

Full Title: Mean entropy predicts implantable cardioverter-defibrillator therapy using cardiac magnetic resonance texture analysis of scar heterogeneity

Short Title: Mean entropy predicts appropriate ICD therapy

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Keywords

Ventricular arrhythmia, scar heterogeneity, [texture analysis](#) entropy, late gadolinium enhancement

Abstract

Background: Risk stratification of ventricular arrhythmia (VA) remains complex in both ischemic and non-ischemic populations.

Objective: Cardiac Magnetic Resonance texture analysis (CMR-TA) to determine whether scar tissue heterogeneity indices (e.g. entropy) predicts appropriate ICD therapy. We hypothesised a higher degree of scar inhomogeneity is associated with appropriate ICD therapy.

Methods: Consecutive patients underwent CMR imaging prior to ICD implantation. Left ventricular scar was manually segmented throughout the short axis stack. CMR-TA was performed using a [commercially available research software \(TexRAD, part of Feedback Medical Ltd - www.fbkmed.com, Cambridge, UK\)](#). CMR-TA comprised filtration-histogram technique where the filtration step employed a Laplacian of Gaussian band-pass filter to extract and augment/enhance features of different sizes and variation in signal-intensity corresponding to ~~to create a~~ medium texture scaled map from which histogram analysis of pixel intensity ~~was used to calculate~~ mean entropy. The primary endpoint was appropriate ICD therapy.

Results: 114 patients underwent CMR-TA (ICM n=70, NICM n=44) with a median follow-up of 955 [IQR 691-1185] days. Filtered mean entropy was significantly higher in the ICM group (5.7 ± 0.7 vs. 5.5 ± 0.7 , $p=0.045$). Overall, 33 patients received appropriate ICD therapy. Using optimised cut-offs from ROC curves, Kaplan–Meier survival analysis demonstrated time until first appropriate therapy was significantly shorter in the filtered high mean entropy group ($p=0.003$). Multivariable analysis showed filtered mean entropy was the sole predictor of appropriate ICD therapy (HR 1.882, 95% CI 1.083-3.271, $p=0.025$). In the ICM group, filtered mean entropy remained an independent predictor of appropriate ICD therapy whereas in the NICM group, $T1^{\text{native}}$ was the sole predictor of the primary endpoint.

Conclusion: Filtered mean entropy was a strong predictor of appropriate ICD therapy suggesting a potential role for CMR-TA in predicting VA and risk-stratifying patients for ICD implantation.

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Introduction

Appropriate therapy occurs in approximately one third of patients implanted with an implantable cardioverter-defibrillator (ICD) and therefore better risk stratification tools to identify those patients at higher risk of ventricular arrhythmia (VA) is required.^{1,2} Identifying patients at risk of VAs may also play an important role in the identification of patients who may benefit from prophylactic ventricular tachycardia (VT) ablation.

Cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) is accepted as the non-invasive imaging reference standard for identifying ventricular scar or fibrosis with increasing evidence that the presence and extent of left ventricular (LV) scar predicts VA.³⁻⁶ Even small areas of ventricular scar that do not necessarily cause significant LV systolic dysfunction, may result in life-threatening VAs and ventricular scar extent and morphology has been proposed as a sensitive marker of VA.⁷⁻¹⁰ Advanced CMR tissue characterisation of scar core and grayzone tissue (scar penumbra) has been shown to predict VA in patients with ischaemic cardiomyopathy (ICM).^{9,11} In patients with non-ischaemic cardiomyopathy (NICM), diffuse myocardial fibrosis acts as a potential substrate for VA and we have previously shown that T1^{native} values predict appropriate ICD therapy and VA in ICM and NICM patients^{9,10} These techniques require a learning curve with specialised protocols for T1 mapping and signal intensity derived values for grayzone analysis. Furthermore, these scar assessment methods do not fully characterise the tissue as they do not examine the entire array of pixels available from a CMR acquisition of ventricular scar and they do not consider fibrosis heterogeneity. Numerical simulation studies have shown spatial heterogeneity of fibrosis correlates directly with VA risk and is more evident as spatial size and degree of heterogeneity both increase.¹²

Quantitative texture analysis is a new technique that uses software formerly used for the assessment and stratification of solid tumours.^{13,14} Cardiac Magnetic Resonance Texture Analysis (CMR-TA) quantifies the entire distribution of pixel intensities within a region of ventricular scar from LGE imaging. A filtration-histogram technique is used which highlights image features of a specified size [and variation in signal intensity](#), followed by histogram analysis of the filtered image as previously described.¹⁴ From this, statistical parameters are derived including entropy, a measure of randomness/[irregularity](#) that characterises the complexity of an image by evaluating homogenous versus heterogenous pixels. In essence, a set of completely white pixels would have an entropy value of zero but as the scar image becomes more complex, numerous different pixel values are detected

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and the entropy value increases enabling the evaluation of complexity of ventricular scar within the myocardium. Our institution recently reported the use of CMR-TA in post-myocardial infarction patients with greater tissue heterogeneity being associated with a greater incidence of adverse outcomes.¹⁵

We therefore hypothesised that **mean** entropy calculated from CMR-TA would predict appropriate ICD therapy in patients undergoing ICD implantation.

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Methods

Study population

Consecutive patients undergoing primary and secondary prevention ICD implantation between May 2011 and January 2013 were prospectively enrolled from two cardiac centres. We have previously assessed grayzone and T1 mapping indices to assess VAs in patients included in this cohort.⁹ All study participants were on optimal heart failure +/- anti-arrhythmic therapy and underwent coronary angiography and CMR assessment prior to device implantation. ICM was defined by standard criteria (prior myocardial infarction, presence of any epicardial coronary artery stenosis >75% or coronary revascularization with a scar pattern consistent with myocardial infarction on CMR imaging). Absence of the above criteria were defined as NICM. Primary prevention was defined as ICD implantation to reduce sudden cardiac death (SCD) in at-risk individuals who had not yet experienced an aborted cardiac arrest or life-threatening arrhythmia. Secondary prevention was defined as ICD implantation to reduce SCD in patients who already had experienced an aborted cardiac arrest or life-threatening arrhythmia. The study protocol was approved by the South East London Research Ethics Committee and conducted in accordance with the Declaration of Helsinki.

CMR imaging protocol and analysis

We have previously described the CMR imaging protocol.^{9,10} In summary, CMR imaging was performed using a 1.5 Tesla (T) scanner with a 32-channel cardiac phased array surface coil (Philips Healthcare, Best, The Netherlands). Following a Look-Locker acquisition to identify the optimum inversion time, an inversion-recovery gradient-echo pulse sequence was used to acquire a stack of short axis slices 10-15 minutes after Gadobutrol 0.2 mmol/kg body weight contrast injection (Bayer Schering Pharma, Berlin, Germany) for LGE assessment from which scar indices were calculated. CMR-derived scar indices for 2 standard deviation (SD) method (Scar^{-2SD}), full-width half-maximum (FWHM) method (Grayzone^{-2SD-FWHM}) and T1 mapping have been previously described.^{9,10,16} Both scar and grayzone

indices were indexed as percentage of the LV mass for analysis. Two independent CMR experts blinded to the study endpoint visually assessed the CMR LGE images separately and resolved any discrepancies mutually.

Cardiac Magnetic Resonance Tissue Analysis (CMR-TA)

Patients without visible scar were excluded from the study. All areas of visible scar throughout the short axis stack of the LV were manually segmented and analysed using [a commercially available](#) TexRAD research software (~~TexRAD Ltd., www.texrad.com~~, Feedback ~~Medical Ltd, Plc~~, Cambridge, UK - [www.fbkmmed.com](#)). Manual segmentation was performed by a CMR-trained cardiologist blinded to the study endpoint and patient identifiers. For [inter-rater](#) agreement, a second CMR-trained cardiologist performed manual segmentation blinded to the initial assessors' results. CMR-TA was performed as previously described with regions of interest (ROI) drawn around areas of LGE, carefully incorporating the scar border and excluding surrounding myocardium.¹⁵ [CMR-TA comprised filtration-histogram technique where the s](#)Segmented LV LGE short axis images were subsequently filtered using a Laplacian of Gaussian band-pass filter to extract and [enhance/augment](#) features of different sizes [and variation in signal intensity](#) based on the spatial scale filter (SSF) values from 2-6mm (SSF2-6) radius [where SSF=2mm, SSF=3-5mm and SSF=6mm](#) corresponded ~~ing~~ to fine, medium and coarse texture scales respectively (Figure 1) as previously described.^{14,15} Quantification of the scar texture with histogram analysis of pixel intensity was then performed, generating statistical parameters including entropy. For the purposes of this study, we evaluated whether filtered mean entropy with a medium spatial scale filter ([SSF=4 i.e. medium texture](#)) predicted appropriate ICD therapy in patients with ICM and NICM undergoing ICD implantation ~~and and~~ compared the results to unfiltered/[without-filtration](#) (raw/[conventional](#) LGE image) mean entropy (SSF0) [as control \(against the filtered medium texture\)](#), $T1^{native}$, $Grayzone^{2SD-FWHM}$ and scar [core](#) ($scar^{-2SD}$).

Follow-up and endpoint

All patients received an ICD or cardiac resynchronisation therapy ICD (CRT-D). A standardized program for appropriate VA detection and ICD therapy with anti-tachycardia pacing (ATP) or shock therapy was used as previously described.⁹ VAs >170 beats/minute (detection count >16 intervals) were treated with ATP initially, then shock therapy for unsuccessful ATP. First-line shock therapy was used for VAs >210 beats/min (detection count 24/30 intervals). Patients were followed up at three-month intervals by an experienced device physiologist who evaluated any recorded events with an electrophysiologist with both investigators blinded to the CMR data. The primary endpoint was delivery of appropriate ICD therapy for VT or ventricular fibrillation (VF) documented by the device.

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Statistical analysis

Discrete data are presented as n values with corresponding percentages in parentheses and continuous data as mean \pm 1 standard deviation. Time to events are shown as median with interquartile range (IQR) in brackets. Discrete demographic variables were compared using the Fisher's exact test. Continuous data were assessed for normality using the Shapiro-Wilk test where a p value ≤ 0.05 was accepted as normally distributed data. Normally distributed data were subsequently compared with an independent samples t-test. Continuous data that was not normally distributed were compared using the Wilcoxon signed-rank test. The first episode of appropriate ICD therapy for VT or VF was considered as the event of interest for quantifying various associations. Inter-rater agreement was evaluated using a Bland-Altman plot and linear regression analysis. Univariate and multivariate Cox proportional hazard regressions were performed to determine independent predictors of appropriate ICD therapy. Separate multivariable models were used to avoid multicollinearity where variables correlated. To avoid overfitting, we restricted our multivariable models to a maximum of five variables for the combined ICM and NICM group analysis and three variables when assessing ICM and NICM groups independently. Variables found to be statistically significant at univariable analysis as well as important clinical covariates were used as the basis for multivariable analysis. A value of $p \leq 0.05$ was considered to be statistically significant. All reported associations are presented as hazard ratio (HRs) with corresponding 95% CIs. Receiver operating characteristic (ROC) curves for mean entropy (SSF4) and unfiltered mean entropy were plotted to identify optimal threshold values (cut-offs) determined by Youden's index against which clinical variable???. Optimised threshold values were retrospectively used to dichotomize study subjects into high mean entropy and low mean entropy groups determined by whether subjects had met the primary endpoint. Kaplan–Meier survival curves were subsequently plotted to evaluate cumulative event rates and the log-rank test was employed to assess differences between the survival distributions. Statistical analysis was performed using SPSS Statistics (IBM Corporation. Released 2017. IBM Statistical Package for the Social Sciences (SPSS) Statistics for Apple Macintosh, Version 24.0.0.1. Armonk, NY: IBM Corporation).

Results

A total of 114 patients underwent CMR-TA, 70 (61.4%) with ICM and 44 (38.6%) with NICM. In the NICM cohort, aetiologies were 41/44 (93.2%) idiopathic dilated cardiomyopathy, 2/44 (4.5%) hypertrophic cardiomyopathy and 1/44 (2.3%) sarcoidosis. Primary prevention ICD implantation occurred in 78/114 (68.4%) patients. Demographics are presented in Table 1. Patients with ICM were

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older (67.1 ± 10.2 vs. 58.6 ± 15.3 years, $p = 0.005$) with a significantly greater number of patients with LV ejection fractions (LVEF) $\delta 35\%$ (84.3% vs. 63.6% , $p = 0.014$). Filtered mean entropy (SSF4) was significantly higher in the ICM group (5.7 ± 0.7 vs. 5.5 ± 0.7 , $p = 0.045$) as was unfiltered mean entropy (4.6 ± 0.4 vs. 4.3 ± 0.5 , $p = 0.003$). The ICM group had significantly higher scar indices of regional fibrosis with grayzone and scar core compared to the NICM group (Grayzone^{-2SD-FWHM} 10.1 ± 4.9 vs. 7.1 ± 6.0 , $p = 0.002$; Scar^{-2SD} 25.0 ± 9.1 vs. 16.2 ± 13.3 , $p < 0.001$; Scar^{-FWHM} 15.0 ± 6.5 vs. 9.0 ± 8.6 , $p < 0.001$). Both groups were balanced for gender and other comorbidities listed in Table 1.

Primary endpoint

During a median follow-up of 955 [IQR 691-1185] days, 33 (28.9%) patients met the primary endpoint. The median time to first appropriate ICD therapy was 329 [116-529] days for the entire cohort and similar between ICM and NICM groups (340 [101-515] vs. 329 [204-532], $p = 0.824$). The cumulative event rate for the primary endpoint was similar between ICM and NICM groups (18/70, 25.7% vs. 15/44, 34.1%, $p = 0.398$). There was a greater proportion of appropriate ICD therapy in the secondary vs. primary prevention indication group (15/36, 41.7% vs. 18/78, 23.1%, $p = 0.049$).

Predictors of appropriate ICD therapy

For the entire cohort ($n=114$), univariate analysis showed secondary prevention, mean entropy (medium texture), T1^{-native}, Grayzone^{-2SD-FWHM} and Scar^{-2SD} were associated with appropriate ICD therapy (Supplementary Table 1). Avoiding multicollinearity, separate multivariable analyses showed mean entropy with a medium texture (SSF4), T1^{-native}, Grayzone^{-2SD-FWHM} and Scar^{-2SD} remained independent predictors of appropriate ICD therapy in the combined ICM and NICM cohort undergoing ICD implantation (Figure 2).

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Predictors of appropriate ICD therapy in the ICM group

For the ICM group, univariate analysis showed mean entropy (medium texture) was associated with the primary endpoint (Supplementary Table 2) and remained an independent predictor of appropriate ICD therapy when tested in a multivariable model including age and LVEF $\delta 35\%$ covariates (Figure 3A).

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Predictors of appropriate ICD therapy in the NICM group

For the NICM group, univariable analysis showed only T1^{-native} was associated with the primary endpoint (Supplementary Table 3) and remained an independent predictor of appropriate ICD therapy when tested in a multivariable model including LVEF $\delta 35\%$ and T1^{-native} covariates (Figure 4C).

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Survival analysis

Kaplan-Meier survival analysis (Figure 5A) demonstrated that the time until first appropriate ICD therapy was significantly shorter in the medium texture high mean entropy group with an optimised cut off of > 5.465 (Log rank 8.9, $p = 0.003$). Furthermore, in the medium texture high mean entropy group there were significantly higher rates of appropriate ICD therapy over time with more than 40% having appropriate ICD therapy compared to the medium texture low mean entropy group that had $<20\%$ appropriate ICD therapy events. Figure 5B shows the time until first appropriate ICD therapy was similar in the unfiltered high and low mean entropy groups with an optimised cut off of > 4.520 (Log rank 1.8, $p = 0.182$). Moreover, there was no significant difference in number of events of appropriate ICD therapy over time between the unfiltered high and low mean entropy groups.

Reproducibility of CMR Texture Analysis for mean entropy

CMR-TA was repeated in a subgroup of 15 randomly selected patients from the study cohort (ICM $n=8$, NICM $n=7$). The mean inter-rater difference for medium texture mean entropy was 0.0067 (limits of agreement -1.89 to 1.90) and displayed on a Bland-Altman plot (Figure 6). Linear regression showed no statistical inter-rater difference ($p = 0.516$, 95% CI -0.614 - 1.162).

Discussion

To our knowledge the present study is the first to demonstrate that medium texture mean entropy (as a measure of scar heterogeneity) is an independent predictor of appropriate ICD therapy for VT and VF in a cohort of ICD patients with ICM and NICM. It also confirms our previous findings that $T1^{native}$, scar core ($Scar^{-2SD}$) and Grayzone^{-2SD-FWHM} are independent predictors of appropriate ICD therapy in patients with mixed ICM and NICM aetiologies. Furthermore, $T1^{native}$ remained the only CMR-derived scar index that independently predicted ICD therapy in patients with NICM.

Filtered CMR Texture Analysis

We demonstrate mean entropy, following the application of a medium filter (medium texture, $SSF=4$), is an independent predictor of appropriate ICD therapy in our combined cohort of patients with ICM and NICM (HR 1.8 [1.083-3.271], $p = 0.025$). The same was true when we tested coarse ($SSF5$ & $SSF6$) and fine ($SSF2$ & $SSF3$) mean entropy textures as measures of scar heterogeneity, however, for simplicity we have only presented the results of medium texture mean entropy as all textures appear to improve the predictive ability of mean entropy compared to unfiltered mean entropy. In addition,

T1^{-native}, scar core (Scar^{-2SD}) and Greyzone^{-2SD-FWHM} were independent predictors of appropriate ICD therapy in the mixed cohort when tested in separate multivariable models.

In the ICM group, medium texture mean entropy remained an independent predictor of appropriate ICD therapy. We believe the key strength of the filtration method to generate scar textures is that it is more sensitive in identifying subtle tissue heterogeneity by filtering out image noise and accentuating key **biologically relevant features** of LGE, thereby adding a layer of reproducibility and robustness in calculating **mean entropy**. Image filtration may also allow evaluation of how mean entropy varies over time in future studies. Mean entropy is also likely to be more reproducible than T1 mapping as T1 indices vary between different CMR scanners and magnet strengths. A standard white blood LGE sequence protocol is all that is required to perform CMR-TA and our technique of segmenting total visible scar has a short learning curve and could potentially be automated in the future. Texture analysis could readily be integrated into conventional CMR analysis software and potentially used as an independent risk predictor to aid ICD implantation decisions in patients with scar. However, this is most likely to be of greatest benefit in risk stratification when combined with other important clinical covariates, including LVEF, as part of a risk prediction calculation. Further larger randomised multi-centre studies would be of significant value in assessing the usefulness of CMR-TA in ICD risk stratification.

In the NICM group, **filtered mean entropy was not predictive of the primary endpoint**, however T1^{-native} was an independent predictor of appropriate ICD therapy and in keeping with our previous findings.^{10,17} Since NICM is often characterised by diffuse fibrosis, it is therefore consistent that T1^{-native} remains predictive of ICD therapy, whereas mean entropy does not and may reflect that diffuse fibrosis is too small and interspersed to be detected using the filtration-histogram method.

Comparison with previous studies

In our study unfiltered mean entropy (SSF0) did not predict the primary endpoint for the entire cohort or within distinct ICM or NICM groups. This is in contrast to the recent findings of the **Harvard-Leiden collaboration** who used a different software platform in a cohort of 130 NICM patients, with visible scar in 56.9% of patients.¹⁸ This may also be explained by several methodological differences between the studies. Muthalaly et al. segmented the entire myocardium using unfiltered LGE images to derive entropy compared to our method of total scar segmentation with the application of spatial scale filters to generate scar textures from which entropy was calculated. There is no standardised method for scar segmentation to derive entropy, although in the ICM population, segmenting all visible scar or a

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selection of visible scar within the LV seems appropriate. The main challenge lies in quantifying the heterogeneity of diffuse scar patterns seen in patients with NICM or indeed in patients with no visible LGE. A potential limitation of our method in segmenting visible diffuse scar for the NICM group is reproducibility. We have demonstrated in this study and previous studies,^{9,10} that T1^{-native} values derived from the mid septum outside of visible scar are predictive of appropriate ICD therapy in the NICM group, supporting the use of T1^{-native} values as an inherent tissue-specific index that is effective in differentiating healthy myocardium from diffusely diseased tissue.

Predictors of appropriate ICD therapy and clinical translation

We took a cohort of ICM and NICM patients who had visible scar and performed CMR-TA as we believe that segmenting visible scar and applying a spatial scale filter to identify subtle scar features, particularly in the ICM population has greater robustness and stronger predictive value than other quantitative assessment methods of LV scar heterogeneity. A key strength of this study is that we included patients with secondary prevention ICD indication and only patients with visible scar, and therefore it is important to note that the predictive value of mean entropy is therefore likely to be robust in this already high-risk group. Filtered mean entropy provides a more sophisticated [objective method of quantifying scar heterogeneity which is reproducible and easier to perform, particularly for the ICM group in comparison to the T1^{-native}, scar core and gray_zone indices, which is reproducible and easier to perform, particularly for the ICM group.](#) Additionally, our technique of careful scar segmentation included the scar border (gray_zone), allowing the filtration step to enhance scar texture heterogeneity by filtering out image noise and [an enhancing subtle biologically relevant features and avoiding](#) inadvertent inclusion of 'healthy' myocardium thereby strengthening the robustness and reproducibility of the CMR-TA technique. Figure 7 compares the medium textures and unfiltered LGE images of a high mean entropy patient (A) who met the primary end point and a low mean entropy patient (B) who did not have ICD therapy. Moreover, CMR-TA has potential use in identifying which patients remain at high risk of VA, which is of growing interest in prophylactic VT ablation in the ICM cohort, where it could play a role in patient selection. [Its use in the NICM population is less clear given our findings significantly differ from the Harvard-Leiden groups,¹⁸ albeit with different scar inclusion methods and therefore method refinement and further larger multi-centre studies are warranted.](#)

Study limitations

The findings in our study are subject to the inherent limitations of non-randomised controlled studies, [although this does allow for standardisation of imaging protocols and scar segmentation.](#) Additionally, use of appropriate ICD therapy as a surrogate endpoint does not necessarily parallel sudden

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arrhythmic death. Right ventricular scar was not evaluated which may contribute to the overall scar burden and arrhythmic substrate. Patients without scar were excluded to assess the predictive value of CMR-TA in a higher-risk population with scar, however, this study is therefore not entirely representative of all patients with cardiomyopathy. All subjects were scanned on the same 1.5T scanner, therefore we do not know how filtered mean entropy values vary with 3T or indeed different manufacturers. Muthalaly et al. (2018), noted a difference in unfiltered entropy values between 1.5T and 3T in their NICM cohort and therefore further assessment is required in future studies.¹⁸ Furthermore, we do not know whether there is temporal variation in entropy values and also recognise that inversion times, timing of LGE acquisition and additional imaging factors are unknown and required assessment. We used a standardised device therapy protocol mirroring our institutions guidelines when the study commenced in 2011. The MADIT-RIT study later demonstrated optimised ICD programming by reducing ICD therapy which may potentially have reduced the event rate of this study.¹⁹ Nevertheless, by standardising ICD programming in our cohort, it is unlikely that device programming would have introduced any systemic bias in the associations studied. Moreover, many patients had initial VF or recurrent VT leading to device therapy suggesting our results remain valid.

Conclusion

Filtered mean entropy was a strong predictor of appropriate ICD therapy suggesting a potential role for CMR-TA in predicting VA and risk-stratifying patients for ICD implantation. To our knowledge, this is the first study to demonstrate that filtered mean entropy derived from quantitative texture analysis can be used to accurately predict appropriate ICD therapy in a mixed cohort of patients with ischaemic and non-ischaemic cardiomyopathy.

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Supplementary Table 1: Univariable analysis of appropriate ICD therapy for the entire cohort

Variable	Hazard Ratio	95% C.I.	<i>p</i> value
Age	0.977	0.953-1.001	0.061
Male gender	2.046	0.719-5.822	0.180
Hypertension	0.565	0.285-1.123	0.103
Atrial fibrillation	0.658	0.313-1.382	0.269
Secondary prevention	2.207	1.109-4.391	0.024
QRS>120 milliseconds	1.075	0.518-2.229	0.847
LVEF δ 35%	1.508	0.623-3.654	0.363
Renal function (eGFR 60 mL/min/1.73m ²)	1.010	0.993-1.027	0.254
CRT device	1.011	0.509-2.006	0.976
History of myocardial infarction	0.808	0.402-1.625	0.550
ICM	0.724	0.364-1.437	0.355
Bystander CAD	1.021	0.311-3.347	0.973
Mean Entropy (medium texture)	1.687	1.028-2.769	0.038
Mean Entropy (unfiltered)	1.231	0.597-2.541	0.573
T1^{-native}	1.008	1.003-1.013	0.002
Grayzone^{-2SD-FWHM}	1.100	1.039-1.165	0.001
Scar^{-2SD}	1.039	1.008-1.072	0.013
Scar ^{-FWHM}	1.034	0.991-1.077	0.121

Univariable Cox regression to determine variables associated with appropriate ICD therapy for VT or VF for all patients with ischaemic and non-ischaemic cardiomyopathy (n=114). Mean entropy (medium texture) was derived from applying a medium spatial scale filter (SSF=4)-4. Mean entropy (unfiltered) was derived without using a SSF (SSF=0). $p \leq 0.05$ was considered to be statistically significant.

Abbreviations: ICD = implantable cardioverter-defibrillator, C.I. = confidence interval, LVEF = left ventricular ejection fraction derived by cardiac magnetic resonance imaging, CRT = cardiac resynchronisation therapy, CAD = coronary artery disease, T1^{-native} = pre-contrast T1 values, SD = standard deviation, FWHM = full width half mass, SSF = spatial scale filter

Table 1: Patient demographics according to heart failure aetiology

Demographics	ICM (n=70)	NICM (n=44)	Total (n=114)	p value
Mean age (years±SD)	67.1±10.2	58.6±15.3	63.9±13.1	0.005
Male	56(80.0%)	34(77.3%)	90(78.9%)	0.815
Diabetes mellitus	13(18.6%)	6(13.6%)	19(16.7%)	0.609
Hypertension	25(35.7%)	14(31.8%)	39(34.2%)	0.691
Atrial fibrillation	14(20.0%)	14(31.8%)	28(24.6%)	0.183
Renal function (eGFR mL/min/1.73m ²)	66.8±20.4	69.9±17.0	68.0±19.1	0.406
Secondary prevention	23(32.9%)	13(29.5%)	36(31.6%)	0.837
CRT device	37(52.9%)	25(56.8%)	62(54.4%)	0.704
QRS>120ms	27(42.9%)	22(55.0%)	49(47.6%)	0.312
CMR LVEFδ35%	59(84.3%)	28(63.6%)	87(76.3%)	0.014
Mean Entropy (medium texture)	5.7±0.7	5.5±0.7	5.6±0.7	0.045
Mean entropy (unfiltered)	4.6±0.4	4.3±0.5	4.5±0.5	0.003
T1 ^{-native}	1051±73.1	1079±76.7	1062±75.3	0.079
Grayzone ^{-2SD-FWHM}	10.1±4.9	7.1±6.0	8.9±5.5	0.002
Scar ^{-2SD}	25.0±9.1	16.2±13.3	21.6±11.7	<0.001
Scar ^{-FWHM}	15.0±6.5	9.0±8.6	12.7±7.9	<0.001

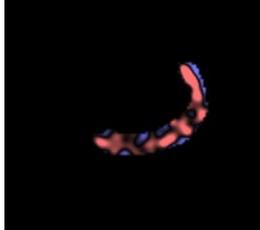
Patient demographics calculated on 114 consecutive patients. Mean entropy (medium texture) was derived following spatial scale filter (SSF=4)-4 application. Mean entropy (unfiltered) was derived without SSF (SSF=0).

Abbreviations: eGFR = estimated glomerular filtration rate

SSF6 Coarse texture



SSF4 Medium texture



SSF 2 Fine texture



SSF 0 Unfiltered image

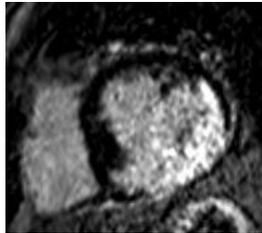
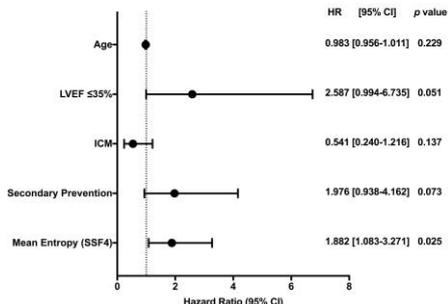


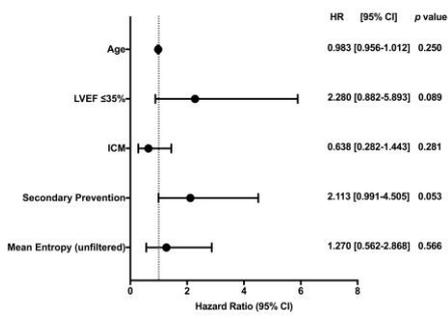
Figure 1: Cardiac magnetic resonance late gadolinium enhanced filtered images with coarse spatial scaled filter (SSF6), medium (SSF4) and fine (SSF2) lesion textures respectively and corresponding unfiltered left ventricular scar.

Commented [1]:
I would put the unfiltered top left followed by fine (top-right), medium (bottom-left) and coarse texture (bottom-right)

A: Mean Entropy (SSF4)



B: Mean Entropy (unfiltered)



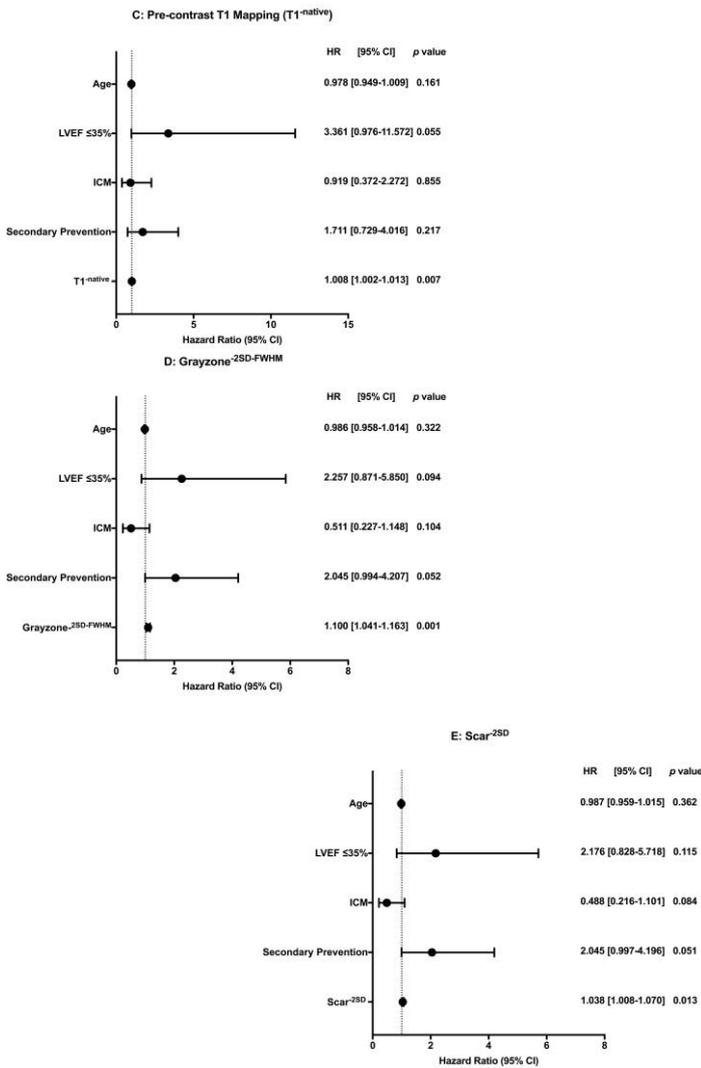


Figure 2: Separate multivariable Cox regression analyses to determine independent predictors of appropriate ICD therapy for combined ischaemic and non-ischaemic cardiomyopathy groups (n=114). Mean entropy (SSF4) was derived from applying a medium [SS-SF](#) and generating a medium texture. Mean entropy (unfiltered/[conventional-image](#)) was computed without a SSF ([i.e. SSF=0](#)).

Abbreviations: C.I. = confidence interval, LVEF = left ventricular ejection fraction derived by cardiac magnetic resonance imaging, ICM = ischaemic cardiomyopathy aetiology, SSF = spatial scale filter, T1^{-native} = pre-contrast T1 values.

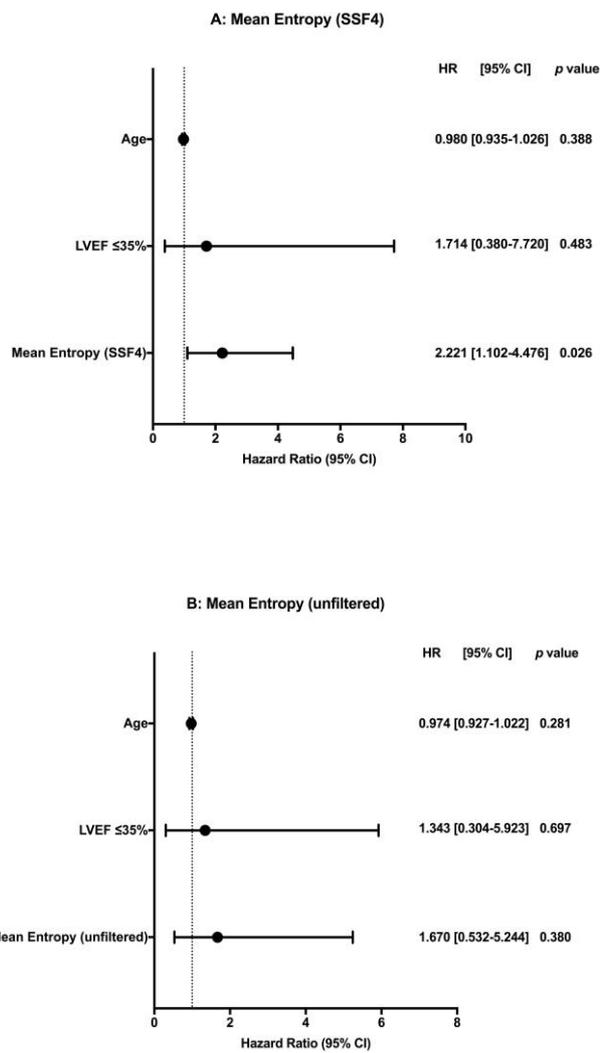


Figure 3: Multivariable Cox regression analyses to determine independent predictors of appropriate ICD therapy for patients with ischaemic cardiomyopathy (n=70). Mean entropy (SSF4) was derived from applying a medium spatial scale filter (SSF) and generating a medium texture. Mean entropy (unfiltered) was computed without a SSF.

Abbreviations: C.I. = confidence interval, LVEF = left ventricular ejection fraction derived by cardiac magnetic resonance imaging, SSF = spatial scale filter

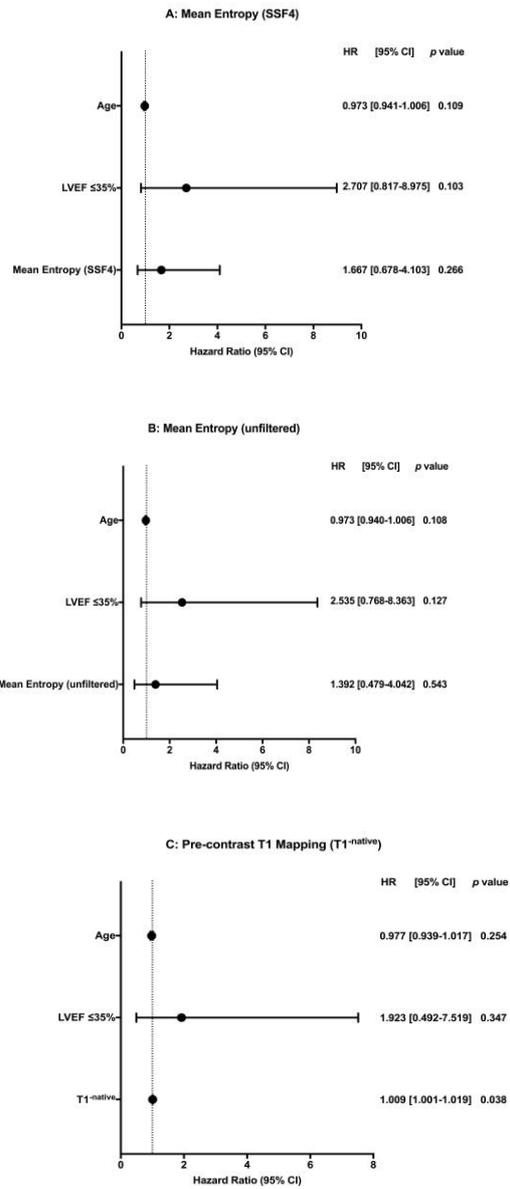
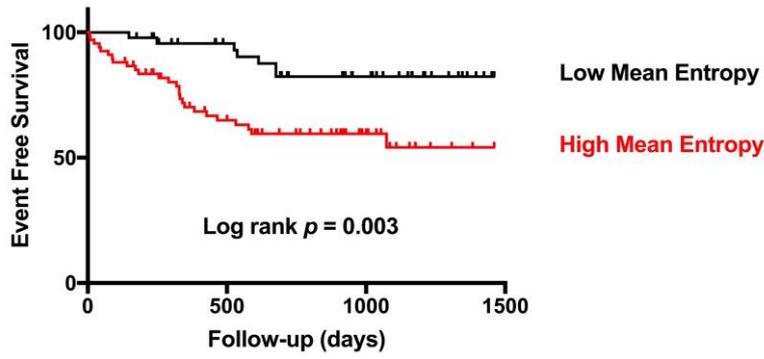


Figure 4: Multivariable Cox regression analyses to determine independent predictors of appropriate ICD therapy for patients with non-ischaemic cardiomyopathy (n=44). Mean entropy (SSF4) was derived from applying a medium spatial scale filter (SSF) and generating a medium texture. Mean entropy (unfiltered) was computed without a SSF.

Abbreviations: C.I. = confidence interval, LVEF = left ventricular ejection fraction derived by cardiac magnetic resonance imaging, SSF = spatial scale filter, T1^{native} = pre-contrast T1 values

A: Mean Entropy (Medium Texture SSF4)



B: Mean Entropy (unfiltered)

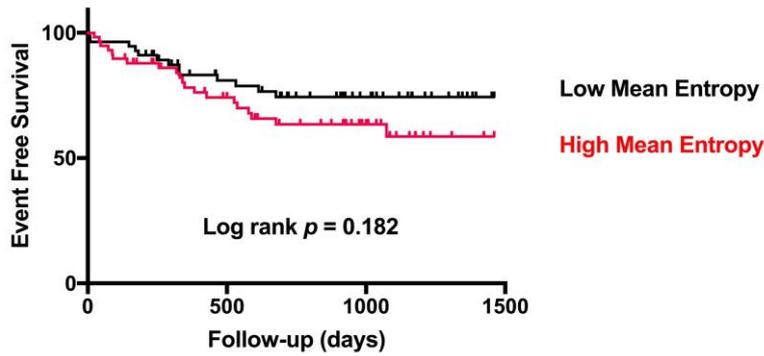


Figure 5: Kaplan-Meier survival analyses showing difference in event free survival when patients are stratified according to mean entropy with a medium texture (A) and unfiltered image (B) for the entire cohort. Mean entropy (SSF4) was derived from applying a medium spatial scale filter (SSF=4) and generating a medium texture. Mean entropy (unfiltered) was computed without a SSF=0. Thresholds used to stratify patients are optimised cut-off values derived from Youden's index. High mean entropy >5.465. Low mean entropy ≤5.465

Bland-Altman plot showing interrater agreement for medium texture mean entropy

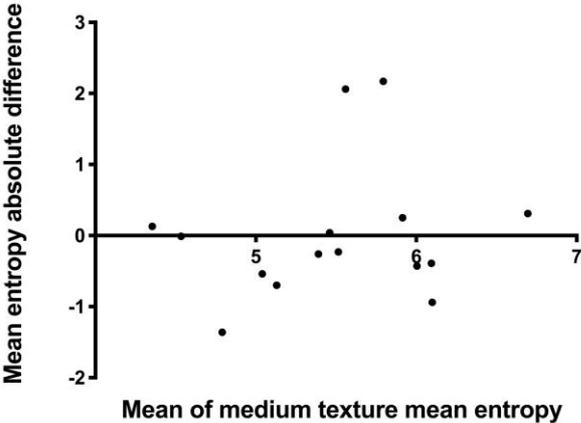


Figure 6: Bland-Altman plot showing interrater agreement for medium texture mean entropy (SSF4). Mean entropy (SSF4) was derived from applying a medium spatial scale filter (SSF) and generating a medium texture. The interrater mean difference = 0.0067 (limits of agreement -1.89 to 1.90)

SSF0 Unfiltered images

SSF4 Medium Texture

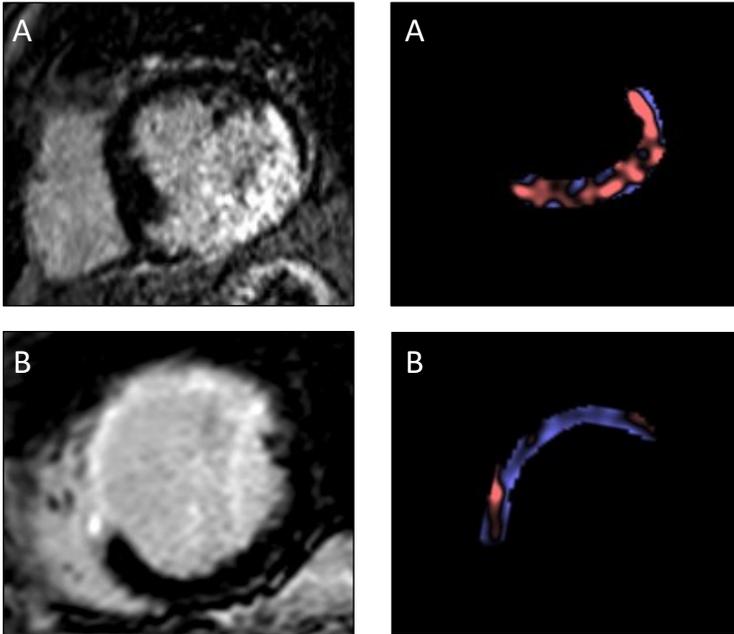


Figure 7 Visual comparison of unfiltered LGE images (left) and medium scar textures (right) of a high mean entropy patient (A) who met the primary end point and a low mean entropy patient (B) who did not have ICD therapy.

Key:

A: Patient with severe LVSD secondary to ICM, primary prevention ICD implantation, transmural ischaemic scar with high mean entropy value of 6.32. This patient met the primary endpoint of appropriate ICD therapy at 319 days after ICD implantation.

B: Patient with severe LVSD secondary to ICM, primary prevention ICD implantation, transmural ischaemic scar with low mean entropy value of 4.39. This patient did not meet the primary endpoint of appropriate ICD therapy during 1395 days follow-up.