervation, increasing the risk of malignant arrhythmias.

The use of SPECT or PET in VA/SCD was not assessed in many studies. From the available studies, Kioka et al., found that WR correlated with an increased risk of SCD [39]. Whereas Nagahara, et al., demonstrated that H/M can be utilised as an independent predictor for appropriate ICD therapy [40]. A larger trial; ADMIRE-HF confirmed these findings by demonstrating 237/961 HF subjects with reduced H/M on SPECT scan experienced arrhythmic events: HR 0.37, $p = 0.02$ [41]. Although this trial provided the independent prognostic value of MIBG, studies on SPECT interlinking with the previously mentioned SCD risk identifiers and NICM are very limited, identifying a potentially promising field for research.

Similarly, PET is a valuable imaging technique that enables the detection of areas of inflammation within the heart, particularly in cases involving cardiac sarcoidosis. Through the use of radiotracers like F-fluorodeoxyglucose (FDG), PET allows for the visualisation of non-viable tissue, which may serve as a substrate for the development of re-entrant arrhythmias. Additionally, PET provides myocardial blood flow measurements (the gold standard for myocardial perfusion imaging (MPI)) that help detect areas of inadequate blood flow due to granulomas (i.e. in sarcoidosis) or active inflammation [42].

Gupta, et al., studied the use of PET scan among 439 patients with $EF < 35\%$ and showed that scar alone, and not reversible ischemia was significantly associated with ICD firing and SCD [43]. Combining MPI with imaging of cardiac inflammation using (FDG) has identified higher-risk cardiac sarcoidosis patients independent of LVEF and clinical markers [44]. Although limited in research, this capability to identify and visualise such inflammatory and non-viable tissue can significantly aid in the diagnosis and management of cardiac conditions, leading to improved patient outcomes.

1.11 Arrhythmogenic substrate detection software

There are currently two notable types of segmentation software available for medical imaging: inHeart and ADAS 3D. Both of these software options are specifically designed to process and analyse imaging acquired through CT or CMR techniques. Their primary function is to prepare and facilitate the import of processed images into leading three-dimensional (3D) electro-anatomical mapping (EAM) systems widely used in the field of medical imaging and cardiology.

1.12 InHEART

The inHeart software conducts the segmentation of crucial anatomic features, including wall thinning, epicardial fat, myocardial fatty metaplasia, phrenic nerves, and coronary arteries. It utilises CMR or CT imaging data to generate 3D cardiac models. For CT, wall thickness of ≤ 5 mm, or hypoattenuation of ≤ 10 Hounsfield Units (HU), is identified as scar tissue, with wall thickness of ≤ 2 mm being considered dense scar. Signal intensity of $> 35\%$ of the maximum is the threshold for denoting scar tissue in CMR images. Utilising inHeart segmentation, channels are typically classified as either regions with a thickness of ≤ 5 mm, having a difference of ≥ 1 mm compared to adjacent tissue, along with channels traversing

part or the entire scar, or alternatively, channels of healthy tissue positioned between two sections of CMR-defined scar tissue [20].

1.13 ADAS

The Automatic Detection of Arrhythmogenic Substrate (ADAS) software has been specifically designed to delineate the ventricular architecture and integrate it into EAM systems. By utilising either CMR or CT data, the ADAS software is able to process and generate detailed ventricular scar maps. These scar maps vividly depict the potential conduction channels of preserved myocardium within areas of dense scar, which are commonly referred to as “border-zone corridors”. These scar maps of viable myocardium inside dense fibrosis, provide crucial insights into arrhythmogenic isthmuses and thus serve as important targets for cardiac ablation procedures. Additionally, the software facilitates the manual or automatic generation of scar maps based on LGE or late iodine enhancement, which can then be imported into the 3D EAM system, thereby greatly enhancing the precision and efficacy of various procedures related to cardiac interventions and arrhythmia management [45].

In CMR analysis, ADAS relies on pixel signal intensity (PSI) to identify scar tissue. The myocardium is divided into segments using a semi-automated approach. Subsequently, the LV is further divided into a number of layers (typically 9) from the endocardium to the epicardium. PSI maps are then generated at each layer, utilising a pixel intensity of $> 60 \pm 5\%$ as the threshold for dense scar and $< 40 \pm 5\%$ as the threshold for normal tissue. Reconstruction of each layer map is then carried out to produce a 3D model of the scar [20].

During CT imaging, ADAS utilises the measurement of wall thickness as an indicator for scar tissue. Although not validated in large-scale studies, the established cut-offs in the left ventricle are < 2 mm for dense scar and > 5 mm for normal tissue. Additionally, it is essential to emphasise that operators have the capability to manually adjust the threshold values in order to identify conduction channels [45].

Several studies have supported the use of inHeart and ADAS 3D in pre-procedural planning and reduced arrhythmic recurrences [46–49]. Nevertheless, both software have some important considerations to keep in mind. It is essential to recognise that the accuracy and usefulness of processed images showing arrhythmogenic substrate heavily depend on the quality of the CT or MRI-acquired images.

It is also crucial to acknowledge that the accuracy of merging into the 3D EAM can vary based on variable anatomy, such as chamber volume and heart orientation, which can impact otherwise standardised merging protocols. Lastly, being mindful of a potentially long time interval between image acquisition and its use for segmentation is important, as it can have an impact on anatomical accuracy at the actual time of the procedure [20]. The effectiveness of inHeart and ADAS 3D software relies on precise image acquisition that reflects the patient’s anatomy at the time of evaluation. Factors like cardiac chamber volume, anatomical variations, and the timing between image acquisition and use can affect software accuracy in identifying conduction channels for VA ablation planning.

1.14 Future of cardiac imaging

The recent technological advancements in medical imaging techniques such as MRI, CT scans, and PET scans have become significantly more accurate in diagnosing various health conditions [3]. Researchers are now directing their efforts towards exploring the potential of machine learning algorithms to further enhance the precision, efficiency, and capabilities of these imaging techniques, aiming to revolutionise the field of medical diagnostics.

Machine Learning is a subcategory of artificial intelligence with overwhelming potential to assist medical professionals. The ideology supporting machine learning is that this method can be used to understand better and predict risks and clinical situations of patients individually to support critical decisions made by clinicians [50].

ML can potentially introduce great benefits to echocardiography, as it can effectively and quickly analyse and measure maximal wall thickness to a high level and identify different risk categories based on disease phenotypes. Furthermore, ML can enhance risk assessment by evaluating multiple risk factors of disease progression and SCD. One highly promising statistic is that previous studies have discovered ML to have up to 80% sensitivity and 72% specificity, which, compared to the 58% sensitivity and 81% specificity of the ESC risk assessment guidelines, is incredible, thanks to the lower risk of underestimating risk for SCD in HCM patients [51].

ML is currently being heavily researched in CMR. One significant benefit that ML could prove to have is a higher accuracy in the analysis of LGE since human accuracy is lower than ML in regards to a large quantity of data, as seen

in CMR [6, 51]. One study performed by Okada et al. demonstrated that a supervised ML prediction model for VA in ischaemic cardiomyopathy based on CMR LGE could effectively quantify data, with an AUC of 0.72, demonstrating good performance and a respectable negative predictive value of 0.91 for VA [52]. In addition to ML's success in LGE, it has also proven beneficial in CMR when measuring ECV and T1 mapping, allowing for consistent, efficient description of diffused fibrosis, which in turn complements the usage of LGE. ECV and T1 mapping are valuable tools in assessing the risk of ventricular arrhythmia in patients with structural heart disease, as they can identify risk before significant deterioration in LVEF occurs. However, obtaining and interpreting these measurements can be challenging for practitioners, creating an opportunity for ML to provide significant benefits [53]. However, there are potential risks associated with using ML to enhance CMR. For instance, if ML algorithms are used to improve CMR image quality, there is a risk of overestimating myocardial fibrosis through noise reduction algorithms, especially if the wrong type of algorithm is employed [54]. Incorporating these inaccurate figures into an algorithm to predict the risk of SCD could result in an overestimation of risk.

CT is an imaging method that has only recently started to be used in SCD risk stratification. Currently, the majority of studies involving cardiac CT and ML focus on atherosclerosis diagnosis.⁶ The development of ML to predict SCD in NICM with CT is currently very niche, with minimal studies undertaken to investigate its potential. Despite limitations, research on MPI has yielded promising results. A study involving 2619 patients indicated that combining clinical information and MPI imaging within an ML algorithm for predicting MACE led to significantly higher predictive accuracy for 3-year risk compared to physician-led diagnosis. The AUC scores were 0.81 for the combined approach versus 0.65 for physician-led diagnosis. When using MPI imaging alone, the AUC was even higher at 0.78 [55, 56].

However, one downside of using ML in predicting SCD is the possibility of missing values in clinical variables, which could significantly reduce the accuracy of the ML models. This was demonstrated in the analysis of the REFINE SPECT registry [57]. Over a mean follow-up period of 4.7 years, 3541 patients experienced at least one major adverse cardiovascular event (MACE). Among these patients, those with no missing values achieved a predictive AUC value of 0.799. In contrast, all seven models with missing values had a lower AUC, ranging from 0.778 to 0.681, suggestive of variable influences that need to be considered when using ML models for prediction analysis. Despite the advancements in ML in nuclear imaging, some authors believe that these models will never replace the expertise of imaging specialists [58]. This is because advanced imaging and ML models enhance diagnostic capabilities, but they lack the contextual judgment of specialists who can interpret artifacts, nuances, and patient-specific factors. Imaging expertise remains essential to tailor findings to individual patient contexts, and ensure accurate diagnosis and management. Nevertheless, ML has the potential to enhance cardiac imaging by automating segmentation, identifying complex patterns, and integrating multi-parametric data, thus improving accuracy in arrhythmia risk prediction. In MRI and CT, ML could streamline analysis of large datasets, making processes more efficient and potentially revealing subtle features missed in manual interpretation.

2 Conclusion

Risk stratification of SCD in NICM patients proposes an exciting field of research, and a substantial amount of research is necessary to enhance the accessibility and efficacy of advanced imaging methods, which would in turn make it possible for a broader range of patients to undergo risk assessment using these modalities. Nonetheless, current findings indicate encouraging results, suggesting that cardiac imaging could be widely employed in the future to significantly improve the accuracy of SCD prediction for NICM patients.

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Declarations

Competing interests Toby Paterson and Vivetha Pooranachandran have no conflict of interest or financial ties to disclose

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