# Late Gadolinium Enhancement Dispersion for predicting malignant arrhythmic events in patient with non-ischemic Dilated Cardiomyopathy

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**ABSTRACT**

**Background:** Arrhythmic risk stratification in patients with non-ischemic dilated cardiomyopathy (DCM) remains challenging. The LGE-dispersion mapping is a novel method for the quantification of tissue heterogeneity through the Global Dispersion Score (GDS). We sought to evaluate the usefulness of GDS in arrhythmic risk stratification of DCM patients.

**Methods:** consecutive non-ischemic DCM patients underwent cardiac magnetic resonance imaging. GDS was calculated in LGE images. During a follow-up of 3.3 years (2 to 6 years) the combined endpoint of sudden cardiac death and appropriate implantable cardioverter-defibrillator intervention was considered.

**Results:** The final population included 510 patients (mean age was 56±15 years). LVEF was > 35% in 241 patients (47%). LGE was present in 225 patients (45%). Median extent of LGE was 12% of LV mass (interquartile range -IQR- 6-20%). Among patients with positive LGE, GDS was 0.14 (IQR 0.08-0.20). During follow-up 81 patients had malignant ventricular arrhythmias (8 SCD, 73 appropriate ICD interventions). At Kaplan-Meier analysis, patients with GDS > 0.10 had worse prognosis than those with lower values of GDS ($p < 0.0001$). At multivariate analysis, GDS > 0.10 (HR 2.9, 95% CI 1.7-5, $p = 0.0002$) was an independent predictor of events. The prognostic value of GDS was confirmed in subgroups of patients with LVEF ≤ 35% and >35%.

**Conclusion**: GDS is a useful marker to identify DCM patients at higher risk for malignant arrhythmic events regardless LVEF and extent of LGE.

**Keywords:**

Dilated cardiomyopathy; ventricular arrhythmias; Late gadolinium Enhancement; Cardiac Magnetic resonance

**Condensed abstract:**

Late Gadolinium enhancement dispersion mapping was performed in 510 consecutive patients with non-ischemic dilated cardiomyopathy (DCM). Patients with Global Dispersion Score (GDS) >0.10 had higher risk to present malignant ventricular arrhythmias (MVA) during the follow-up. At multivariable analysis GDS>0.10 was an independent predictor of MVA with an incremental prognostic role compared to the other predictors, including midwall/ring-like LGE and non-sustained ventricular tachycardia. GDS was the only independent predictor of MVA in the subgroup of patients with ejection fraction ≤35% and it was associated with MVA in all bivariate models in patients with ejection fraction >35%.

## INTRODUCTION

Non-ischemic dilated cardiomyopathy (DCM) is a common heart muscle disorder (1:2500 adults), often genetic, defined by the presence of left ventricular or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease (1). Sudden cardiac death (SCD) accounts for 30% of all deaths in patients with DCM (2). The arrhythmic stratification in patients with DCM remains extremely challenging and is currently heavily reliant on the assessment of left ventricular ejection fraction (LVEF), as evidenced by its use as the primary determinant of device implantation (implantable cardioverter-defibrillator, ICD) (3). Although LVEF is an important prognostic factor in DCM, many patients with significant LVEF impairment may still be at low risk for SCD, moreover most patients who experience SCD do not have severely reduced LVEF (4,5). LV systolic function, assessed by EF, does not always correlate with the myocardial substrate required for ventricular tachycardia (VT)/ventricular fibrillation (VF), instead myocardial fibrosis was recognized as an anatomical substrate for malignant ventricular arrhythmias (MVA) and SCD (6). Cardiac magnetic resonance (CMR) has a crucial role for the diagnosis of DCM and non-invasive detection and quantification of myocardial fibrosis with late gadolinium enhancement (LGE) technique (7). LGE is strongly and independently associated with ventricular arrhythmias (VA) or SCD and is an incremental predictor of mortality in patients with DCM (8,9). Also LGE pattern has important prognostic implications, regardless LVEF. Halliday et al demonstrated that midwall septal LGE pattern in DCM with mild or moderate reductions in LVEF is associated with high risk of SCD (10). However, myocardial scar, detected as LGE, regardless of its pattern or global extent, has different presentation, distribution and signal intensity not previously evaluated in DCM. The LGE-dispersion mapping (LGE-DM) is a novel method of analysis of LGE that lead to calculate the Global Dispersion Score (GDS), which is a quantitative marker of the signal heterogeneity, dispersion, and irregularity of myocardial scar (11). The GDS provided a better risk stratification in patients with hypertrophic cardiomyopathy and a low-

intermediate 5-year risk of SCD (11). The aim of this study is to propose the GDS, calculated by LGE-dispersion mapping, to assess arrhythmic risk and prognosis in patients with DCM.

## METHODS

### Patients

In this a multicenter study, consecutive 510 DCM patients were prospectively enrolled from 2002 to 2020 and clinically followed-up. CMR with LGE was performed in all of this 510 patients at the time of enrolment. Then, LGE images were retrospectively analyzed for the evaluation of GDS. Based on European Society of Cardiology (ESC) criteria[1], the diagnosis of DCM was performed using the following criteria: 1) LV or biventricular systolic disfunction (LVEF <45%) and dilatation that are not explained by loading conditions or coronary artery disease; 2) LV or biventricular global systolic dysfunction (LVEF <45%) without dilatation, not explained by abnormal loading conditions or coronary artery disease. LV dilatation was defined by LV end-diastolic volume indexed by body surface area (EDVi) >2SD above normal range[12]. Exclusion criteria were: 1) contraindication to CMR; 2) GFR <30 ml/min (contraindication to Gadolinium-based contrast agent); 3) NYHA class IV; 4) presence of coronary artery disease at coronary angiography and/or coronary angio-TC. After enrolment 10 patients were excluded for suboptimal LGE images. The final population included 510 patients. Patients were evaluated either as hospital patients or outpatients. Before the CMR scan, clinical information were collected. This observational and retrospective study received approval from the institutional internal review board and complies with the Declaration of Helsinki's guidelines. Prior to enrollment, informed permission was provided by all patients.

### CMR Acquisition Protocol

All the CMR scans were performed using 1.5 T whole-body CMR machines with dedicated cardiac coil. According to the protocols recommended by the Society for Cardiovascular Magnetic Resonance, a short-axis breath-hold balanced steady-state free-precession (bSSFP) image was used to evaluate global LV function, acquired with the following parameters: 30 phases, slice thickness 8 mm, no gap, 8 views per segment, 35 to 40 cm field of view, phase field of view 1, matrix 224×224, reconstruction matrix 256×256, 45° flip angle, repetition time 4 ms and echo time 2 ms. LGE images were acquired about 10 minutes after the administration of 0.5 molar gadolinium contrast agent (0.2 mmol/kg) in short and long-axis views, using an inversion recovery T1-weighted gradient-echo sequence, acquired with the following parameters: field of view 35 to 40 mm, slice thickness 8 mm, no gap, repetition time 3 to 5 ms, echo time 1 to 3, a flip angle of 20°, matrix 224×224, and reconstruction matrix 256×256. Using a TI-scout, the appropriate inversion time identify to null normal myocardium.

**Postprocessing Image Analysis**

Three certified CMR readers with level III accreditation from the European Association of Cardiovascular Imaging performed offline, blinded evaluations of CMR images. Functional parameters and LV mass were measured by the analysis of short-axis cine images using a commercially available software package (cvi42, Circle International Corporation, Canada), as recommended. In short-axis images, the maximum LV end-diastolic wall thickness was measured. The extent of LGE and LGE- Dispersion was measured using a previous validated home-made software, the LGE dispersion tool (11). This software is available for research purposes by contacting the first author via email. Briefly, the endocardial and epicardial contours were manually traced in each LGE short axis image. A region of interest was put in a section of the myocardium without LGE. In this area of interest, the average signal strength and standard deviation (SD) were measured. Myocardial voxels were deemed to be hyperenhanced if their signal intensity was more than the average signal intensity of the region of interest plus 5 SDs. In the entire LV myocardium,

the proportion of hyperenhanced voxels was calculated and expressed as percentage to total LV mass. Then, a 2-colors parametric map was obtained (figure 1), where normal myocardium was depicted in blue and enhanced myocardium in yellow. Dispersion mapping was automatically generated from the analysis of these 2-colors parametric maps as previously reported (11). Briefly, a local measure of heterogeneity was computed from the analysis of a 3×3 pixel grid over a central pixel. A score, named dispersion score, from 0 to 8 was assigned to each pixel, where 0 was assigned when all 8 of the surrounding pixels had the same classification (normal or enhanced) of the central pixel, whereas score was 8 when all the surrounding pixels had different classification than the central pixel (figure 1). This count was performed for every enhanced pixel of the LV myocardium. Finally, the Global Dispersion Score (GDS) was calculated as the average score of all pixels. A dispersion map was generated from each LGE image, assigning a different color to different dispersion score for each pixel. Some examples of dispersion maps are shown in **central illustration**.

**Clinical Follow-Up**

After CMR examinations, all patients underwent follow-up. Clinical data were collected using a questionnaire filled by a doctor during routine ambulatory visits, or by calling the patient's family or general practitioner. Follow-up was updated every year. Malignant ventricular arrhythmias (MVA) that were documented included: sudden cardiac death (SCD), resuscitated cardiac arrest, and the proper ICD shock or anti-tachycardia pacing, sustained ventricular tachycardia (SVT). ICD interventions were designated as appropriate if triggered by life-threatening arrhythmias: ventricular tachycardia above the programmed cut-off of the ICD (12 intervals at >180 beats/min) or ventricular fibrillation. Sustained ventricular tachycardia lasting ≥30 s at ≥100 beats/min. The referring cardiologist interrogated the ICD to check the appropriateness of the shock/anti-tachycardia pacing. ECG Holter monitoring was repeated every 6 months. An expert panel of 3 investigators finally decided on and verified the incidence of MVA.

**Statistical Analysis**

A Kolmogorov-Smirnov test was used to test each variable for normal distribution. Normally distributed variables were shown as mean ±SD, while non-normally distributed variables as median ($25^{th}$-$75^{th}$). Depending on the situation, the Fisher exact test or the $\chi^2$ test was used to compare categorical variables. The Wilcoxon non-parametric test or the t test, depending on the situation, was used to compare continuous variables. Bonferroni correction was applied where necessary. A maximally selected rank statistical analysis was used to define the optimal cut-off of the GDS for survival analysis using the maxstat package of R software. The log-rank test was used to create and compare longitudinal curves between groups using the Kaplan-Meier time-to-event approach. Univariate and multivariable Cox regression analysis with competing risk analysis was used to explore the impact of each significant variable in univariate analysis to predict the occurrence of hard cardiac endpoints. The reclassification of the risk of MVA was determined using the net reclassification improvement (NRI) analysis for hard cardiac events. The Harrell-C statistic was used for in multivariable models. A $p<0.05$ was considered statistically significant.

**RESULTS**

The final population included 510 patients with non-ischemic DCM (292 males; 57%) with a mean age of 56±15 years. The general characteristics of the population are shown in Table 1. Family history of SCD was recorded in 89(18%) patients. The average LVEF was 35%±11, LVEF was >35% in 241 patients (47%). 256(50%) were in NYHA class I at the moment of CMR, 196(39%) in NYHA class II and 58(11%) in NYHA class III. Median NT-pro-BNP was 1150 (466-2276) pg/ml. LBBB was present in 104(20%) patients. At 24h Holter monitoring 148 patients (29%) showed NSVT. CMR was performed a median of 7(2-17) months after first diagnosis. LGE was present in

225(45%) of patients with a median extent of LGE was 12% (6-20%) of LV mass. A midwall septal LGE pattern was found in 116 (22%), whereas a sub-epicardial pattern in 68(12%). The median GDS was 0(0-0.12). Among patients with positive LGE, GDS was 0.14(0.08-0.20).

**Follow Up in the whole population**

Clinical follow-up was performed for 3.3 years (2 – 6). During this time, ICD was implanted in 239 (47%) of patients, 122 of them also including heart resynchronization therapy. During the follow-up, 81 patients had MVA: 8 SCD, 27 ICD intervention with appropriate shock for VF/VT, and 46 appropriate interventions with anti-tachycardia pacing. During the follow-up further 53 patients died for heart-failure non-related to arrhythmic complications. Characteristics of patients with and without MVA are reported in Table 2**.** Patients with MVA were significantly older ($p<0.01$), more often in a NYHA class > 1 ($p = 0.01$), with more frequently episode of NSVT. Patients who experimented events had higher LVEDVi ($p < 0.001$), lower LVEF ($p < 0.001$), with more frequently positive LGE ($p < 0.001$) with greater extent ($p < 0.001$) and more frequently a mid-wall septal/ring-like distribution ($p < 0.001$). Finally, patients with events showed a higher GDS than those without (a median of 0.15, $25^{th}$-$75^{th}$ 0.05-0.20 vs 0, $25^{th}$-$75^{th}$ 0-0.09, $p< 0.001$).

The Kaplan-Meier analysis showed that patients with positive LGE had higher probability of MVA than those without as evident (figure 2, left panel). Patients with mid-wall septal and/or ring-like pattern of LGE had worse prognosis than those with other pattern of LGE (figure 2, right panel).

At maximally selected rank statistical analysis the optimal cut-point for GDS for predicting malignant ventricular arrhythmic events (figure 3) was >0.10.

The differences among patients with negative LGE (GDS=0), patients with positive LGE and GDS≤ 0.10 and those with GDS>10 are reported in table 3. Patients with GDS>0.10 were significantly younger, with more diuretic therapy and presented greater LV mass and more

frequently sub-epicardial LGE than those with GDS≤ 0.10. Compared to patients with GDS=0, those with GDS>0.10 were more frequently males, were more often in diuretic therapy, presented more frequently episode of NSVT and with signs of more advanced disease at CMR (higher LV EDVi and LV mass, lower LVEF and greater extent of LGE).

The Kaplan-Meier analysis showed that patients with GDS>0.10 had greater risk to have MVA than those with lower values of GDS ($p < 0.0001$) in the whole population (**central illustration**). The prognostic role of GDS persisted also considering only patients with positive mid-wall septal/ring-like LGE (figure 4). As evident in table 4, Among patients with mid-wall septal/ring-like LGE the prevalence of MVA passed from 17% in those with GDS ≤0.10 to 40% when GDS was >0.1 (p=0.0016).

At univariate Cox regression analysis, age, male sex, NYHA class >I, NSVT, LVEDVi, LVEF, LV Mass, RVEF, positive LGE, the extent of LGE, midwall septal LGE and GDS (threshold >0.10) were associated with occurrence of MVA (table 5).

At multivariate Cox regression with competing risk analysis analysis (table 6), age (HR 1.03, 95% CI 1.01-1.05, p=0.02), NSVT (HR 2.4, 95% CI 1.4-4.2, p=0.001), LV mass (HR 1.01, 95%CI 1.01-1.02, p=0.04), midwall septal/ring-like LGE (HR 3.3, 95% CI 1.8-5.8, p=0.0002) and GDS >0.10 (HR 2.9, 95% CI 1.7-5, p=0.0002) were independent predictor of MVA.

In figure 5, the incremental value for predicting MVA by stepwise inclusion of GDS>0.10 in models progressively including left ventricular mass (LV-mass), non-sustained ventricular tachycardia (NSVT), mid-wall/ring-like LGE and in addition to age.

GDS>0.10 allowed a significant net reclassification of the risk of MVA compared to Age >60 years (NRI 0.17, 95% CI 0.02-0.31, p = 0.03), to NSVT (NRI 0.34, 95% CI 0.18-0.48, p < 0.0001), and to LV mass index > 80 g/m$^2$ (NRI 0.17, 95% CI 0.02-0.32, p = 0.025).

GDS>0.10 did not allow a significant net reclassification compared to mid-wall/ring-like LG, but the addition of GDS>0.10 to mid-wall/ring-like LGE allowed a significant net reclassification of the risk of MVA in 12% of patients compared to mid-wall/ring-like LGE alone (NRI 0.12, 95% CI 0.05-0.18, p =0.0003).

In patients with LV EF ≤35%, 60 MVA occurred during the follow-up. The Kaplan-Meier analysis showed that in this subgroup of patients with GDS>0.10 had worse prognosis than those with lower values of GDS (log-rank p = 0.0001, figure 6).

In Table 7, it is shown the univariate regression analysis for predicting events in this subgroup of patients: age, LVEF, LV mass, positive LGE, mid-wall septal/ring-like LGE and GDS>0.10 were significantly associated with events. These parameters were evaluated in the multivariate regression analysis (Table 8) demonstrating that GDS>0.10 was the only independent predictor of event (HR 19.4, 95% CI 6.9-42, p=0.0009) in patients with LVEF ≤35%.

***Patients with LVEF>35%***

In patients with LV EF>35% 21 MVA events occurred. The Kaplan-Meier analysis showed that in this subgroup of patients with GDS>0.1 had worse prognosis than those with lower values of GDS (log-rank p = 0.0002, figure 6).

A further univariate regression analysis was performed in this subgroup (table 8): Age, positive LGE, midwall septal LGE, subepicardial LGE and GDS>0.10 were associated with events. Since the low number of events in this subgroup of patients, 4 different models of bivariate analysis were performed (Table 9), all including GDS>0.10 and another variable with a significant association with events at the univariate analysis. As evident in table, GDS>0.10 was a significant predictor of events in all models of bivariate analysis.

## DISCUSSION

Main results of the present study may be summarized as follows: 1) in non-ischemic DCM, GDS is a novel prognostic marker, permitting to identify a subgroup of patients at higher risk of ventricular arryhtmias; 2) GDS has an incremental prognostic role over the presence of LGE and particularly the combination of mid-wall septal/ring-liker LGE plus GDS>0.10 is associated with a 5-year risk of MVA of 39%; 3) GDA was the only independent predictor of MVA in the subgroup of patients with LV EF ≤35% and it was significantly associated with MVA in the subgroup with LV EF >25% in all the bivariate models.

The 2022 AHA/ACC/HFSA guidelines for the management of heart failure suggest ICD implantation in patients with LVEF ≤35% and NYHA class II or III symptoms on chronic guideline-directed medical therapy, who have reasonable expectation of survival for >1 year (12). ICD was also indicated in patients with LVEF ≤45% with more arrhythmogenic genotype.

A similar approach was suggested by the new 2023 ESC guidelines for the management of cardiomyopathies that recommend ICD implantation for primary prevention in patients with non-ischemic DCM s with an LVEF ≤35% and symptomatic heart failure despite 3 months of optimal medical therapy (13). The same guidelines suggest ICD implantation also in patients with LVEF >35% presenting with high-risk genotype and/or with additional risk factors as syncope or positive LGE at CMR.

The benefic effect of ICD for prevention of SCD was demonstrated by different randomized clinical trial for secondary prevention in patients who had been resuscitated from a cardiac. In The MADIT-II (Multicenter Automatic Defibrillator Implantation trial II) trial a significant survival benefit was demonstrated in patients with ischemic LV dysfunction with LVEF ≤30% (14). In non-ischemic

DCM the net benefit of ICD implantation for the overall survival is still debated because its effect is mitigated by the fact that a large percentage of patients dies for heart failure-related causes or, in older patients, for non-cardiac causes.

Three randomized controlled trials studies, the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), the DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) and the DANISH (The Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) trials had discordant results of the impact of ICD in non-ischemic DCM (15-17). The SCD-HefT study found a significant benefit of ICD in the overall survival but it enrolled patients before the 2001 and patients were not in optimal medical therapy, as only 69% of patients were in beta-blockers therapy, 20% assumed mineralocorticoid-receptor antagonist, and in no patients CRT (15). In the DEFINITE trial, which had similar limitations, enrolling patients between 1998 and 2002 and with no patients who receiving CRT, no significant prognostic benefit was found in patients receiving ICD (16). More recently, the DANISH trial, demonstrated that ICD therapy was not associated with a significant improvement in overall survival but only improved the risk of sudden cardiac death (17). In that trial, 31% of patients had non cardiac cause of death and 40% heart failure-related death. Results of those trials highlight the need for novel prognostic marker in DCM.

Many studies concordantly attributed a prognostic role of LGE in DCM (7-9). Patients with positive LGE are at high risk for MVA and SCD with an incremental predictor of mortality in patients with DCM. Among patients with positive LGE those with midwall septal and/or ring-like LGE pattern are at greater risk than those with other patterns of LGE (10).

In our population LGE was positive in 45% of DCM, a prevalence that is concordant with previous studies where the prevalence of LGE in DCM ranged from 30 to 46% (10,18,19). The presence of LGE is associated with an increased risk of all-cause mortality, heart failure

hospitalization, and SCD in patients with DCM (20) . Concordantly with previous data, in our study midwall septal/ring-like LGE was an independent predictor of MVA at multivariate analysis. This result highlights the important prognostic role of pattern of LGE and its distribution in the myocardial wall regardless its extent (10). The midwall septal/ring-like pattern was prognostically relevant also in other cardiac conditions. ITAMY study demonstrated that in patients with acute myocarditis and preserved LVEF, LGE in the midwall layer of the anteroseptal myocardial segment is associated with a worse prognosis than other patterns of presentation (21).

We evaluated a further aspect of LGE by the LGE-dispersion mapping that is a texture analysis technique that enables the assessment of the inter-relationships among pixels, the quantification of the gray-level patterns, and other statistical properties that characterize the texture of an image. LGE-dispersion mapping guarantees assessment and quantification of severity of dispersion and heterogeneity of cardiac fibrosis, trough the calculation of the GDS (11). We previously tested GDS in a population of HCM demonstrating its prognostic role for predicting MVA (11). In that study, LGE dispersion maps were generated starting from three-colors parametric map, considering normal myocardium, hyper-enhanced myocardium and mid-enhancement myocardium, because in HCM mild-enhancement was considered a marker of increased risk of MVA (22,23). In the present study a dichotomic approach was used by considering only normal myocardium and enhanced myocardium. This choice was made because the prevalence of positive LGE in DCM was lower than in HCM, with generally lower extent and because the myocardial walls in DCM may be very thinned and making the characterization of LGE more problematic. Notwithstanding, results of this study suggest an important prognostic role of GDS even in DCM.

Intrinsically, the GDS include in different aspects: the presence of LGE, because GDS = 0 in absence of LGE; the extent of LGE, because the more voxel are enhanced, the higher is probability to have of greater value of dispersion; the pattern of LGE, because midwall LGE, being surrounded

by normal myocardium, had higher probability to have a greater dispersion than subepicardial LGE; and, obviously, the dispersion of LGE within myocardium, that is a marker of entropy of LGE.

High value of GDS represents irregularly shaped myocardial scars that, in DCM, can be more arrhythmogenic than a gross, inert, homogeneous single scar. Our results demonstrated that GDS>0.10 was associated with a higher risk of hard cardiac events independently from the extent of LGE. Patients with GDS>0.10 are significantly younger, more often in diuretic therapy, they present more frequently episode of NSVT and signs of more advanced disease at CMR (higher LVEDVi, higher LV mass, lower LVEF), compared with patients with lower score of GDS. Therefore, high value of GDS were related to a worse clinical status of patients. At multivariable analysis GDS>0.10 resulted an independent predictor of MVA together with age, NSVT, LV mass and midwall septal/ring-like LGE. GDS had an additive prognostic role on the statistical model combining all these parameters.

The additive role of GDS was also seen among patients with midwall septal/ring-like LGE. In this subgroup of patients, the prevalence of MVA passed from 17% in those with low GDS to 40% in those with GDS>0.10, meaning that the heterogeneity of scar is a relevant factor even in this high-risk pattern of LGE.

The prognostic role of GDS>0.10 remained also by dividing the population for the severity of LV dysfunction. Indeed, GDS was the only independent predictor of cardiac events in patients with LVEF ≤35% and was a significant predictor of events in all models of bivariate analysis in patients with LVEF >35%. In this latter group of patients the analysis was limited by the low number of events and further larger studies are needed to confirm the prognostic role of GDS in these patients.

Some study limitations should be mentioned. First, the GDS was measured in plane, by the 2-dimensional analysis after comparing the 8 surrounding voxels to the central voxel. A 3-dimensional analysis, also considering the voxels of contiguous slices could have been more accurate. However, we used a 2-dimensional–LGE pulse sequence with 8 mm of slice thickness. Two-dimensional LGE was the most common technique to assess LGE in clinical practice.

Second, T1-, T2-, and extracellular volume mapping techniques were not used in this study, because they were not available at our institutions during patients' enrollment. LGE dispersion and T1- or ECV-mapping could be compared in future studies.

Third, during the enrolment of patients, genetic evaluation was performed only in a minority of patients because at that time it was not a mandatory feature for prognostic evaluation of DCM.

Finally, patient's enrolment lasted for 18 years. During this time novel therapy for heart failure were proposed, and this may have some implication for the prognosis of patients. However, the change in therapy during the follow-up is a common risk for all long-time prognostic study.

## CONCLUSION

GDS is a quantitative marker of the signal heterogeneity, dispersion, and irregularity of myocardial fibrosis in DCM. GDS>0.10 was the only independent predictor of MVA in patients with LVEF ≤35% and was a significant predictor of events in patients with LVEF >35%. GDS is a useful tool to identify DCM patients at a higher risk for hard cardiac events regardless LVEF and extent of LGE.

**CLINICAL PERSPECTIVE:**

**Competency in patient care and procedural skills**: In patients with non-ischemic Dilated Cardiomyopathy, patients with high Global Dispersion Score (GDS) are at greater risk of malignant ventricular events. GDS has an additive prognostic role compared with non-sustained ventricular tachycardia, midwall septal/ring-liker LGE and LV mass.

**Translational outlook:** Further studies are needed to evaluate the association between high GDS and the presence of pathogen genetic mutations associated with high arrhythmic risk.

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## Figure legends

**Figure 1: Method for quantification of the global dispersion score (GDS)**. Late gadolinium enhancement (LGE) images were analyzed and voxels were divided into 2 groups: enhanced and nonenhanced. Enhanced voxel were defined as having signal intensity (SI) >mean + 5SD of normal myocardium. For each enhanced voxel, the surrounding 8 voxels were analyzed and the number of adjacent voxels with different aspect from the central voxel were counted and a dispersion score was assigned from 0, when all the surrounding voxels enhanced as the central voxel, to 8, when the enhanced voxel was surrounded by 8 non-enhanced voxel. Then a LGE-dispersion map was generated assigning a color-scale to each voxel based on the dispersion score. Finally, the Global Dispersion Score (GDS) was calculated as the average score measured in the whole left ventricular myocardium.

**Central illustration: Prognostic role of Global Dispersion Score (GDS) in non-ischemic Dilated Cardiomyopathy (DCM).** The upper panel shows two examples of global dispersion mapping of patients with non ischemic dilated cardiomyopathy: A) a case of DCM with cardiac arrest during the follow-up presenting a low extent of LGE (the contoured original LGE images in left panel, in middle panel the two-color parametric map) but a high GDS (0.15, right panel); B) a case of DCM without events during the follow up but showing a greater extent of LGE (22% of LV mass, left and middle panels) but a lower GDS (right panel) than the previous patient. In the lower panel shows the Kaplan-Meier survival curve analysis comparing patients with GDS ≤ or >0.10. The graph demonstrated that patients with DCM with GDS >0.10 had greater probability of Malignant Ventricular Arrhythmias than others (log-rank P<0.0001).

**Figure 1: Methods for generating Dispersion Maps:** In the dataset of short axis views of Late Gadolinium Enhancement (LGE) images, endocardial and epicardial contours of left ventricular myocardium were manually traces (left panel). Automatically a 2 colors parameteric map (middle image) was generated by identifying in blue non enhanced myocardium and in yellow enhanced myocardium (defined as having signal intensity >mean of normal myocardium +5 SD). Then, a

dispersion map is generated from the parametric map and the Global Dispersion Score (GDS) calculated as explained in the methods section.

**Figure 2: Prognostic role of Late Gadolinium Enhancement (LGE) in the whole population:** In the left panel, the Kaplan-Meier survival curves analysis demonstrated that patients with LGE were at higher risk of MVA than those without. As shown the survival curves of right panel, patients with mid-wall septal and/or ring-like LGE had worse prognosis than those with other pattern of LGE.

**Figure 3: Maximally selected rank statistical analysis for determining the optimal cut-point of Global Dispersion Score to predict Malignant Ventricular Arrhythmias (MVA).** From this analysis, the optimal cut-off of GDS was >0.10

**Figure 4: Prognostic role of Global Dispersion Score (GDS) in patients with mid-wall septal/ring-like LGE.**

**Figure 5: Incremental value in predicting malignant ventricular arrhytmias (MVA) by stepwise inclusion of left ventricular mass (LV-mass), non-sustained ventricular tachycardia (NSVT), mid-wall/ring-like LGE and GDS>0.10 in addition to age.**

**Figure 6: Prognostic role of Global Dispersion Score (GDS) in patients with LVEF ≤ 35% and in those with LVEF >35%.** Kaplan-Meier survival curves analysis show that GDS >0.10 was associated with a higher probability of malignant ventricular arryhtmias both in patients with LVEF >35% and in those with LVEF ≤35%.

**Table 1. Clinical and CMR characteristics of the population.**

| Variables: | | Value: |
|---|---|---|
| n. | | 510 |
| Age | mean ± SD | 56±15 |
| Males | n (%) | 292(57%) |
| BSA | mean ± SD | 1.89±0.2 |
| BMI | mean ± SD | 26±4 |
| Family HIstory of CAD | n (%) | 76(15%) |
| Family History of DCM | n (%) | 125(25%) |
| Family History of SCD | n (%) | 89(18%) |
| Systemic Hypertension | n (%) | 190(37%) |
| Hypercholesterolemia | n (%) | 175 (34%) |
| Diabetes | n (%) | 57 (11%) |
| Smoking | n (%) | 97(19%) |
| NYHA I | n (%) | 256 (50%) |
| NYHA II | n (%) | 196 (39%) |
| NYHA III | n (%) | 58 (11%) |
| NT-pro-BNP | median ($25^{th}$-$75^{th}$) | 1150 (466-2276) |
| Troponin I | median ($25^{th}$-$75^{th}$) | 10 (10-40) |
| PVC>1000/24H | n (%) | 103 (20%) |
| NSVT | n (%) | 148 (29%) |
| History of AF-Flutter | n (%) | 133 (26%) |
| LBBB | n (%) | 104 (20%) |

| | | |
|---|---|---|
| RBBB | n (%) | 8 (2%) |
| QRS | median ($25^{th}$-$75^{th}$) | 111(101-142) |
| QRS>120ms | n (%) | 183(36%) |
| COPD | n (%) | 16 (3%) |
| **Therapy:** | | |
| Beta Blockers | n (%) | 462 (90%) |
| ACE inibithors/ARB | n (%) | 458(90%) |
| ARNI | n (%) | 25(5%) |
| MRA | n (%) | 320 (64%) |
| Diuretics | n (%) | 286 (56%) |
| Antiarrhythmics ( amiodarone) | n (%) | 60 (12%) |
| **CMR findings:** | | |
| LV EDVi (ml/m2) | mean ±SD | 127±37 |
| LV EF (%) | mean ±SD | 35 ±11 |
| LVMi (gr/m2) | median ($25^{th}$-$75^{th}$) | 140(116-177) |
| RV EDVi (ml/m2) | mean ±SD | 78 ±20 |
| RV EF (%) | mean ±SD | 53±10 |
| LGE positive | n (%) | 234(45%) |
| LGE (% of LV mass) | median ($25^{th}$-$75^{th}$) | 12(6-20) |
| Midwall Septal/ring-like LGE | n (%) | 185(36%) |
| Other pattern of LGE | n (%) | 49(10%) |
| Global dispersion score (GDS) | median ($25^{th}$-$75^{th}$) | 0 (0-0.12) |

AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; EDVi, end-diastolic volume index; EF, ejection fraction; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVMi, left ventricular mass index; MRA, mineral receptor antagonisti; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; RBBB, right bundle branch block; RV, right ventricle; SCD, sudden cardiac death.

**Table 2: Characteristics of the population with and without Malignant Ventricular Arrhythmias.**

| | | Malignant Ventricular Arrhythmias | | |
|---|---|---|---|---|
| | | **No** | **Yes** | **P value** |
| **n.** | | 429 | 81 | |
| age | mean ± SD | 54 ± 14 | 61 ± 13 | **<0.01** |
| Males | n (%) | 243 (57%) | 49 (61%) | 0.52 |
| BSA | mean ± SD | 1.89 ± 0.23 | 1.90 ± 0.21 | 0.53 |
| Systemic Hypertension | n (%) | 153 (36%) | 37 (46%) | 0.22 |
| Hypercholesterolemia | n (%) | 158 (37 %) | 22 (27%) | 0.10 |
| Diabetes | n (%) | 44 (10%) | 13 (16%) | 0.27 |
| Smoking | n (%) | 87 (20%) | 10(12%) | 0.18 |
| NYHA>1 | n (%) | 204 (48%) | 51 (63%) | **0.01** |
| NT-pro-BNP | median ($25^{th}$-$75^{th}$) | 1133(427-2010) | 1209(529-2990) | 0.49 |
| Troponin I | median ($25^{th}$-$75^{th}$) | 10(10-35) | 22(12-40) | 0.28 |
| PVC>1000/24H | n (%) | 78(18%) | 25(31%) | **0.02** |
| NSVT | n (%) | 193(45%) | 60(74%) | **<0.001** |
| LBBB | n (%) | 78(18%) | 26(32%) | **0.007** |
| QRS>120ms | mean ± SD | 110(101-141) | 120(103-152) | 0.31 |
| **Therapy:** | | | | |
| Beta Blockers | n (%) | 381 (90%) | 81 (100%) | **<0.001** |
| ACE inhibitors/ARB | n (%) | 382 (89%) | 76(94%) | 0.20 |
| MRA | n (%) | 254(60%) | 66(82%) | **<0.001** |
| Diuretics | n (%) | 225 (51%) | 61(75%) | **<0.001** |
| Antiarrhythmics (amiodarone) | n (%) | 50 (10%) | 10(12%) | 0.91 |
| **CMR findings:** | | | | |
| LV EDVi (ml/m2) | mean ± SD | 124 ± 26 | 139 ± 33 | **<0.001** |
| LV EF (%) | mean ± SD | 36 ± 9 | 30 ± 9 | **<0.001** |
| LVMi (gr/m2) | mean ± SD | 145 ± 28 | 178 ± 29 | **<0.001** |
| RV EDVi (ml/m2) | mean ± SD | 78 ± 15 | 78 ± 18 | 0.86 |
| RV EF (%) | mean ± SD | 54 ± 8 | 51 ± 7 | 0.10 |
| LGE positive | n (%) | 170 (39%) | 64(79%) | **<0.001** |
| LGE (% of LV mass) | median ($25^{th}$-$75^{th}$) | 0 (0-9) | 5 (2-13) | **<0.001** |
| LGE (grams of LV mass) | median ($25^{th}$-$75^{th}$) | 0(0-18) | 9(1-26) | **<0.001** |
| Midwall Septal/ring-like LGE | n (%) | 126(29%) | 59(72%) | **<0.001** |
| Other pattern of LGE | n (%) | 44(10%) | 5(6%) | 0.25 |
| Global dispersion score (GDS) | median ($25^{th}$-$75^{th}$) | 0 (0-0.09) | 0.15(0.05-0.2) | **<0.001** |

ARB, angiotensin II receptor blocker; BSA, body surface area; EDVi, end-diastolic volume index; EF, ejection fraction; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVMi, left ventricular mass index; MRA, mineral receptor antagonisti; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; RV, right ventricle.

**Table 3: Characteristics of the population with no LGE, Low and high Global Dispersion Score (GDS).**

| | | Negatove LGE (GDS=0) | Low GDS (GDS≤0.10) | High GDS (GDS>0.10) | P value |
|---|---|---|---|---|---|
| n. | | 277 | 84 | 149 | |
| Age | mean ± SD | 54±10[2] | 60±10[1,3] | 55±9[2] | **0.005** |
| Males | n (%) | 145(53%)[3] | 48(57%) | 99 (66%)[1] | **0.02** |
| BSA | mean ± SD | 1.89±0.2 | 1.85±0.2 | 1.91±0.2 | 0.15 |
| Systemic Hypertension | n (%) | 107 (39%) | 28(33%) | 55 (37%) | 0.78 |
| Hypercholesterolemia | n (%) | 101 (37%) | 35 (42%) | 39 (26%) | 0.09 |
| Diabetes | n (%) | 25 ( 9%) | 11 (13%) | 21 (14%) | 0.44 |
| Smoking | n (%) | 48 (17%) | 25 (30%) | 24 (16%) | 0.06 |
| NYHA>1 | n (%) | 130 (47%) | 50 (60%) | 76 (51%) | 0.15 |
| NT-pro-BNP | median ($25^{th}$-$75^{th}$) | 1219(478-2109) | 736(323-2581) | 1202(596-2360) | 0.43 |
| Troponin I | median ($25^{th}$-$75^{th}$) | 10(10-22) | 17(10-39) | 21(10-40) | 0.27 |
| PVC>1000/24H | n (%) | 47(17%)[3] | 11(12%) | 45(31%)[1] | **0.004** |
| NSVT | n (%) | 64(26%)[3] | 22(26%) | 62(43%)[1] | **0.0007** |
| LBBB | n (%) | 49(18%) | 20(24%) | 35(24%) | 0.64 |
| QRS>120ms | mean ± SD | 118±26 | 124±30 | 130±30 | 0.13 |
| **Therapy:** | | | | | |
| Beta Blockers | n (%) | 243 (88%)[2] | 81 (96%)[1] | 138 (95%) | **0.005** |
| ACE inibithors/ARB | n (%) | 242 (88%) | 80 (95%) | 136 (91%) | 0.10 |
| MRA | n (%) | 158(57%)[3] | 57(68%) | 105(70%)[1] | **0.02** |
| Diuretics | n (%) | 137(50%)[3] | 46(55%)[3] | 103(71%)[1,2] | **0.0004** |
| Antiarrhythmics ( amiodarone) | n (%) | 27(10%) | 13 ( 15%) | 20 ( 13%) | 0.20 |
| **CMR findings:** | | | | | |
| LV EDVi (ml/m2) | mean ±SD | 120±33[2,3] | 131±23[1] | 135±30[1] | **<0.001** |
| LV EF (%) | mean ±SD | 38±10[2,3] | 32±10[1] | 31±10[1] | **<0.001** |
| LVMi (gr/m2) | mean ±SD | 145±26[3] | 146±25[3] | 162±32[1,2] | **0.007** |
| RV EDVi (ml/m2) | mean ±SD | 77±20 | 79±20 | 79±25 | 0.72 |
| RV EF (%) | mean ±SD | 56±7[2,3] | 50±8[1] | 52±9[1] | **<0.001** |
| LGE (% of LV mass) | median ($25^{th}$-$75^{th}$) | 0(0-0)[2,3] | 9 ( 6-15)[1,3] | 13 (6-22)[1,2] | **<0.001** |
| Midwall Septal/ring-like LGE | n (%) | - | 65(77%) | 120(80%) | 0.59 |
| Other pattern of LGE | n (%) | - | 20(22%) | 29(19%) | 0.72 |

ARB, angiotensin II receptor blocker; BMI, body mass index; BSA, body surface area; EDVi, end-diastolic volume index; EF, ejection fraction; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVMi, left ventricular mass index; MRA, mineral receptor antagonisti; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; RV, right ventricle.

**Table 4: incidence of cardiac events during follow-up**

| | No LGE | Other LGE pattern & GDS≤0.10 | Other LGE pattern & GDS>0.10 | Mid-wall septal/ring-like LGE & GDS≤0.10 | Mid-wall septal/ring-like LGE % GDS>0.10 |
|---|---|---|---|---|---|
| **n.** | 276 | 20 | 29 | 65 | 120 |
| **Malignant Ventricular arrhythmias** | 17(6%)[4,5] | 1(5%)[5] | 4(14%)[5] | 11(17%)[5] | 48(40%)[1,2,3,4] |
| **Sudden cardiac death** | 0[5] | 0 | 1(3%) | 1(2%) | 6(5%)[1] |
| **Resuscitated cardiac arrest** | 0 | 0 | 0 | 0 | 0 |
| **Appropriate ICD intervention** | 17(6%)[4,5] | 1(5%)[5] | 3(10%)[5] | 10(15%)[1,5] | 42(35%)[1,2,3,4] |
| **5-year event probability** | 0.03(0.01-0.05) | 0.10(0.01-0.29) | 0.16(0.02-0.33) | 0.17(0.06-0.30) | 0.39(0.29-0.49) |

LGE, Late Gadolinium enhancement; GDS, Global Dispersion Score; ICD, implanted cardioverter defibrillator. [1], significant p value vs No LGE; [2], significant p value vs Other LGE pattern GDS ≤0.10; [3], significant p value vs Other LGE pattern GDS >0.10 ;[4], significant p value vs Mid-wall septal/ring-like LGE & GDS≤0.10; [5], significant p value vs Mid-wall septal/ring-like LGE & GDS>0.10.

**Table 5: Univariate Cox Logistic Regression Analysis for the risk of Malignant Ventricular Arrhythmias.**

| **Variables** | ***Univariate*** | | |
|---|---|---|---|
| | HR | 95% CI | P value |
| age | 1.04 | 1.02-1.05 | **0.0001** |
| Males | 1.60 | 1.03-2.5 | **0.004** |
| BSA | 1.60 | 0.63-4 | 0.33 |
| Systemic Hypertension | 1.47 | 0.95-2.3 | 0.09 |
| Hypercholesterolemia | 0.46 | 0.27-1.77 | 0.4 |
| Diabetes | 1.53 | 0.84-2.8 | 0.16 |
| Smoking | 0.6 | 0.3-1.2 | 0.13 |
| NYHA>1 | 1.85 | 1.18-2.9 | **0.008** |
| NT-pro-BNP | 1.01 | 0.98-1.02 | 0.96 |
| Troponin I | 1.01 | 0.98-1.01 | 0.33 |
| NSVT | 2.02 | 1.27-3.2 | **0.003** |
| QRS duration | 1.01 | 0.99-1.01 | 0.47 |
| LV EDVi (ml/m2) | 1.01 | 1.01-1.02 | **<0.0001** |
| LV EF (%) | 0.93 | 0.91-0.96 | **<0.0001** |
| LVMi (gr/m2) | 1.01 | 1.01-1.02 | **<0.0001** |
| RV EDVi (ml/m2) | 1.01 | 0.99-1.01 | 0.90 |
| RV EF (%) | 0.97 | 0.96-0.99 | **0.004** |
| LGE positive | 6.2 | 3.6-10.7 | **<0.0001** |
| LGE (% of LV mass) | 1.02 | 1.01-1.04 | **0.007** |
| Midwall Septal LGE | 6.5 | 4.1-10.1 | **<0.0001** |
| Subepicardial LGE | 2.04 | 1.18-3.5 | **0.01** |
| Global dispersion score (GDS) | 30.3 | 9.9-92 | **<0.0001** |
| GDS >0.10 | 6.1 | 3.9-9.7 | **<0.0001** |

BSA, body surface area; EDVi, end-diastolic volume index; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; LVMi, left ventricular mass index; NSVT, nonsustained ventricular tachycardia; RV, right ventricle.

**Table 6: Multivariate Cox Logistic Regression with competing risk Analysis for the risk of Malignant Ventricular Arrhythmias.**

| Variables | Multivariate | | |
|---|---|---|---|
| | HR | 95% CI | P value |
| age | 1.03 | 1.01-1.05 | **0.02** |
| Males | 1.80 | 0.63 -1.8 | 0.78 |
| NYHA>1 | 1.30 | 0.77-2.2 | 0.33 |
| NSVT | 2.4 | 1.4-4.2 | **0.001** |
| LV EDVi (ml/m2) | 0.98 | 0.98-1.02 | 0.65 |
| LV EF (%) | 0.98 | 0.94-1.02 | 0.25 |
| LVMi (gr/m2) | 1.01 | 1.01-1.02 | **0.04** |
| RV EF (%) | 0.99 | 0.97-1.02 | 0.49 |
| LGE positive | 1.7 | 0.6-4.9 | 0.31 |
| LGE (% of LV mass) | 0.98 | 0.95-1.02 | 0.30 |
| Midwall Septal LGE | 3.3 | 1.8-5.8 | **0.0002** |
| GDS >0.10 | 2.9 | 1.7-5 | **0.0002** |

Harrell's C 0.81 (0.77-0.86)

EDVi, end-diastolic volume index; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; LVMi, left ventricular mass index; NSVT, nonsustained ventricular tachycardia; RV, right ventricle.

**Table 7: Univariate Cox Logistic Regression Analysis for the risk of MVA in patients with LVEF ≤ 35%.**

| **Variables** | ***Univariate*** | | |
|---|---|---|---|
| | HR | 95% CI | P value |
| age | 1.03 | 1.02-1.05 | **0.01** |
| Males | 1.60 | 0.9-2.7 | 0.07 |
| BSA | 1.50 | 0.5-4.4 | 0.48 |
| Systemic Hypertension | 1.2 | 0.7-1.9 | 0.51 |
| Hypercholesterolemia | 0.46 | 0.29-1.77 | 0.3 |
| Diabetes | 0.98 | 0.5-1.9 | 0.94 |
| Smoking | 0.6 | 0.28-1.2 | 0.16 |
| NYHA>1 | 1.07 | 0.6-1.8 | 0.81 |
| NT-pro-BNP | 1.01 | 0.99-1.01 | 0.99 |
| Troponin I | 0.99 | 0.99-1.01 | 0.71 |
| NSVT | 1.6 | 0.9-2.7 | 0.07 |
| QRS duration | 0.99 | 0.99-1.1 | 0.87 |
| LV EDVi (ml/m2) | 1.01 | 0.99-1.01 | 0.19 |
| LV EF (%) | 0.96 | 0.92-0.99 | **0.03** |
| LVMi (gr/m2) | 1.01 | 1.01-1.02 | **0.003** |
| RV EDVi (ml/m2) | 1.01 | 0.99-1.01 | 0.59 |
| RV EF (%) | 0.99 | 0.97-1.01 | 0.31 |
| LGE positive | 4.5 | 2.3-8.7 | **<0.0001** |
| LGE (% of LV mass) | 1.01 | 0.98-1.02 | 0.88 |
| Midwall Septal LGE | 5.3 | 3.1-9 | **<0.0001** |
| Subepicardial LGE | 1.44 | 0.75-2.8 | 0.27 |
| Global dispersion score (GDS) | 7.3 | 1.9-27 | **0.003** |
| GDS >0.10 | 4.7 | 2.7-8 | **<0.0001** |

BSA, body surface area; EDVi, end-diastolic volume index; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; LVMi, left ventricular mass index; NSVT, nonsustained ventricular tachycardia; RV, right ventricle.

**Table 8: Multivariate Cox Logistic Regression with competing risk analysis for predicting MVA in patients with LVEF ≤ 35%.**

| Variables | Multivariate | | |
|---|---|---|---|
| | HR | 95% CI | P value |
| age | 1.03 | 0.99-1.07 | 0.08 |
| LV EF (%) | 1.04 | 0.94-1.15 | 0.42 |
| LVMi (gr/m2) | 1.01 | 0.99-1.02 | 0.85 |
| LGE positive | 0.47 | 0.03-8.3 | 0.61 |
| Midwall Septal LGE | 2.0 | 0.71-5.6 | 0.19 |
| GDS >0.10 | 19.4 | 6.9-42 | **0.0009** |

Harrell's C 0.79 (0.68-0.90)

EDVi, end-diastolic volume index; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; LVMi, left ventricular mass index; NSVT, nonsustained ventricular tachycardia; RV, right ventricle.

**Table 9: Univariate Cox Logistic Regression Analysis for the risk of MVA in patients with LVEF > 35%.**

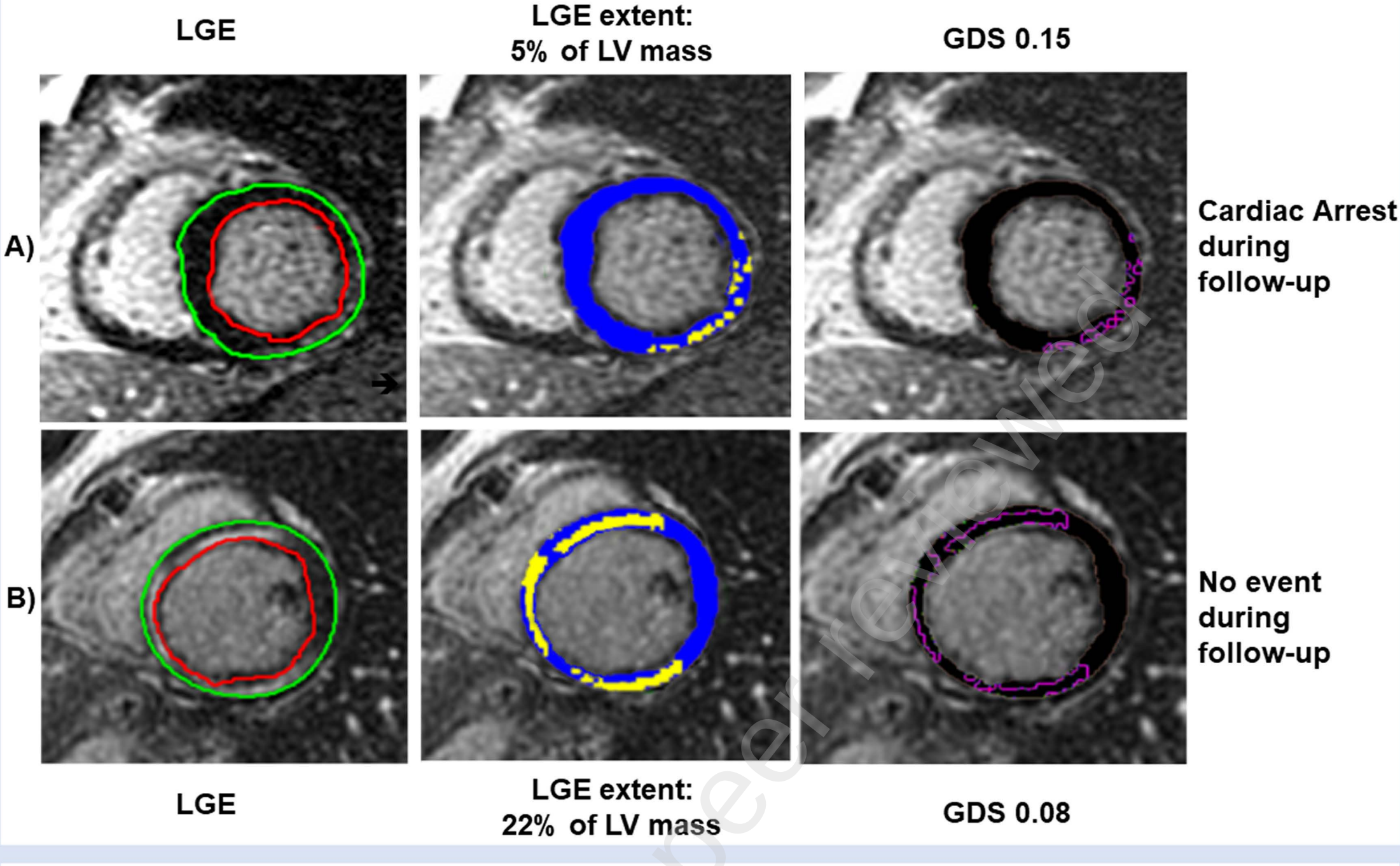
| **Variables** | ***Univariate*** | | |
|---|---|---|---|
| | HR | 95% CI | P value |
| age | 1.03 | 1.01-1.07 | **0.04** |
| Males | 1.31 | 0.5-3.2 | 0.55 |
| BSA | 4.5 | 0.6-30 | 0.12 |
| Systemic Hypertension | 2.17 | 0.88-5.3 | 0.09 |
| Hypercholesterolemia | 0.72 | 0.27-1.89 | 0.51 |
| Diabetes | 2.4 | 0.7-8.3 | 0.16 |
| Smoking | 0.51 | 0.11-2.2 | 0.37 |
| NYHA>1 | 1.47 | 0.58-3.8 | 0.41 |
| NT-pro-BNP | 0.99 | 0.98-1.02 | 0.08 |
| Troponin I | 1.07 | 0.98-1.02 | 0.23 |
| NSVT | 2.42 | 0.9-6.5 | 0.07 |
| QRS duration | 1.01 | 0.99-1.02 | 0.36 |
| LV EDVi (ml/m2) | 1.01 | 0.99-1.02 | 0.38 |
| LV EF (%) | 0.98 | 0.89-1.07 | 0.75 |
| LVMi (gr/m2) | 1.01 | 0.99-1.02 | 0.34 |
| RV EDVi (ml/m2) | 1.01 | 0.98-1.02 | 0.95 |
| RV EF (%) | 1.01 | 0.95-1.05 | 0.86 |
| LGE positive | 4.9 | 1.8-13 | **0.002** |
| Midwall Septal LGE | 4.4 | 1.8-11.1 | **0.001** |
| Subepicardial LGE | 3.6 | 1.3-10 | **0.01** |
| GDS >0.10 | 4.8 | 1.9-12 | **0.0006** |

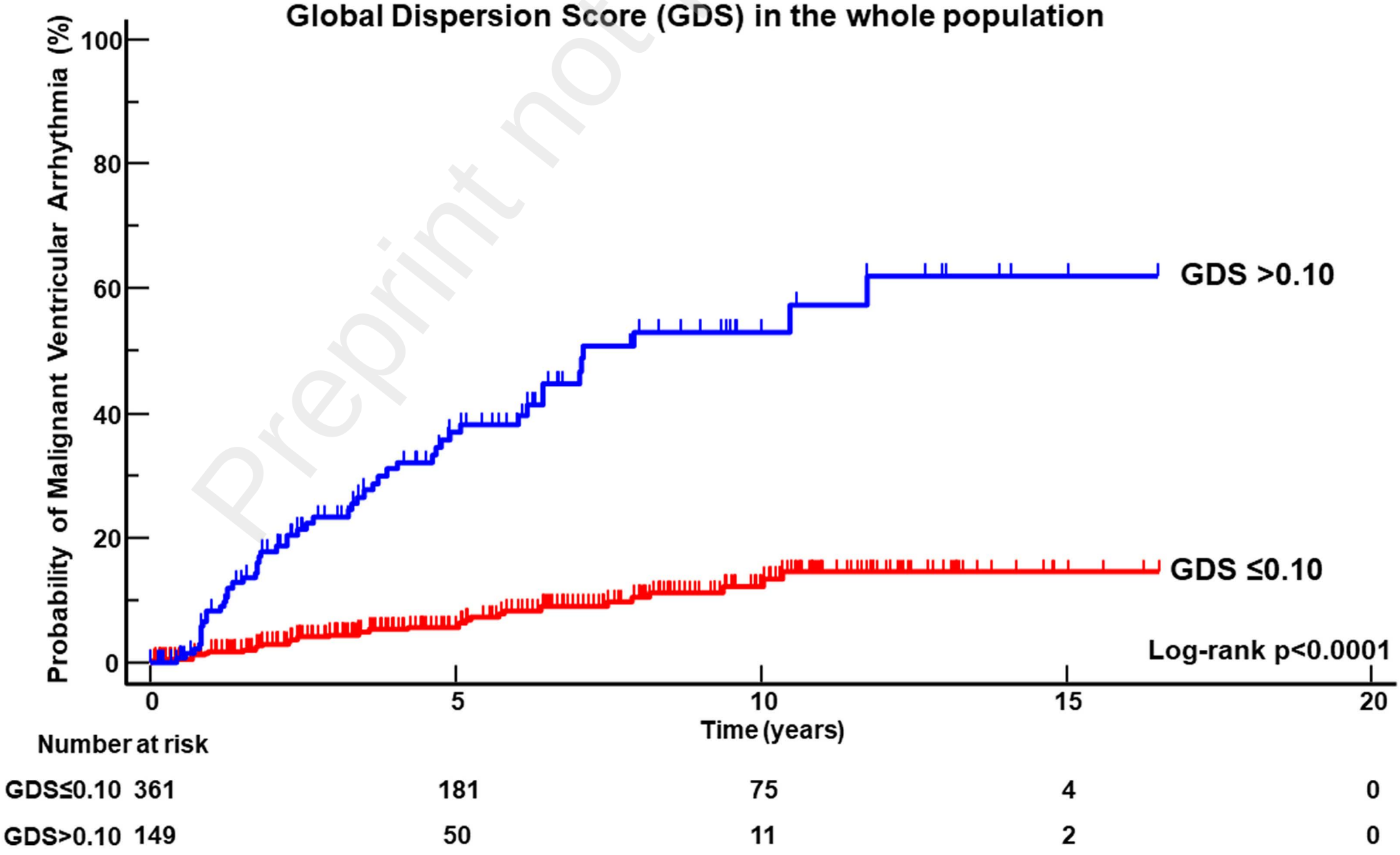
BSA, body surface area; EDVi, end-diastolic volume index; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; LVMi, left ventricular mass index; NSVT, nonsustained ventricular tachycardia; RV, right ventricle.

**Table 10: Bivariate Models of Cox Logistic Regression Analysis for the risk of MVA in patients with LVEF>35%.**

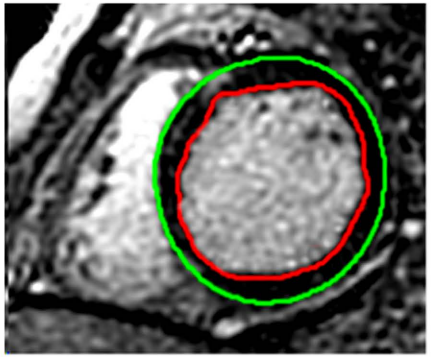
| **Variables** | **Bivariate** | | |
|---|---|---|---|
| | **Model I** | | |
| | HR | 95% CI | P value |
| age | 1.04 | 1.01-1.07 | **0.03** |
| GDS>0.1 | 5.1 | 2.07 -12.7 | **0.0004** |
| *Harrell's C 0.79 (0.69-0.88)* | | | |
| *$R^2$ 0.12* | | | |
| | **Model II** | | |
| LGE positive | 3.0 | 0.76-12 | 0.12 |
| GDS>0.1 | 2.2 | 1.1-8.2 | **0.02** |
| *Harrell's C 0.70 (0.57-0.84)* | | | |
| *$R^2$ 0.17* | | | |
| | **Model III** | | |
| Midwall Septal LGE | 2.7 | 0.95-7.6 | 0.06 |
| GDS>0.1 | 3.1 | 1.1-8.7 | **0.03** |
| *Harrell's C 0.72 (0.60-0.84)* | | | |
| *$R^2$ 0.17* | | | |
| | **Model IV** | | |
| Subepicardial LGE | 1.1 | 0.3-3.9 | 0.88 |
| GDS>0.1 | 4.6 | 1.5-14 | **0.008** |
| *Harrell's C 0.68 (0.56-0.80)* | | | |
| *$R^2$ 0.09* | | | |

510 patients with non-ischemic DCM

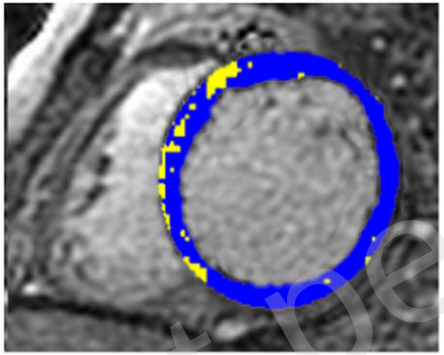


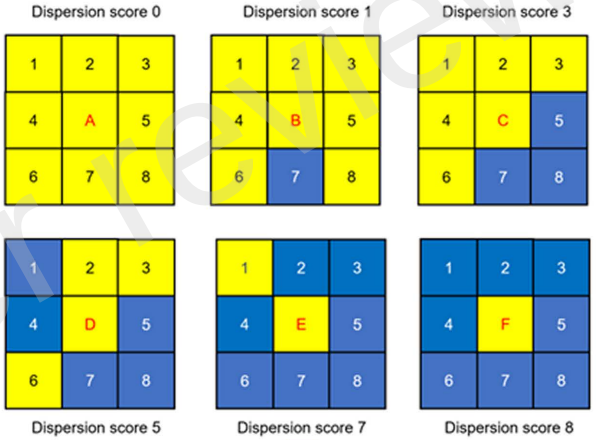
LGE images contouring

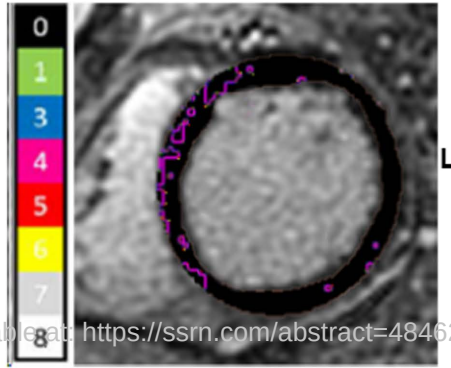


2-color parametric map
(enhancement = SI >mean+5SD)



Automatic assignment of
a Dispersion Score (1-8) for each enhanced voxel

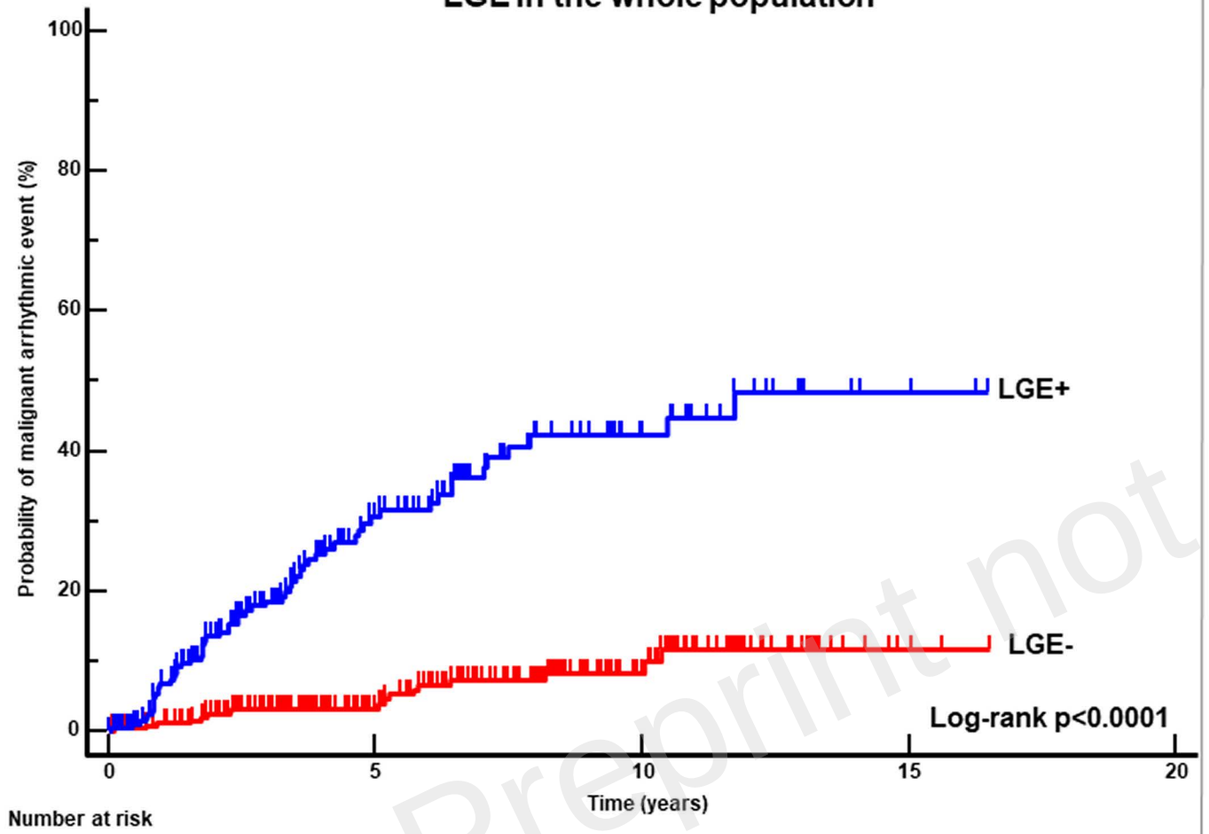



LGE-dispersion Mapping

Global Dispersion Score (GDS) = the average Dispersion Score of all the enhanced voxels

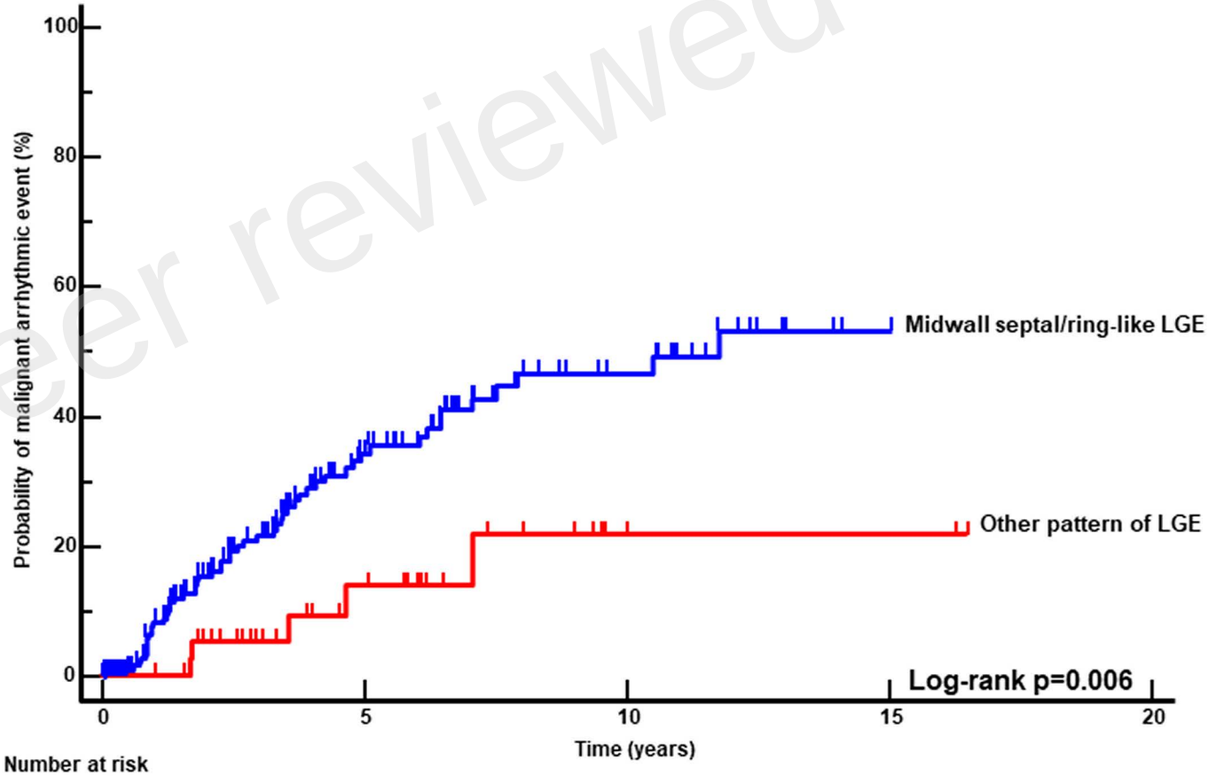
## LGE in the whole population




Number at risk

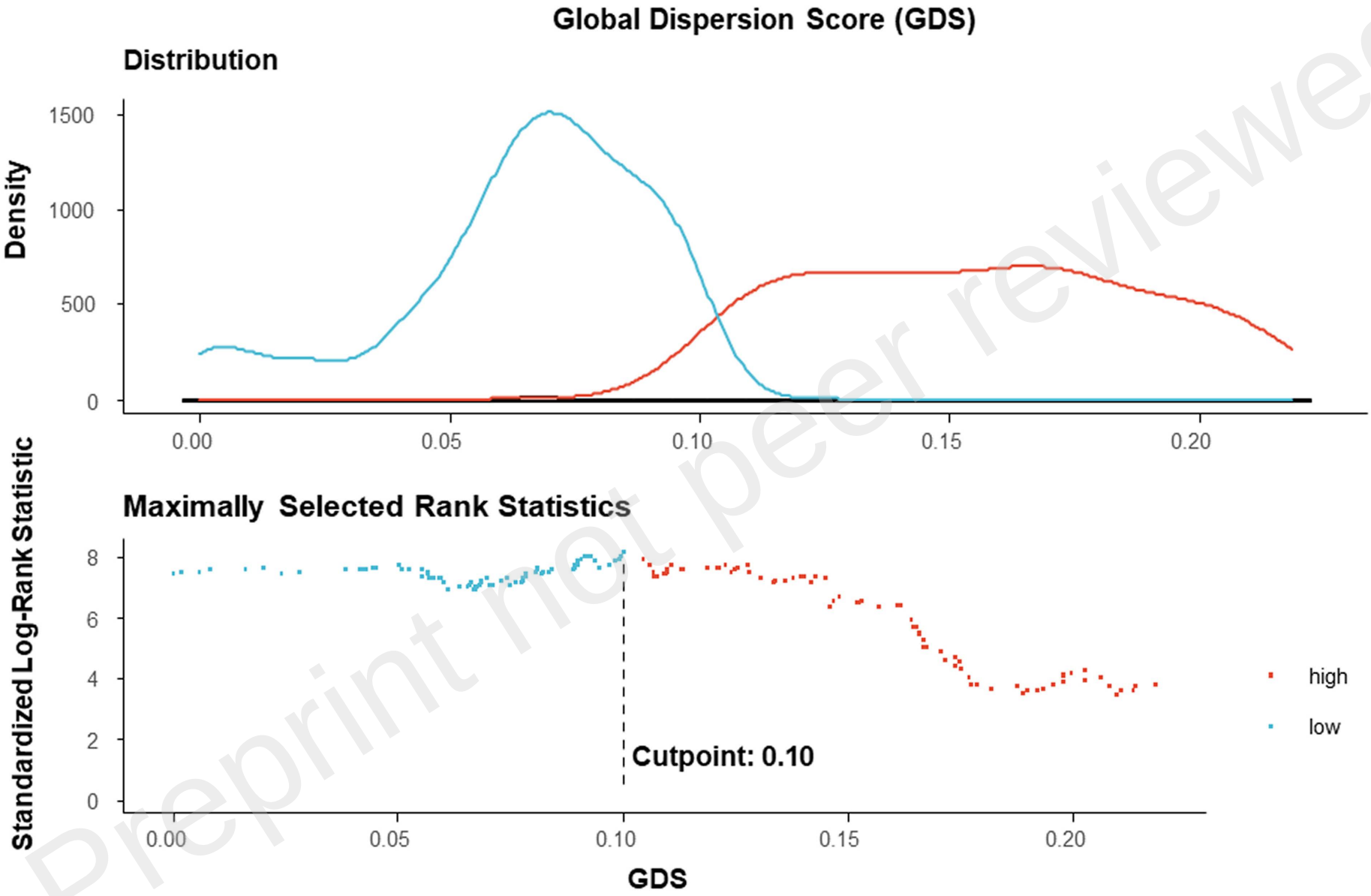
| | | | | | |
|---|---|---|---|---|---|
| LGE+ | 232 | 149 | 61 | 3 | 0 |
| LGE- | 278 | 73 | 23 | 3 | 0 |

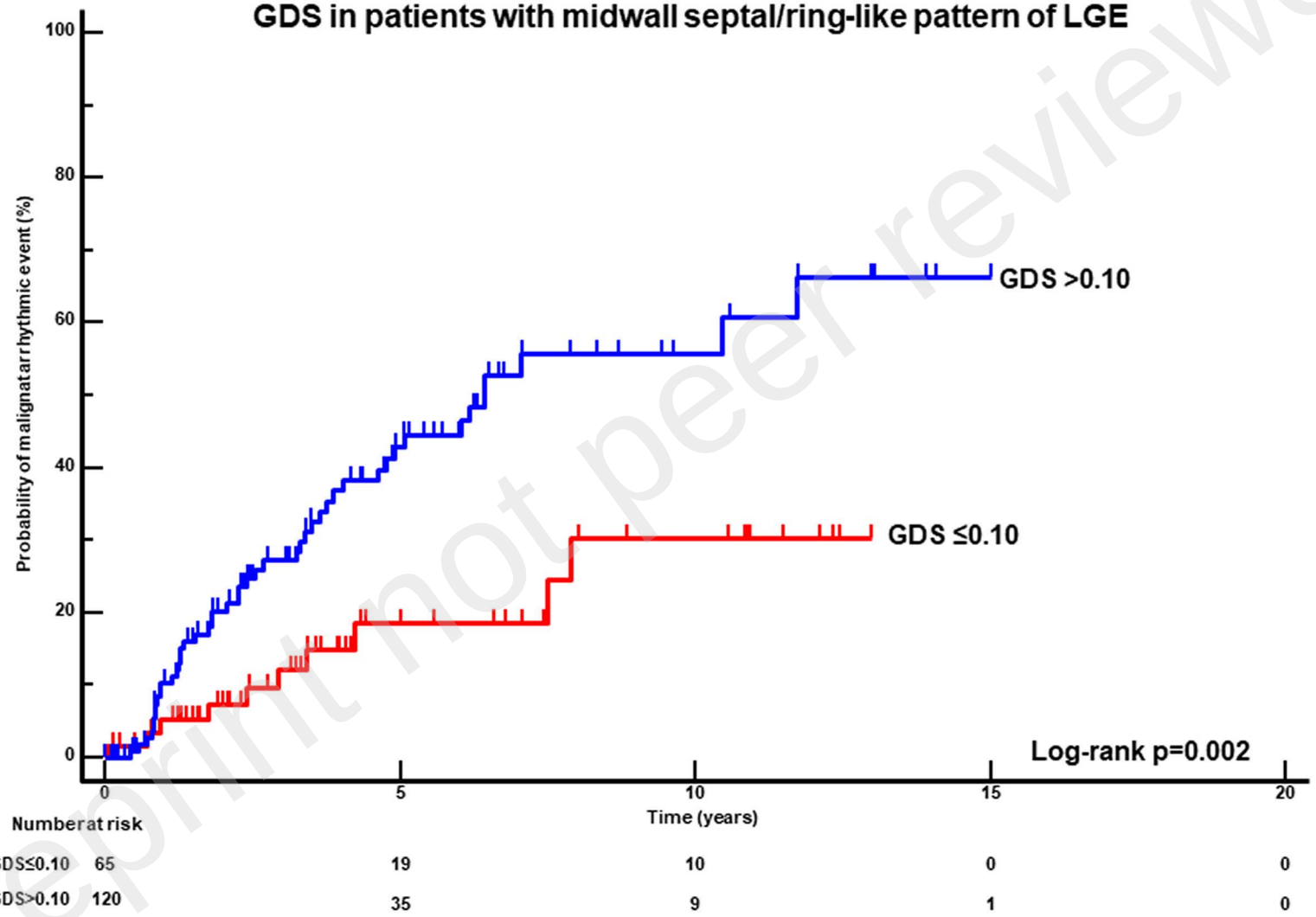
## Pattern of LGE in the whole population

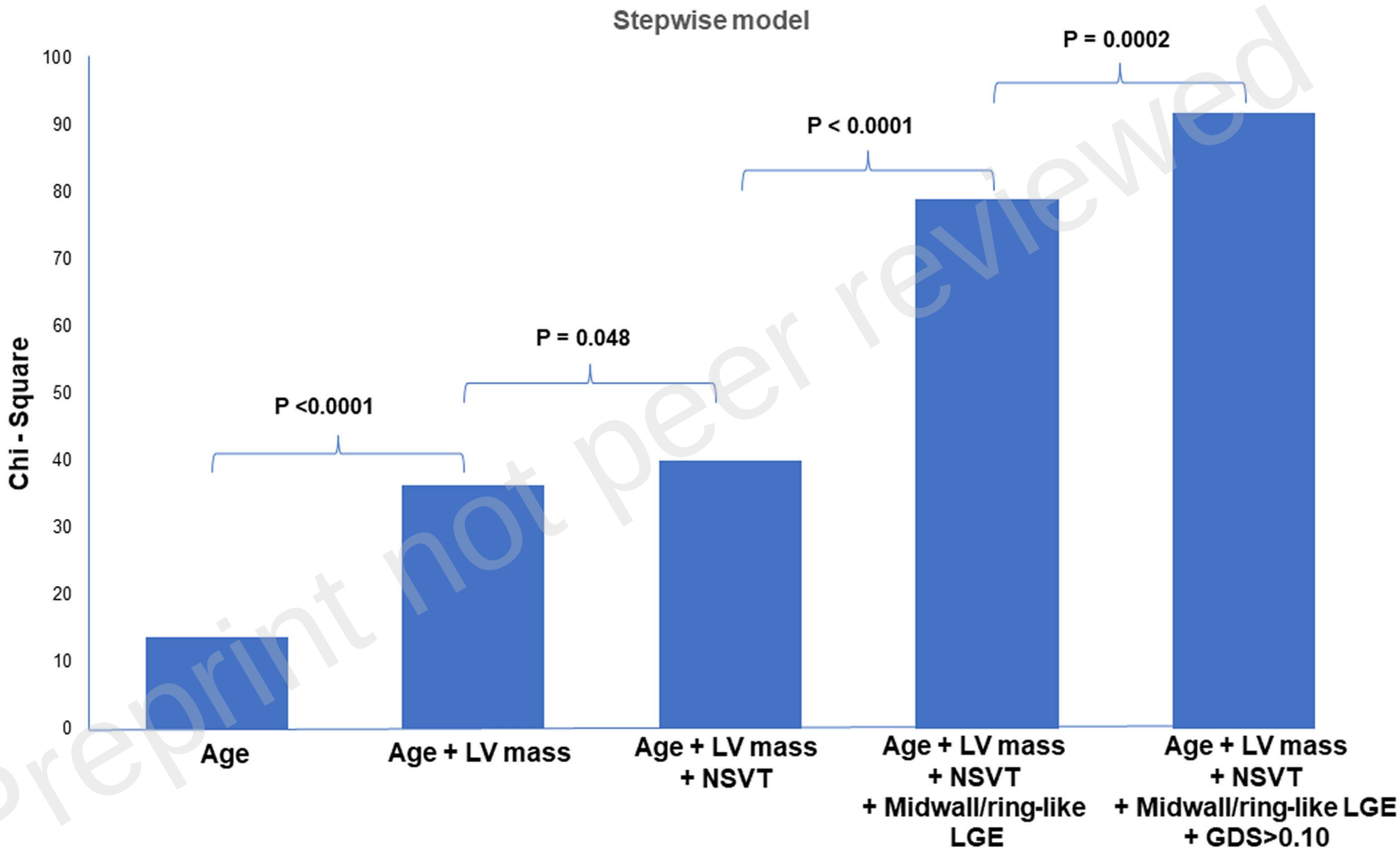



Number at risk

| | | | | | |
|---|---|---|---|---|---|
| Other pattern | 49 | 18 | 2 | 2 | 0 |
| Midwall Sep./ring | 185 | 56 | 21 | 1 | 0 |








| -2 Log Likelihood | 432 | 410 | 406 | 367 | 354 |
|---|---|---|---|---|---|