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## 1 **Background**

2 In recent years, advances in the management of myocardial infarction (MI) have led to  
3 significant improvements in patient survival. However, though patients overcome the index  
4 event, many are left with impaired left ventricular function and carry a risk of life-threatening  
5 arrhythmia secondary to impaired left ventricle (LV) function and the presence of myocardial  
6 scar. The occurrence of ventricular arrhythmia can result in cardiac arrest and sudden cardiac  
7 death (SCD)<sup>1</sup>. Recent guidance recommends implantable cardioverter defibrillator (ICD)  
8 implantation for patients deemed at high risk for such events. Currently, ICD is recommended  
9 for patients after MI in the presence of significant LV dysfunction<sup>1,2</sup>. However, arrhythmias and  
10 SCD are also seen in patients with preserved LV ejection fraction (EF) and the incidence of  
11 appropriate shocks in patients receiving an ICD on the basis of current guidelines is low<sup>3</sup>.  
12 Therefore, there remains significant debate about how to best identify high-risk patients and  
13 avoid the implantation of unnecessary devices. Many patients now routinely undergo cardiac  
14 magnetic resonance (CMR) with late gadolinium enhancement (LGE) as part of their evaluation.  
15 This test is considered the reference standard for the identification of myocardial scar and  
16 fibrosis, and for the quantification of LVEF. Previous data demonstrate that even small areas of  
17 scar, which do not impact on LVEF, can result in arrhythmic events and it has previously been  
18 suggested that scar could be a sensitive marker of increased arrhythmic risk<sup>4-6</sup>. On a  
19 histopathological level, scar is complex and previous studies using contrast-enhanced CMR  
20 delineated two distinct patterns: (1) the scar core, made up of fibrous tissue, characterised by  
21 higher signal intensity on LGE images; and (2) heterogeneous tissue, containing necrotic tissue  
22 interspersed with bundles of viable myocytes, associated with lower signal intensity compared

23 with the core of the scar <sup>7</sup>. It has been suggested that slow local conduction through these  
24 heterogeneous regions of scar could be responsible for development of lethal re-entrant  
25 arrhythmias <sup>8,9</sup>. Recent studies performed with the aid of numerical simulations have shown  
26 that the spatial heterogeneity of fibrosis correlates directly with the risk of arrhythmia and that  
27 this is more pronounced with the increase of both the spatial size and the degree of  
28 heterogeneity <sup>10</sup>.

29 Quantitative texture analysis (TA) is a tool previously described for the assessment and  
30 stratification of solid tumours <sup>11,12</sup>. To the best of our knowledge, TA has not previously been  
31 applied to the analysis of CMR images, if we exclude some preliminary work [REDACTED]  
32 [REDACTED] <sup>13</sup>. CMR-TA has the potential to be applied to the analysis of LGE images, providing  
33 additional information on scar heterogeneity <sup>13</sup>. One such TA technique is the filtration-  
34 histogram approach where the filtration step extracts and enhances features or objects of  
35 different sizes, allowing quantification using histogram-based statistical parameters, which  
36 evaluate the grey-level pixel distribution. This filtration-histogram technique has been shown to  
37 describe the different components of macroscopic heterogeneity <sup>11</sup>. This is done in terms of  
38 standard descriptors such as mean, standard deviation, skewness and kurtosis <sup>12,14</sup>. The aim of  
39 this exploratory study was to apply quantitative CMR-TA to the assessment of LGE images in  
40 patients with previous MI and to determine whether texture analysis-derived indices may  
41 provide insights to facilitate better risk stratification in this cohort.

42

43 **Materials and Methods**

44 ***Patient population***

45 Patients referred on clinical grounds for CMR assessment of myocardial viability were  
46 retrospectively identified using electronic hospital records. The study population consisted of  
47 consecutive patients who had undergone CMR, with evidence of sub-endocardial or transmural  
48 ischaemic scar on LGE imaging. Patients with suspected infiltrative cardiomyopathy (including  
49 cardiac haemochromatosis, amyloidosis or sarcoidosis), myocarditis, or non-ischaemic  
50 cardiomyopathies, such hypertrophic cardiomyopathy or dilated cardiomyopathy, were  
51 excluded. In order to exclude histologically evolving scar, patients with a recent (<60 days)  
52 history of acute coronary syndrome were also excluded. All patients gave written consent to  
53 the CMR scan. Local research ethics committee approval was granted (REC 15/NS/003) for  
54 retrospective analysis of the data.

55 ***CMR imaging protocol***

56 CMR imaging was performed using standardised acquisition protocols using a 1.5-T CMR system  
57 with a 32-channel cardiac phased array surface coil (Philips Healthcare, Best, The Netherlands)  
58 <sup>15</sup>. The standard clinical CMR study consisted of a stack of breath-hold short axis cine steady-  
59 state free precession slices covering the LV (slice thickness 8mm, in plane spatial resolution  
60 448x448). These were acquired for quantification of left ventricular (LV) volumes, function and  
61 mass according to standardised post-processing methods <sup>16</sup>. An inversion-recovery gradient-  
62 echo pulse sequence for LGE assessment was used to acquire a stack of short axis slices 15-20  
63 minutes after contrast injection (Gadobutrol, Bayer-Schering Pharma, Berlin, Germany,

64 0.2mmol/kg body weight). Typical acquisition parameters for LGE imaging were TR/TE/turbo  
65 gradient factor of 3.5ms/2.0ms/25, enabling a temporal resolution of 88 ms.

66 LGE images were used to identify and measure the extent of ischaemic scar (percentage of total  
67 LV mass) and for texture analysis post-processing. To this purpose, a commercially available  
68 software package was used (CMR42, v5.6.4, Circle Cardiovascular Imaging, Calgary, Canada).

### 69 ***CMR texture analysis – CMR-TA***

70 CMR-TA was performed on LGE images selected at basal, mid-ventricular and apical level  
71 according to standard anatomical positions<sup>15</sup>. Areas of scar at each level were manually  
72 segmented and then analysed using TexRAD research software (TexRAD Ltd., www.texrad.com,  
73 Feedback Plc, Cambridge, UK). In brief, a region of interest (ROI) was drawn around areas of  
74 enhancement ensuring that the scar border but no surrounding tissue was included. The ROI  
75 therefore encompassed the scar core and the heterogenous region. If there were multiple scars  
76 in a short axis slice, values were averaged together. Manual segmentation of scar core and  
77 heterogenous region was performed with the consensus of two expert CMR readers blinded to  
78 patient identifiers and clinical data.

79 Images were then filtered using a Laplacian of Gaussian band-pass (similar to a non-orthogonal  
80 Wavelet approach) filtration step to extract and enhance features of different sizes based on  
81 the spatial scale filter (SSF) values varying from 2-6mm in radius (where 2mm corresponds to  
82 fine texture features, 3-5mm corresponds to medium texture features and 6mm corresponds to  
83 coarse texture features; [Figure 1](#)). Following image filtration, histogram analysis of pixel  
84 intensity was performed to quantify each filtered image texture map in terms of statistical

85 parameters such as mean, standard deviation, entropy, skewness and kurtosis. With this  
86 filtration approach, the Gaussian part of the filter reduces the impact of noise component and  
87 the Laplacian part enhances subtle features (biologically relevant "heterogeneity") quantifiable  
88 by the histogram analysis. These features are potentially relevant for disease diagnosis and  
89 prognostic assessment and are not visible to the naked eye on conventional (unfiltered) images.  
90 A detailed description of the filtration-histogram technique can be found in the literature <sup>12</sup>.  
91 Skewness is a statistical term that describes the asymmetry of a data set from the normal  
92 distribution. A negative skewness is where the data points are skewed to the right of a normal  
93 bell-shaped curve, whereas a positive skewness involves a leftward skew of the data points.  
94 Meanwhile kurtosis quantifies the sharpness of the peak of a frequency-distribution curve. A  
95 positive kurtosis indicates a more peaked histogram than a normal distribution, whilst a data-  
96 set that is flatter than a normal distribution correlates with a negative kurtosis (Figure 2). In this  
97 study, average, maximum and minimum skewness and kurtosis were measured in each patient.

#### 98 ***Outcome measures and follow up***

99 Patients were followed up from the point of their initial CMR scan. The primary end-point was a  
100 composite of ventricular fibrillation (VF), sustained ventricular tachycardia (VT) (defined as  
101 ventricular tachycardia with a rate  $>120 \text{ min}^{-1}$  lasting longer than 30 seconds) with  
102 haemodynamic compromise and/or requiring cardioversion, appropriate ICD discharge or  
103 unexplained syncope.

#### 104 ***Statistical analysis***

105 Continuous variables are expressed as mean  $\pm$  standard deviation (SD), or as median and  
106 interquartile range (IQR) in cases where the data were not normally distributed. Categorical  
107 data are summarised as frequencies and percentages. The Student's *t* test was used to compare  
108 mean values of continuous data between the group of patients who suffered events and those  
109 who did not. Where the data was non-normally distributed, the Mann-Whitney U test was used  
110 for group-wise comparison. The relationship of the various imaging and clinical markers with  
111 patient survival were assessed using Kaplan-Meier (KM) survival analysis. Only characteristics  
112 significantly different between the two groups at the Student's *t* test or Mann-Whitney test  
113 were included in the univariable analysis. This was undertaken to minimise the issue of multiple  
114 statistical testing and reduce the false discovery rates resulting from multiple testing. Optimal  
115 thresholds for the above identified texture parameters were determined using Receiver  
116 Operating Characteristics (ROC) analysis and employed for KM analysis. The log-rank test was  
117 employed to assess the difference between the survival distributions. In case of the other  
118 clinical and imaging parameters, previously validated thresholds were employed for the KM  
119 analysis. KM curves for patients above and below each threshold were constructed to display  
120 the proportion of patients surviving at a given time. We evaluated the survival probability  
121 according to the factors significant on univariable analysis using the Cox proportional hazards  
122 model. Multivariable analysis was used to adjust for potential confounding. The intra- and inter-  
123 observer reproducibility of TA was quantified using the intraclass coefficient of correlation.

124 All data were analysed using Microsoft Excel and IBM SPSS Statistics version 22 for Macintosh,  
125 with two-tailed values of  $p < 0.05$  considered significant.

126

## 127 **Results**

128 The study cohort consisted of 76 patients with a median period of follow up of 371.5 days (IQR  
129 135-645 days). During follow up, eight patients (10.5%) developed VT, two patients (2.6%)  
130 suffered at least one episode of VF and five patients (6.6%) experienced syncopal events  
131 suspected to relate to ventricular arrhythmias, leading to ICD implantation. This comprised a  
132 total of 14 patients (18%) with events at follow up. Baseline characteristics of patients are  
133 summarised in [Table 1](#). The mean age of patients was  $61.5 \pm 11.4$  years, 80% were male, 60%  
134 had undergone prior revascularisation and the mean LVEF was 50% ( $\pm 10\%$ ). Five patients had  
135 ICD implantation during follow-up and all of these patients were within the events group.

136

### 137 ***Predictors of adverse events***

#### 138 *Baseline characteristics*

139 Patient characteristics related to the primary endpoint are listed in [Table 1](#). There was no  
140 significant difference in gender or clinical variables between those who suffered events  
141 compared to those who did not, though patients in the event group were significantly older.  
142 Furthermore, patients who suffered ventricular arrhythmic events or unexplained syncope  
143 following MI had an on average higher LV end-diastolic volume (EDV), higher end-systolic  
144 volume (ESV), larger left atrium (LA) and lower left ventricular ejection fraction (LVEF). Notably,  
145 there was no relationship between the total scar burden and occurrence of events.



146 CMR-TA to assess scar heterogeneity

147 The median amount of tissue analysed was 2.9g of tissue (IQR, 2.0g to 4.3g) in the events group  
148 and 2.7g (IQR, 1.9g to 4.5g) in the group that did not suffer events ( $p= 0.61$ ).

149 [Table 2](#) represents the means  $\pm$  SD for all the texture parameters employed in the study and  
150 their relationship to events on univariable analysis. Patients who had an event had a higher  
151 average and maximum kurtosis ( $kurtosis_{avg}$  and  $kurtosis_{max}$ ), a trend seen across all filter levels  
152 but only statistically significant in the coarser filter scales, SSF=5 ( $p=0.007$  and  $0.005$   
153 respectively) and SSF=6 ( $p=0.015$  and  $0.025$  respectively). Minimum skewness ( $skewness_{min}$ ) at  
154 fine filter scale (SSF=2) was found to be significantly lower in the events group ( $p=0.046$ ).

155 **Survival analysis**

156 [Figure 3](#) shows KM survival plots based on previously validated thresholds and testing the  
157 association between clinical factors and prognosis<sup>17</sup>. Age ( $>65$  years,  $p = 0.03$ ), LVEF ( $<35\%$ ,  
158  $p=0.048$ ) and indexed LVEDV ( $>86$  ml/m<sup>2</sup>,  $p=0.006$ ) stratified patients for events. LA area ( $>24$   
159 cm<sup>2</sup>) was the only factor, amongst those tested, not statistically associated with a higher event  
160 rate ( $p=0.27$ ).

161 [Table 3](#) and [Figure 4](#) demonstrate the results from KM analysis only using the texture  
162 parameters highlighted above, which significantly differentiated between patients' groups.  
163 Specifically, a higher  $kurtosis_{max}$  and  $kurtosis_{avg}$  value at coarse texture scale (SSF=5 and SSF=6)  
164 and lower  $skewness_{min}$  value at fine texture scale (SSF=2) predicted poor survival ([Table 3](#)).

165 Interestingly, none of the patients reclassified by TA as low risk had any events, with the  
166 exception of one patient in the analysis by kurtosis<sub>avg</sub> at SSF=5. This was not the case for other  
167 significant imaging and clinical markers of survival (e.g. age, LVEF, LA area and LVEDV), where  
168 several events occurred in both groups.

### 169 ***Predictors of survival***

170 The Cox model was used to identify factors involved in prediction of survival. When the Cox  
171 model including TA parameters significant on univariate analysis were tested and corrected for  
172 confounders such as age and LVEF, kurtosis<sub>avg</sub> at SSF=5 TA and LVEF retained significant  
173 independent association with events (p=0.007 and p=0.006, respectively), whereas age and  
174 other TA parameters were no longer significant.

### 175 ***Reproducibility analysis***

176 Reproducibly analysis was performed on TA parameters which were associated with events at  
177 univariate analysis. Intra-observer reproducibility was excellent for skewness SSF=2 (r=0.96),  
178 kurtosis SSF=5 (r=0.99) and kurtosis SSF=6 (r=0.99). Inter-observer reproducibility was good for  
179 skewness SSF=2 (r=0.98). Good inter-observer reproducibility was measured for kurtosis SSF=5  
180 (r=0.84) and kurtosis SSF=6 (r=0.89).

### 181 ***ROC analysis***

182 ROC curves for texture analysis and standard parameters to the paper are summarised in [Table](#)  
183 [4](#). ROC curves for kurtosis<sub>avg</sub> SSF=5 and LVEF are demonstrated in [Figure 5](#).

184

185 **Discussion**

186 Myocardial scar heterogeneity as assessed by CMR-TA is associated with arrhythmic events in  
187 patients with previous MI. In particular, a higher kurtosis value at coarse texture scale and  
188 lower skewness value at fine texture scale were associated with an adverse outcome. These  
189 findings echo the results of previous preliminary work using TA [REDACTED] on patients with  
190 existing ICDs, which also demonstrated in a different and smaller group of patients that higher  
191 kurtosis with application of a coarse filter and lower skewness with application of a fine filter  
192 was able to predict post-MI VT or VF<sup>13</sup>. Interestingly, our data did not show any significant  
193 difference in overall scar burden between the event and non-event groups. This possibly  
194 suggests that scar heterogeneity assessed by TA could provide independent and  
195 complementary information to scar burden, although this hypothesis will have to be tested in  
196 future prospective outcome studies. Moreover, our data confirmed the association between  
197 increased age, reduced LVEF, and increased indexed LV EDV with the development of post-MI  
198 arrhythmias.

199 Substantial advances in acute management of myocardial infarction have led to significant  
200 improvements in patient survival. Large numbers of these patients are however left with  
201 impairment of LV function due to myocardial scarring and an increased risk of life-threatening  
202 ventricular arrhythmias. Current guidelines focus on LVEF as the key determinant of the need  
203 for ICD therapy; however, only the minority of patients who undergo implantation on this basis  
204 receive appropriate ICD therapies and, on the other hand, some patients with normal LV

205 function present with arrhythmias or SCD<sup>3</sup>. This has led to significant efforts to refine  
206 biomarkers to guide appropriate risk stratification and ICD implantation.

207 Myocardial scar in patients with previous MI is accepted as a source of ventricular arrhythmias  
208<sup>9,18</sup>. Previous data demonstrated that even small areas of scar, which do not impact on LVEF,  
209 can result in arrhythmic events<sup>4,5</sup>. Bello *et al*<sup>19</sup> was the first to directly analyse the relationship  
210 between some morphological features of myocardial scar and the induction of ventricular  
211 arrhythmia. Scar surface and mass, as characterised by CMR, were shown to be better  
212 predictors of inducible monomorphic VT than LVEF<sup>19</sup>. This study however did not provide any  
213 insight on the role of scar heterogeneity.

214 Electrical mapping studies have shown that the border areas of infarcted myocardial tissue,  
215 found adjacent to dense scar, are responsible for this arrhythmogenicity<sup>7,9,20</sup>. This area, also  
216 known as grey zone, is a heterogeneous region composed of isolated bundles of viable  
217 myocytes interwoven with fibrous tissue<sup>21</sup>. Grey zone regions conduct electrical activity more  
218 slowly than the surrounding myocardium, leading to the development of re-entrant VT<sup>9,22,23</sup>.

219 Subsequent studies have shown that more extensive grey zone at the periphery of a scar  
220 strongly correlates with greater VT inducibility, and that the extent of grey zone provides  
221 incremental prognostic value beyond LVEF<sup>24</sup>. More recently the same findings have been made  
222 in spontaneous VT following myocardial infarction<sup>25</sup>. These studies provide powerful evidence  
223 that factors, other than the presence and extent of scar, play a pivotal role in the pathogenesis  
224 of ventricular arrhythmias.

225 The current study is the first to go beyond the assessment of the extent of the grey zone and to  
226 consider the make-up of the heterogeneous infarct area itself, testing the hypothesis that scar  
227 complexity is linked to the development of arrhythmias. TA was initially developed in the field  
228 of oncology, where the complexity of solid tumour tissue has been shown to predict prognosis,  
229 assess disease severity and treatment response evaluation <sup>11</sup>. Our study demonstrates for the  
230 first time *in vivo* that specific features of the texture of the scar are linked to arrhythmogenicity.  
231 The same features have previously been associated with increased risk of arrhythmic events in  
232 pathologic and computational modelling studies <sup>10</sup>. Our findings are keeping with current  
233 understanding of the pathophysiological mechanisms linking the presence of scar to the onset  
234 of re-entrant arrhythmias.

235 For the interpretation of the biological meaning of the observed values of skewness and  
236 kurtosis, we can refer to previously published literature <sup>12</sup>. Higher kurtosis value indicates  
237 increased visual contrast (intensity variation) in the objects highlighted by filtration in relation  
238 to the background tissue. A lower skewness value indicates the presence of darker areas. In  
239 combination, these features suggest a more heterogeneous scar, comprising areas of grey zone  
240 interspersed with areas of denser scar. Interestingly, there was no significant difference  
241 between the two groups in terms of scar burden, probably indicating that these texture  
242 features of scar heterogeneity could provide independent information from the presence or  
243 absence and the burden of scar.

244 Our findings are in keeping with recent data investigating the role of scar heterogeneity in the  
245 genesis of arrhythmia by means of mathematical models. This study assessed the role of mean

246 fibrosis level and of the extent and spatial size of the heterogeneity and demonstrated that a  
247 more heterogeneous distribution of fibrosis was associated with an increased likelihood of  
248 arrhythmias and that the main mechanism of this dependency was the presence of localised  
249 tissue patches with more severe degrees of fibrosis <sup>10</sup>.

250 LGE images were acquired in this study according to standard clinical practice and SCMR  
251 guidelines, with a relatively short acquisition time in order to limit the amount of motion <sup>15</sup>.  
252 This is a particularly important aspect as motion could potentially result in the inclusion of  
253 blood-pool in the region of interest, particularly when small subendocardial scars are analysed,  
254 or might contribute to a loss of information when finer texture is analysed. A significant  
255 improvement on this side will be allowed by the advent of a new generation of sequences for  
256 “dark-blood” LGE which may further improve scar conspicuity <sup>26,27</sup>.

### 257 **Study limitations**

258 This is a pilot study to assess the potential for TA to be used as an added marker of risk and  
259 estimate the effect size in view of future adequately powered studies to test an independent  
260 association between scar texture features and events. Our results suggest excellent predictivity  
261 for events using TA parameters. However, optimised cut off values were used based on ROC  
262 analysis as this was a pilot exploratory study, whereas cut off values from the literature were  
263 used for the evaluation of standard markers of risk, likely resulting in a relative underestimation  
264 of the predictivity of the latter. We have included multivariable Cox regression analysis and  
265 have demonstrated the presence of an independent association between TA (kurtosis SSF=5  
266 average) and events. Given the pilot nature of this study and the relatively limited sample size,

267 these findings will need to be confirmed by a future prospective study on a larger population of  
268 patients.

269 **Conclusion**

270 The use of texture analysis in addition to standard clinical and functional data derived from  
271 CMR such as the presence of scar and LVEF (e.g. a multi-parametric approach) may provide  
272 additional information to guide risk stratification of patients post myocardial infarction.

273

274 **Abbreviations**

275 Myocardial infarction (MI); Sudden cardiac death (SCD); Left ventricular ejection fraction (LVEF);  
276 Late gadolinium enhancement (LGE); Cardiac magnetic resonance (CMR); Implantable cardiac  
277 defibrillators (ICDs); Left ventricle (LV); Region of interest (ROI); Spatial scale filter (SSF);  
278 Ventricular tachycardia (VT); Ventricular fibrillation (VF); End-diastolic volume (EDV); End-  
279 systolic volume (ESV); Left atrium (LA); Left ventricular ejection fraction (LVEF); New York Heart  
280 Association (NYHA); Texture analysis (TA).

281

282 **Declarations**

283 ***Ethics approval and consent to participate***

284 Local research ethics committee approval was granted (REC 15/NS/003) for retrospective  
285 enrolment of patients and analysis of the imaging and clinical data. All patients gave written  
286 consent to the CMR scan.

287 ***Consent for publication***

288

289 Not applicable.

290

291

292 ***Availability of data and material***

293



294 Anonymized datasets used and/or analyzed during the current study are available from the  
295 corresponding author on reasonable request.

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298

299 *Competing interests*

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390 **Figure and Table Legends**

391 [Figure 1: Texture analysis filtration technique.](#) Late gadolinium enhanced cardiac magnetic resonance  
392 image with the myocardial scar and corresponding images selectively displaying fine (spatial scaled filter  
393 (SSF) 2), medium (SSF4) and coarse (SSF5) lesion texture respectively. These varying textures correspond  
394 to myocardial scar features of different sizes and intensity variations extracted by the image filter.

395 [Figure 2:](#)

396 [A: Graphs demonstrating a negative and positive skewed histogram.](#) Skewness is a measure of the  
397 asymmetry of a distribution. The skewness value can be positive or negative. Negative skew indicated  
398 that the tail on the left side of the histogram is longer or fatter than the right side. Positive skew  
399 indicates that the tail is longer or fatter on the right side than the left side. A zero value occurs when the  
400 tails either side of the mean balance out, indicating an even distribution.

401 [B: An illustration of positive and negative kurtosis compared to a normal distribution.](#) Kurtosis is a  
402 measure of the peakedness of a distribution. The kurtosis value can be positive or negative. In  
403 comparison to a normal (Gaussian) distribution, a positive kurtosis indicates a more peaked histogram. A  
404 negative kurtosis correlates with a flatter histogram than that of a Gaussian distribution.

405 [Figure 3: Kaplan-Meier analysis of standard parameters of arrhythmic risk.](#) The difference in event-free  
406 survival when patients are stratified according to previously validated thresholds for age, LA size,  
407 LVEDV/m<sup>2</sup> and LVEF are demonstrated. LVEF = left ventricular ejection fraction; EDV = end-diastolic  
408 volume; LA = left atrium

409 [Figure 4: Kaplan-Meier survival analysis of texture analysis parameters.](#) Kaplan-Meier curves  
410 demonstrate the difference in event-free survival when patients are stratified according to average  
411 kurtosis when SSF5 (A) and SSF6 (B) filter levels are applied; maximum kurtosis when SSF5 (C) and SSF6

412 are applied; and minimum skewness when SSF2 (E) is applied. The thresholds used to stratify patients  
413 are optimised cut-offs from ROC analysis.

414 SSF = spatial scale filter.

415 [Figure 5: Receiver operating characteristic curves for kurtosis SSF5 average and left ventricular](#)  
416 [ejection fraction \(LVEF\).](#)

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418

419 [Table 1: Demographics and baseline CMR characteristics.](#) Values are mean plus or minus standard  
420 deviation, median and interquartile range or n (%). p Value pertains to the comparison between groups  
421 with and without ventricular arrhythmia/unexplained syncope events. CABG= coronary artery by-pass  
422 graft, PCI= percutaneous coronary intervention, MRI= magnetic resonance imaging, LVEF = left  
423 ventricular ejection fraction; EDV = end-diastolic volume; ESV = end-systolic volume; RVEF = right  
424 ventricular ejection fraction; LA = left atrium; RA = right atrium.

425 [Table 2: Detailed results of TA-CMR for SSF of 2 to 6.](#) Values are mean plus or minus standard deviation.  
426 p Value pertains to the comparison between groups with and without ventricular  
427 arrhythmia/unexplained syncope events. SSF = spatial scale filter.

428 [Table 3: Log rank results.](#) Log rank, p value, optimised thresholds and number of patients within the low  
429 and high risk group are shown, as stratified according to each TA-CMR parameter. SSF = spatial scale  
430 filter.

431 [Table 4: ROC analysis for different predictors of outcome.](#) Detailed results of received operating  
432 characteristics curves for different predictors of outcome identified by univariable analysis. SSF = spatial  
433 scale filter. LVEF = left ventricular ejection fraction.

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<b>Table 1</b>		<b>Baseline Patient Characteristics</b>		
<b>Characteristic</b>	<b>All patients (N = 76)</b>	<b>Ventricular arrhythmia or unexplained syncope (n = 14)</b>	<b>No ventricular arrhythmia or unexplained syncope (n = 62)</b>	<b>p Value</b>
<b>Age (yrs)</b>	61.51 ± 11.4	67.9 ± 10.0	60.1 ± 12.0	<b>0.01</b>
<b>Male</b>	66 (80%)	13 (93%)	53 (85%)	0.4
<b>Clinical history</b>				
Diabetes mellitus	21 (28%)	4 (29%)	17 (27%)	0.96
Hypertension	58 (76%)	11 (79%)	47 (76%)	0.78
Cigarette smoker	19 (25%)	3 (21%)	16 (26%)	0.60
Hypercholesterolemia	47 (62%)	10 (71%)	37 (60%)	0.45
Atrial fibrillation	9 (12%)	1 (7%)	8 (13%)	0.48
<b>Prior revascularisation</b>				
CABG	12 (16%)	3 (21%)	9 (15%)	0.61
PCI	42 (55%)	7 (50%)	35 (56%)	0.59
<b>Cardiac MRI</b>				
Scar burden (% of LV mass)	4.2 ± 2.4	4.9 ± 2.3	4.0 ± 2.4	0.24
LVEF (%)	51.8 (42.5-61.8)	44.5 (25.7-51.2)	54.6 (44.3-62.1)	<b>0.01</b>
LV EDV (ml)	175.4 (140.3-212)	202.5 (179-261.5)	170 (133.5-207.5)	<b>0.02</b>
LV EDV/m2	86.5 (76.3-107)	106 (90-125.3)	83 (75.3-100.3)	<b>0.01</b>
LV ESV (ml)	82 (56.3-119)	106.5 (82-177.5)	73.5 (51.8-114)	<b>0.01</b>
LV ESV/m2	39.5 (29-58.8)	55.5 (43.1-88)	35.5 (27.8-54.8)	<b>0.01</b>
LV mass (g)	105.7 ± 46.7	112.4 ± 54.2	103.9 ± 45.1	0.59
LV mass/m2	60.4 ± 16.4	66.9 ± 19.4	58.9 ± 15.5	0.19
RVEF (%)	58.2 (51.5-63)	57.7 (46.6-65.4)	58.5 (51.6-63)	0.74
RV EDV (ml)	148 (121.3-173)	143.5 (115.5-173.8)	150 (121.8-173.3)	0.88
RV EDV/m2	75 (61.3-87)	71 (58-97.8)	76 (62-86.3)	0.96
RV ESV (ml)	62 (46.3-81.8)	41 (42.8-89.8)	62 (47.8-79.5)	0.79
RV ESV/m2	31 (22-39.5)	31 (21-43.7)	31 (24-40)	0.81
LA (cm <sup>2</sup> )	25.1 ± 5.8	27.6 ± 4.2	24.5 ± 5.9	<b>0.03</b>
RA (cm <sup>2</sup> )	27.9 ± 44.8	23.1 ± 5.5	29.0 ± 49.6	0.36

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Table 2		Texture Analysis Results		
Statistical parameters	All patients (N = 76)	Ventricular arrhythmia or unexplained syncope (n = 14)	No ventricular arrhythmia or unexplained syncope (n = 62)	p Value
<b>SSF2</b>				
Mean intensity	247.3 ± 169.4	244.5 ± 222.36	247.9 ± 157.4	0.960
Standard deviation	542.5 ± 280.5	430.9 ± 249.6	567.7 ± 282.8	0.085
Entropy	6.0 ± 0.6	5.9 ± 0.4	6.0 ± 0.7	0.400
Mean of positive pixels	550.4 ± 283.7	460.0 ± 285.7	570.8 ± 281.5	0.204
Skewness Maximum	0.3 ± 0.3	0.2 ± 0.3	0.3 ± 0.3	0.274
Skewness Average	0.2 ± 0.3	0.1 ± 0.2	0.2 ± 0.3	0.068
Skewness Minimum	0.1 ± 0.3	-0.1 ± 0.2	0.1 ± 0.3	<b>0.046</b>
Kurtosis Maximum	0.1 ± 0.6	0.2 ± 0.6	0.1 ± 0.7	0.488
Kurtosis Average	-0.1 ± 0.5	0 ± 0.3	-0.1 ± 0.5	0.762
Kurtosis Minimum	-0.3 ± 0.5	-0.3 ± 0.3	-0.3 ± 0.5	0.962
<b>SSF3</b>				
Mean intensity	304.5 ± 245.8	343.4 ± 301.2	295.7 ± 233.5	0.586
Standard deviation	593.9 ± 314.6	474.3 ± 299.1	621.0 ± 314.0	0.116
Entropy	6.0 ± 0.63	5.9 ± 0.4	6.0 ± 0.7	0.415
Mean of positive pixels	629.7 ± 336.2	554.2 ± 363.1	646.8 ± 330.5	0.392
Skewness <sub>max</sub>	0.2 ± 0.3	0.2 ± 0.3	0.2 ± 0.3	0.754
Skewness <sub>avg</sub>	0.1 ± 0.3	0.0 ± 0.3	0.1 ± 0.3	0.537
Skewness <sub>min</sub>	-0.1 ± 0.4	-0.2 ± 0.4	0.0 ± 0.4	0.350
Kurtosis <sub>max</sub>	0.0 ± 0.6	0.2 ± 0.7	0.0 ± 0.6	0.287
Kurtosis <sub>avg</sub>	-0.2 ± 0.5	0.0 ± 0.6	-0.2 ± 0.4	0.248
Kurtosis <sub>min</sub>	-0.3 ± 0.5	-0.2 ± 0.7	-0.4 ± 0.5	0.276
<b>SSF4</b>				
Mean intensity	306.7 ± 312.8	394.2 ± 347.8	287.0 ± 304.0	0.301
Standard deviation	606.6 ± 324.1	486.4 ± 314.7	633.8 ± 322.5	0.131
Entropy	6.0 ± 0.6	5.9 ± 0.4	6.0 ± 0.7	0.415
Mean of positive pixels	647.5 ± 360.3	601.8 ± 402.8	657.9 ± 352.7	0.636
Skewness <sub>max</sub>	0.1 ± 0.4	0.2 ± 0.4	0.1 ± 0.4	0.398
Skewness <sub>avg</sub>	-0.1 ± 0.3	0.0 ± 0.3	-0.1 ± 0.3	0.557
Skewness <sub>min</sub>	-0.2 ± 0.4	-0.2 ± 0.4	-0.2 ± 0.3	0.994
Kurtosis <sub>max</sub>	-0.1 ± 0.7	0.2 ± 0.5	-0.1 ± 0.7	0.074
Kurtosis <sub>avg</sub>	-0.3 ± 0.4	-0.1 ± 0.5	-0.4 ± 0.4	0.056
Kurtosis <sub>min</sub>	-0.5 ± 0.4	-0.3 ± 0.6	-0.5 ± 0.4	0.108
<b>SSF5</b>				
Mean intensity	279.2 ± 367.6	408.2 ± 370.3	250.0 ± 363.7	0.163
Standard deviation	609.7 ± 328.1	483.7 ± 310.0	638.2 ± 327.7	0.111
Entropy	6.0 ± 0.6	5.9 ± 0.4	6.0 ± 0.7	0.444
Mean of positive pixels	646.7 ± 373.6	613.2 ± 416.1	654.2 ± 366.6	0.737
Skewness <sub>max</sub>	0.0 ± 0.4	0.1 ± 0.4	0.0 ± 0.4	0.570
Skewness <sub>avg</sub>	-0.1 ± 0.3	-0.1 ± 0.3	-0.1 ± 0.3	0.732
Skewness <sub>min</sub>	-0.3 ± 0.3	-0.3 ± 0.4	-0.3 ± 0.3	0.865
Kurtosis <sub>max</sub>	-0.2 ± 0.5	0.0 ± 0.3	-0.3 ± 0.5	<b>0.005</b>
Kurtosis <sub>avg</sub>	-0.4 ± 0.4	-0.2 ± 0.3	-0.5 ± 0.4	<b>0.007</b>
Kurtosis <sub>min</sub>	-0.6 ± 0.4	-0.4 ± 0.4	-0.7 ± 0.4	0.052
<b>SSF6</b>				
Mean intensity	239.9 ± 409.4	398.0 ± 376.4	204.2 ± 410.9	0.102
Standard deviation	605.0 ± 332.2	476.4 ± 300.4	634.1 ± 334.3	0.097
Entropy	6.0 ± 0.6	5.9 ± 0.4	6.0 ± 0.7	0.540
Mean of positive pixels	631.7 ± 382.0	607.2 ± 417.9	637.2 ± 376.9	0.808
Skewness <sub>max</sub>	0.0 ± 0.4	-0.1 ± 0.4	0.0 ± 0.4	0.713
Skewness <sub>avg</sub>	-0.1 ± 0.3	-0.2 ± 0.4	-0.2 ± 0.3	0.665
Skewness <sub>min</sub>	-0.3 ± 0.3	-0.4 ± 0.4	-0.3 ± 0.4	0.511
Kurtosis <sub>max</sub>	-0.2 ± 0.5	-0.1 ± 0.4	-0.4 ± 0.5	<b>0.025</b>
Kurtosis <sub>avg</sub>	-0.4 ± 0.4	-0.3 ± 0.3	-0.6 ± 0.3	<b>0.015</b>
Kurtosis <sub>min</sub>	-0.6 ± 0.4	-0.5 ± 0.4	-0.7 ± 0.3	0.075



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<b>Table 3</b>	<b>Kaplan Meier Analysis</b>				
	<b>Log Rank</b>	<b>p Value</b>	<b>ROC Analysis Threshold</b>	<b>Number of patients assigned to the low risk group by TA-CMR</b>	<b>Number of patients assigned to the high risk group by TA-CMR</b>
<b>SSF2</b>					
Skewness <sub>min</sub>	4.460	0.035	0.120	25	51
<b>SSF5</b>					
Kurtosis <sub>max</sub>	5.319	0.021	-0.445	53	23
Kurtosis <sub>avg</sub>	6.397	0.011	-0.493	45	31
<b>SSF6</b>					
Kurtosis <sub>max</sub>	8.407	0.004	-0.465	47	29
Kurtosis <sub>avg</sub>	6.343	0.012	-0.628	51	25

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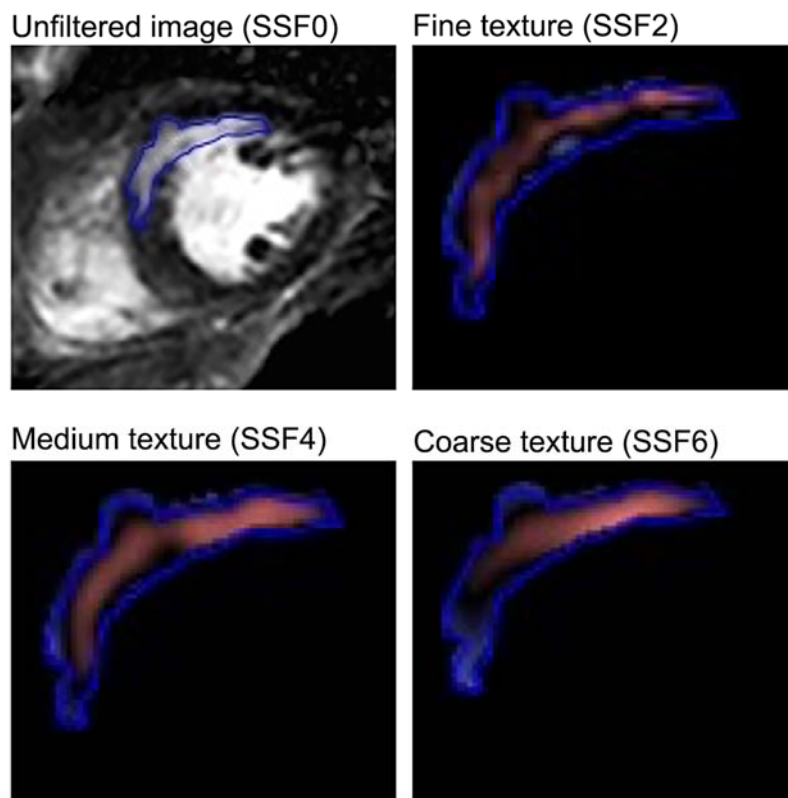
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Test result variables	Detailed results of ROC analysis for different predictors of outcome				
	Area	SE	p-value	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Age	0.7	0.075	0.02	0.554	0.847
LVEF	0.715	0.082	0.012	0.554	0.876
Kurtosis <sub>avg</sub> SSF=5	0.73	0.064	0.008	0.605	0.855
Kurtosis <sub>max</sub> SSF=5	0.729	0.063	0.008	0.604	0.853
Kurtosis <sub>min</sub> SSF=5	0.654	0.077	0.073	0.504	0.805
Kurtosis <sub>avg</sub> SSF=6	0.715	0.066	0.012	0.586	0.845
Kurtosis <sub>max</sub> SSF=6	0.705	0.063	0.017	0.582	0.828
Kurtosis <sub>min</sub> SSF=6	0.656	0.079	0.07	0.5	0.811
Skewness <sub>avg</sub> SSF=2	0.589	0.089	0.299	0.415	0.763
Skewness <sub>max</sub> SSF=2	0.586	0.087	0.318	0.415	0.757
Skewness <sub>min</sub> SSF=2	0.594	0.076	0.275	0.445	0.742

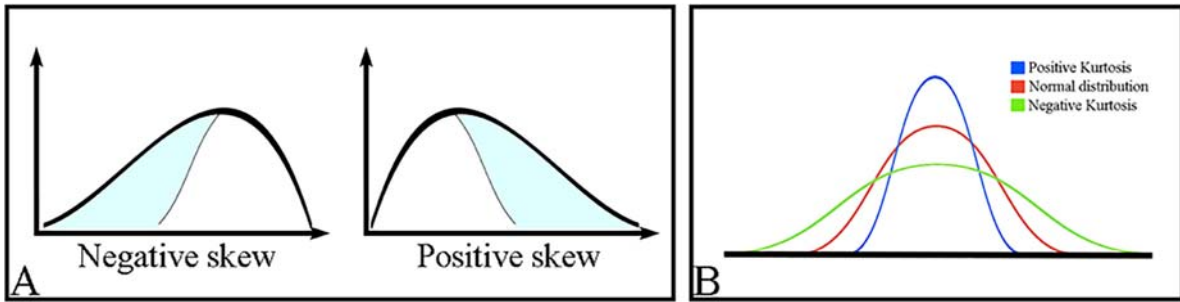
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1 **Figures and Tables**

2 **Fig. 1**



5 Fig. 2

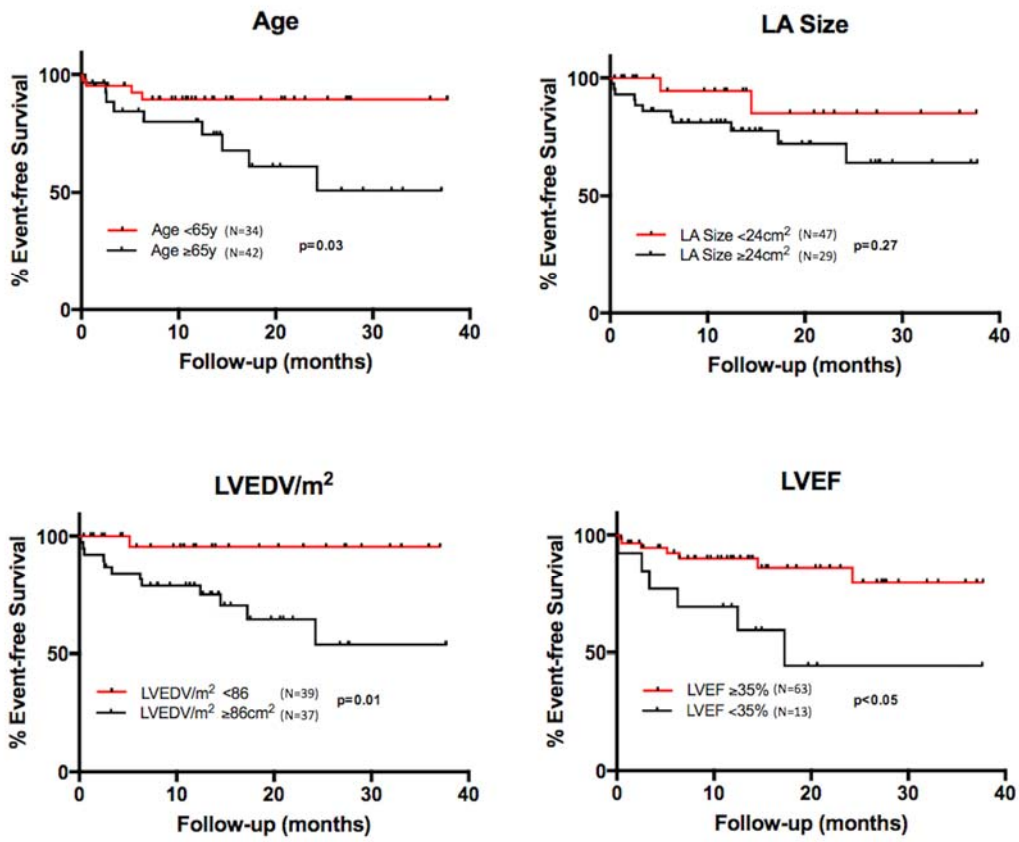


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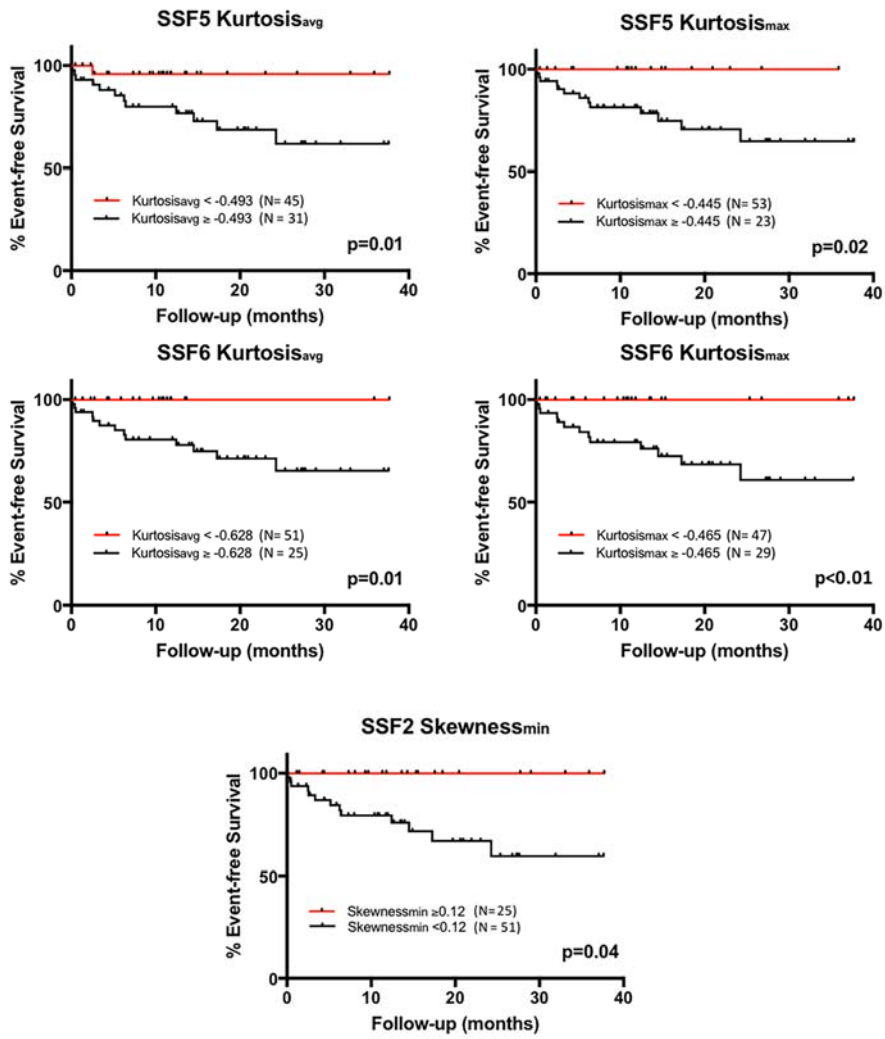
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9 Fig. 3



10 Fig. 4

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12 **Fig. 5**

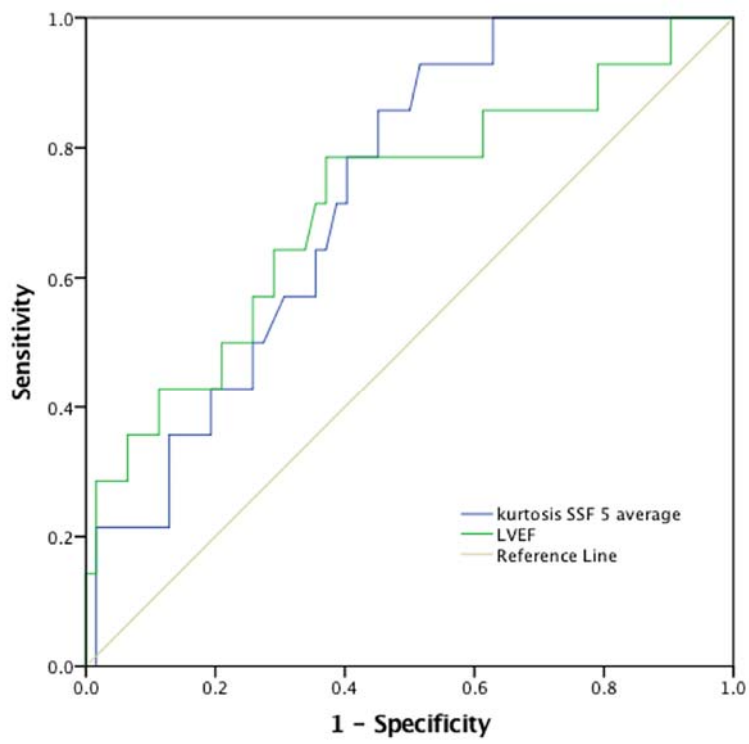
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<b>Table 1 Baseline Patient Characteristics</b>				
<b>Characteristic</b>	<b>All patients (N = 76)</b>	<b>Ventricular arrhythmia or unexplained syncope (n = 14)</b>	<b>No ventricular arrhythmia or unexplained syncope (n = 62)</b>	<b>p Value</b>
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<b>Male</b>	66 (80%)	13 (93%)	53 (85%)	0.4
<b>Clinical history</b>				
Diabetes mellitus	21 (28%)	4 (29%)	17 (27%)	0.96
Hypertension	58 (76%)	11 (79%)	47 (76%)	0.78
Cigarette smoker	19 (25%)	3 (21%)	16 (26%)	0.60
Hypercholesterolemia	47 (62%)	10 (71%)	37 (60%)	0.45
Atrial fibrillation	9 (12%)	1 (7%)	8 (13%)	0.48
<b>Prior revascularisation</b>				
CABG	12 (16%)	3 (21%)	9 (15%)	0.61
PCI	42 (55%)	7 (50%)	35 (56%)	0.59
<b>Cardiac MRI</b>				
Scar burden (% of LV mass)	4.2 ± 2.4	4.9 ± 2.3	4.0 ± 2.4	0.24
LVEF (%)	51.8 (42.5-61.8)	44.5 (25.7-51.2)	54.6 (44.3-62.1)	<b>0.01</b>
LV EDV (ml)	175.4 (140.3-212)	202.5 (179-261.5)	170 (133.5-207.5)	<b>0.02</b>
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LV ESV (ml)	82 (56.3-119)	106.5 (82-177.5)	73.5 (51.8-114)	<b>0.01</b>
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LV mass (g)	105.7 ± 46.7	112.4 ± 54.2	103.9 ± 45.1	0.59
LV mass/m <sup>2</sup>	60.4 ± 16.4	66.9 ± 19.4	58.9 ± 15.5	0.19
RVEF (%)	58.2 (51.5-63)	57.7 (46.6-65.4)	58.5 (51.6-63)	0.74
RV EDV (ml)	148 (121.3-173)	143.5 (115.5-173.8)	150 (121.8-173.3)	0.88
RV EDV/m <sup>2</sup>	75 (61.3-87)	71 (58-97.8)	76 (62-86.3)	0.96
RV ESV (ml)	62 (46.3-81.8)	41 (42.8-89.8)	62 (47.8-79.5)	0.79
RV ESV/m <sup>2</sup>	31 (22-39.5)	31 (21-43.7)	31 (24-40)	0.81
LA (cm <sup>2</sup> )	25.1 ± 5.8	27.6 ± 4.2	24.5 ± 5.9	<b>0.03</b>
RA (cm <sup>2</sup> )	27.9 ± 44.8	23.1 ± 5.5	29.0 ± 49.6	0.36

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Table 2		Texture Analysis Results		
Statistical parameters	All patients (N = 76)	Ventricular arrhythmia or unexplained syncope (n = 14)	No ventricular arrhythmia or unexplained syncope (n = 62)	p Value
<b>SSF2</b>				
Mean intensity	247.3 ± 169.4	244.5 ± 222.36	247.9 ± 157.4	0.960
Standard deviation	542.5 ± 280.5	430.9 ± 249.6	567.7 ± 282.8	0.085
Entropy	6.0 ± 0.6	5.9 ± 0.4	6.0 ± 0.7	0.400
Mean of positive pixels	550.4 ± 283.7	460.0 ± 285.7	570.8 ± 281.5	0.204
Skewness Maximum	0.3 ± 0.3	0.2 ± 0.3	0.3 ± 0.3	0.274
Skewness Average	0.2 ± 0.3	0.1 ± 0.2	0.2 ± 0.3	0.068
Skewness Minimum	0.1 ± 0.3	-0.1 ± 0.2	0.1 ± 0.3	<b>0.046</b>
Kurtosis Maximum	0.1 ± 0.6	0.2 ± 0.6	0.1 ± 0.7	0.488
Kurtosis Average	-0.1 ± 0.5	0 ± 0.3	-0.1 ± 0.5	0.762
Kurtosis Minimum	-0.3 ± 0.5	-0.3 ± 0.3	-0.3 ± 0.5	0.962
<b>SSF3</b>				
Mean intensity	304.5 ± 245.8	343.4 ± 301.2	295.7 ± 233.5	0.586
Standard deviation	593.9 ± 314.6	474.3 ± 299.1	621.0 ± 314.0	0.116
Entropy	6.0 ± 0.63	5.9 ± 0.4	6.0 ± 0.7	0.415
Mean of positive pixels	629.7 ± 336.2	554.2 ± 363.1	646.8 ± 330.5	0.392
Skewness <sub>max</sub>	0.2 ± 0.3	0.2 ± 0.3	0.2 ± 0.3	0.754
Skewness <sub>avg</sub>	0.1 ± 0.3	0.0 ± 0.3	0.1 ± 0.3	0.537
Skewness <sub>min</sub>	-0.1 ± 0.4	-0.2 ± 0.4	0.0 ± 0.4	0.350
Kurtosis <sub>max</sub>	0.0 ± 0.6	0.2 ± 0.7	0.0 ± 0.6	0.287
Kurtosis <sub>avg</sub>	-0.2 ± 0.5	0.0 ± 0.6	-0.2 ± 0.4	0.248
Kurtosis <sub>min</sub>	-0.3 ± 0.5	-0.2 ± 0.7	-0.4 ± 0.5	0.276
<b>SSF4</b>				
Mean intensity	306.7 ± 312.8	394.2 ± 347.8	287.0 ± 304.0	0.301
Standard deviation	606.6 ± 324.1	486.4 ± 314.7	633.8 ± 322.5	0.131
Entropy	6.0 ± 0.6	5.9 ± 0.4	6.0 ± 0.7	0.415
Mean of positive pixels	647.5 ± 360.3	601.8 ± 402.8	657.9 ± 352.7	0.636
Skewness <sub>max</sub>	0.1 ± 0.4	0.2 ± 0.4	0.1 ± 0.4	0.398
Skewness <sub>avg</sub>	-0.1 ± 0.3	0.0 ± 0.3	-0.1 ± 0.3	0.557
Skewness <sub>min</sub>	-0.2 ± 0.4	-0.2 ± 0.4	-0.2 ± 0.3	0.994
Kurtosis <sub>max</sub>	-0.1 ± 0.7	0.2 ± 0.5	-0.1 ± 0.7	0.074
Kurtosis <sub>avg</sub>	-0.3 ± 0.4	-0.1 ± 0.5	-0.4 ± 0.4	0.056
Kurtosis <sub>min</sub>	-0.5 ± 0.4	-0.3 ± 0.6	-0.5 ± 0.4	0.108
<b>SSF5</b>				
Mean intensity	279.2 ± 367.6	408.2 ± 370.3	250.0 ± 363.7	0.163
Standard deviation	609.7 ± 328.1	483.7 ± 310.0	638.2 ± 327.7	0.111
Entropy	6.0 ± 0.6	5.9 ± 0.4	6.0 ± 0.7	0.444
Mean of positive pixels	646.7 ± 373.6	613.2 ± 416.1	654.2 ± 366.6	0.737
Skewness <sub>max</sub>	0.0 ± 0.4	0.1 ± 0.4	0.0 ± 0.4	0.570
Skewness <sub>avg</sub>	-0.1 ± 0.3	-0.1 ± 0.3	-0.1 ± 0.3	0.732
Skewness <sub>min</sub>	-0.3 ± 0.3	-0.3 ± 0.4	-0.3 ± 0.3	0.865
Kurtosis <sub>max</sub>	-0.2 ± 0.5	0.0 ± 0.3	-0.3 ± 0.5	<b>0.005</b>
Kurtosis <sub>avg</sub>	-0.4 ± 0.4	-0.2 ± 0.3	-0.5 ± 0.4	<b>0.007</b>
Kurtosis <sub>min</sub>	-0.6 ± 0.4	-0.4 ± 0.4	-0.7 ± 0.4	0.052
<b>SSF6</b>				
Mean intensity	239.9 ± 409.4	398.0 ± 376.4	204.2 ± 410.9	0.102
Standard deviation	605.0 ± 332.2	476.4 ± 300.4	634.1 ± 334.3	0.097
Entropy	6.0 ± 0.6	5.9 ± 0.4	6.0 ± 0.7	0.540
Mean of positive pixels	631.7 ± 382.0	607.2 ± 417.9	637.2 ± 376.9	0.808
Skewness <sub>max</sub>	0.0 ± 0.4	-0.1 ± 0.4	0.0 ± 0.4	0.713
Skewness <sub>avg</sub>	-0.1 ± 0.3	-0.2 ± 0.4	-0.2 ± 0.3	0.665
Skewness <sub>min</sub>	-0.3 ± 0.3	-0.4 ± 0.4	-0.3 ± 0.4	0.511
Kurtosis <sub>max</sub>	-0.2 ± 0.5	-0.1 ± 0.4	-0.4 ± 0.5	<b>0.025</b>
Kurtosis <sub>avg</sub>	-0.4 ± 0.4	-0.3 ± 0.3	-0.6 ± 0.3	<b>0.015</b>
Kurtosis <sub>min</sub>	-0.6 ± 0.4	-0.5 ± 0.4	-0.7 ± 0.3	0.075

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<b>Table 3</b>	<b>Kaplan Meier Analysis</b>				
	<b>Log Rank</b>	<b>p Value</b>	<b>ROC Analysis Threshold</b>	<b>Number of patients assigned to the low risk group by TA-CMR</b>	<b>Number of patients assigned to the high risk group by TA-CMR</b>
<b>SSF2</b>					
Skewness <sub>min</sub>	4.460	0.035	0.120	25	51
<b>SSF5</b>					
Kurtosis <sub>max</sub>	5.319	0.021	-0.445	53	23
Kurtosis <sub>avg</sub>	6.397	0.011	-0.493	45	31
<b>SSF6</b>					
Kurtosis <sub>max</sub>	8.407	0.004	-0.465	47	29
Kurtosis <sub>avg</sub>	6.343	0.012	-0.628	51	25

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Test result variables	Area	SE	p-value	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
				Age	0.7
LVEF	0.715	0.082	0.012	0.554	0.876
Kurtosis <sub>avg</sub> SSF=5	0.73	0.064	0.008	0.605	0.855
Kurtosis <sub>max</sub> SSF=5	0.729	0.063	0.008	0.604	0.853
Kurtosis <sub>min</sub> SSF=5	0.654	0.077	0.073	0.504	0.805
Kurtosis <sub>avg</sub> SSF=6	0.715	0.066	0.012	0.586	0.845
Kurtosis <sub>max</sub> SSF=6	0.705	0.063	0.017	0.582	0.828
Kurtosis <sub>min</sub> SSF=6	0.656	0.079	0.07	0.5	0.811
Skewness <sub>avg</sub> SSF=2	0.589	0.089	0.299	0.415	0.763
Skewness <sub>max</sub> SSF=2	0.586	0.087	0.318	0.415	0.757
Skewness <sub>min</sub> SSF=2	0.594	0.076	0.275	0.445	0.742

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