Characteristics and long-term survival of patients with left ventricular non-compaction cardiomyopathy

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Abstract

Aims   Left ventricular non-compaction cardiomyopathy (LVNC) is a poorly understood entity resulting in heart failure. Whether it is a distinct form of cardiomyopathy or an anatomical phenotype is a subject of discussion. The current diagnosis is based on morphologic findings by comparing the compacted to non-compacted myocardium. The study aimed to compare demographic and prognostic variables of patients with dilated cardiomyopathy (DCM) and LVNC. Emphasis was given to cardiac magnetic resonance (CMR) imaging analysis. Data on survival were also assessed.
Methods and results   We retrospectively evaluated the characteristics and outcomes of 262 non-ischaemic cardiomyopathy patients with LVNC and DCM phenotypes. Petersen's CMR criteria of non-compacted to the compacted myocardial ratio 2.3 were used to diagnose LVNC. The primary endpoint was a composite endpoint of major adverse cardiovascular events comprising cardiovascular-related death, left ventricular assisted device implantation, or heart transplantation. A total of 262 patients with CMR data were included in the study. One hundred fifty-five patients who fulfilled CMR criteria were diagnosed as LVNC. CMR findings revealed that LVNC patients had higher left ventricular end-diastolic (137.2 ± 51.6, 116.8 ± 44.6, $P = 0.002$) and systolic volume index (98.4 ± 49.5, 85.9 ± 42.7, $P = 0.049$). Cardiac haemodynamics, cardiac output (5.61 ± 2.03, 4.96 ± 1.83; $P = 0.010$), stroke volume (73.9 ± 28.8, 65.1 ± 25.1; $P = 0.013$), and cardiac index (2.85 ± 1.0, 2.37 ± 0.72; $P < 0.0001$), were higher in LVNC patients. Of all the 249 patients, 102 (40.9%) patients demonstrated late gadolinium enhancement (LGE). According to Petersen's criteria, the Kaplan–Meier survival outcome did not reveal significant differences (hazard ratio [HR]: 1.53, 95% confidence interval [CI]: [0.89–2.63], $P = 0.11$). The presence or pattern of LGE did not show significant importance for endpoint-free survival. Most of the sub-epicardial LGE pattern was found in LVNC patients (94.4%). When receiver operator characteristics analysis was applied to NC/C ratio to discriminate the primary endpoint, a higher NC/C ratio of 2.57 was associated with adverse events (HR: 1.90, 95% CI: [1.12–3.24], $P = 0.016$).
Conclusions   Our study questions the criteria being used for the diagnosis of LVNC. Further evaluation of CMR variables and association of these findings with demographic variables and survival is mandatory.

Introduction

Left ventricular non-compaction cardiomyopathy (LVNC) is considered primary genetic cardiomyopathy by the American

Heart Association resulting from disrupted myocardial embryogenesis,[1] and it is covered under unclassified cardiomyopathies by the European Society of Cardiology.[2] LVNC is characterized by morphological–phenotypical imaging

properties like hypertrabeculation, deep trabecular recesses, and compacted and non-compacted myocardial layers.[3]

Patients with LVNC may be asymptomatic or present with signs and symptoms of heart failure (HF), malignant arrhythmias, embolic cerebrovascular events, and decreased survival.[4] The diagnosis is made by demonstrating the presence of specific criteria based mainly upon the relative thickness of the compacted myocardial wall and the lace-like mesh of the trabeculated (non-compacted) layer of cardiac muscle using either echocardiography or cardiac magnetic resonance (CMR).[3,5–8]

Cardiac magnetic resonance enables better visualization of NC/C ratio, distribution of non-compacted areas, and cardiac fibrosis. The NC/C ratio described by Petersen *et al.* is based on the non-compacted and compacted layer thickness. A ratio > 2.3 in diastole is considered LVNC.[8] Other criteria are also suggested by other authors.[3,5–8] Hypertrabeculation of the left ventricle (LV) may also be seen in other cardiomyopathies due to increased preload or afterload remodelling. There are uncertainties whether LVNC is distinct cardiomyopathy or mainly due to pathophysiological phenotypical expression of different cardiomyopathies.[9] However, no gold standard criteria for diagnosing and prognosis differentiate this population from dilated cardiomyopathy (DCM) patients. The clinical significance of LVNC is unknown.[10]

In this study, we studied 262 consecutive LVNC and DCM patients and evaluated the demographic and prognostic variables associated with survival. The diagnosis of LVNC was made with CMR. We also sought whether the presence of the non-compaction phenotype and the degree of LVNC myocardium assessed by CMR influenced the prognosis of these patients.

Methods

The Ege University institutional review board approved the study, and informed consent has been taken from the subjects or first-degree relatives. HF patients with non-ischaemic aetiology admitted to the outpatient clinic and who had CMR for the diagnosis between January 2008 and December 2020 were included in this study. The clinical, echocardiographic, and CMR data of these patients were assessed retrospectively in a single centre. Clinical data were collected from the university's medical records. Patient's follow-up data were obtained from the university patient database, national health database, and, if necessary, telephone interviews with the patient or first-degree relatives.

Patients with HF attributable to ischaemic aetiology, valvular heart disease or unacceptable unloading conditions, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and paediatric patients were excluded. Ischaemic aetiology was proved by coronary angiography, coronary computed tomography, positive myocardial perfusion scintigraphy for ischaemia, or CMR with transmural late gadolinium enhancement (LGE). Stenosis of proximal left anterior descending coronary artery over 50% or two coronary segments with stenosis over 50% were agreed to have the possibility of ischaemic HF aetiology and excluded from the study[11] (*Figure 1*).

Cardiac magnetic resonance imaging assessment

Cardiac magnetic resonance was performed with 1.5 or 3.0 tesla unit scanners (Amira 1.5 Tesla and Verio 3 Tesla, Siemens Healthineers, Erlangen, Germany). Patients were scanned with the electrocardiogram, triggering a 16-channel surface phased array of body coils. CMR images with appropriate image quality were re-evaluated by two radiologists.
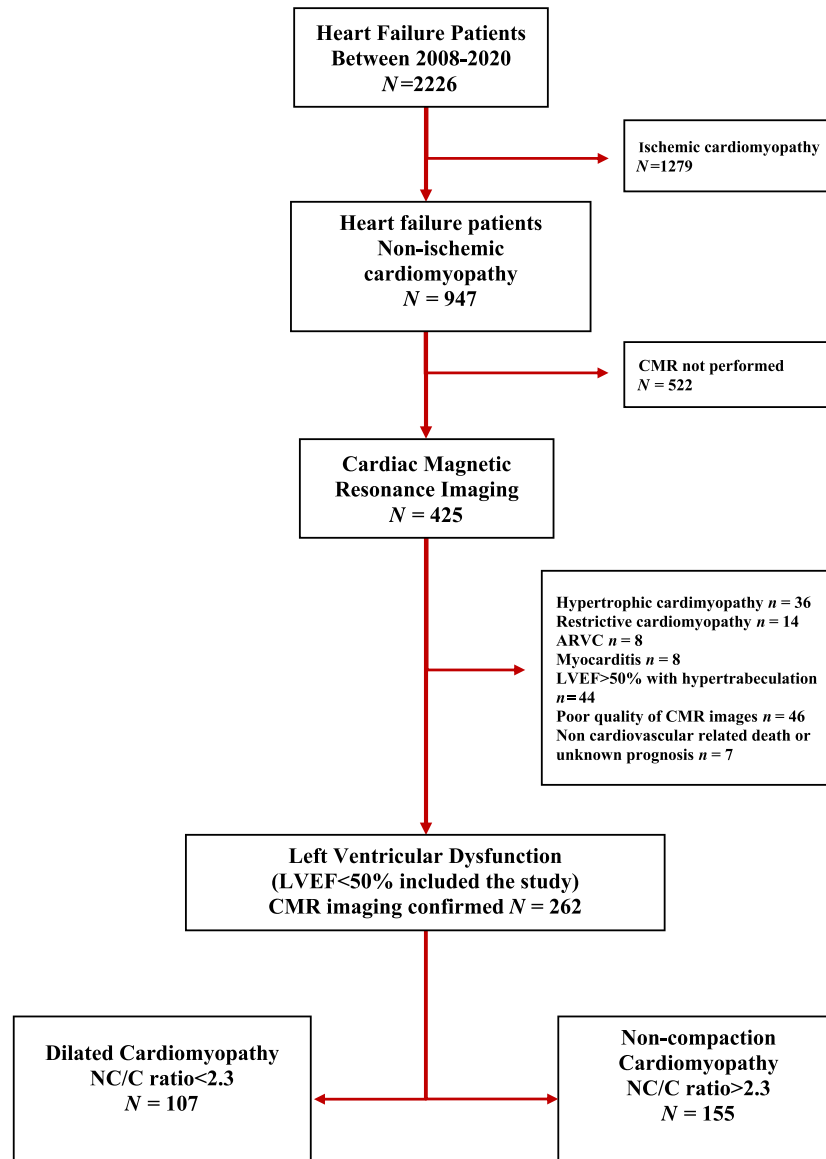
Briefly, 10 to 12 consecutive short-axis images covering the entire LV and 2-, 3-, and 4-chamber long-axis images were acquired with a cine steady-state free precession sequence to assess myocardial function and mass and quantification of non-compaction. Ten to fifteen minutes after injection of 0.2 mmol/kg gadolinium contrast agent, two-dimensional LGE images were acquired in short-axis, two-chamber, and four-chamber views by phase-sensitive inversion recovery sequence (PSIR). Cardiac volume, function, and mass on cardiac images were analysed with software: Medis medical imaging systems-Medis Suite 3.1 (Leiden, Netherlands) by three radiologists for disagreements on data between two readers. A consensus agreement was achieved with the third expert opinion.

The ratio was determined by non-compacted and compacted myocardial ratio calculated distal to the papillary muscle at any segment revealing the highest proportion except the LV apex. As Petersen's criteria, an NC/C myocardial ratio > 2.3 with at least three hypertrabeculations met the LVNC criteria, and NC/C measurements were measured in long-axis views. LGE distribution was reviewed in long-axis and short-axis contrast-enhanced images, and LGE presence was accepted in short-axis and long-axis imaging planes. LGE distributions are visually classified as sub-endocardial, mid-myocardial (mid-wall), sub-epicardial, and right ventricular insertion involvement. Two radiologists determined the LGE distribution pattern. A third senior radiologist was consulted when there was disagreement.

All index patients were assessed with qualified CMR for better visualization of hypertrabeculation measurements, CMR functional analysis, and fibrosis with LGE. LV systolic dysfunction was defined as left ventricular ejection fraction (LVEF) lower than 50% measured with CMR. The patients were classified as LVNC when the non-compacted/compacted myocardial ratio was >2.3.

The data of 425 patients with CMR images were reviewed. Patients with an NC/C ratio > 2.3 were classified as LVNC,

Figure 1 Flow chart of study patients/Consort diagram. ARVC, arrhythmogenic right ventricular cardiomyopathy; C, compacted myocardium; CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction; NC, non-compacted myocardium; NC/C ratio, ratio of the non-compacted segment to compacted segment of the myocardium.

Endpoints

The endpoints were defined as primary and secondary. The primary endpoint of our study was a composite endpoint of major adverse cardiovascular events (MACE) comprising cardiovascular-related death, left ventricular assisted device (LVAD) implantation, or heart transplantation. Cardiovascular-related death was defined as HF-related death or sudden cardiac death. Patients who died due to non-cardiovascular causes or unknown aetiology were excluded from the study. The secondary endpoints were ventricular arrhythmia or appropriate implanted cardioverter-defibrillator (ICD) shocks, HF-related hospitalization, and cerebrovascular events.

and patients with an NC/C ratio lower than 2.3 were considered DCM. A total of 262 patients were included in the study.

Statistical analysis

Statistical analysis was performed using Medcalc 19.0® statistical program and SPSS 25.0 software (IBM SPSS Statistics,

IBM Corporation, Armonk, New York). Distribution normality was tested by the Shapiro–Wilk tests. Continuous variables are calculated as mean, SD, or median (interquartile range [IQR]), and categorical variables as counts and percentages. Comparisons between groups were performed with a two-sided Student's *t*-test, the Wilcoxon–Mann–Whitney *U* test, and χ^2 or Fisher's exact test for categorical variables.

One-way ANOVA test used analysis comparison of continuous variables groups over two and compared each group by post hoc analysis Bonferroni's or Tukey–Kramer's tests. Values of $P < 0.05$ were accepted to be statistically significant.

The cut-off value used to define the groups was NC/C ratio 2.3 (as proposed by Petersen *et al*.). The index date was the date of the CMR. The follow-up duration is estimated using the index date to the first event or last follow-up.

Receiver operator characteristics (ROC) curve analysis was used to calculate discrimination of cardiomyopathies prognostic differences compared with NC/C ratio.

Survival curves were compared with the log-rank (Mantel–Cox) test for all defined endpoints. Hazard ratios (HRs) were calculated with Cox regression hazard models expressed as means and between 95% confidence intervals (CIs) for all cardiomyopathy patients. A comparison was made using Petersen's criteria and a redefined NC/C ratio. Different multivariate models were designed for all cardiomyopathy patients and cardiomyopathy groups. To avoid overfitting and collinearity issues, significant, non-related variables were selected for multivariate analysis. Selected univariate predictors of primary endpoints are proposed for inclusion in multivariate forward and backward stepwise Cox regression models.

Intraobserver and interobserver agreement for non-compaction measurement was tested according to the Bland–Altman method and stated as bias standard deviation (95% CI) and intraclass correlation coefficient (ICC).

Results

Baseline demographics

Two hundred sixty-two patients were enrolled in the study. The patient population's clinical, echocardiographic, and CMR results are presented in *Tables 1–3*, respectively. A total of 64.1% of all patients were male, and the mean age was 42.8 ± 14 years.

As presented in the tables, hypertension was present in 20.9% of the patients, smoking history in 31.5%, and diabetes mellitus in 17.1%. Atrial fibrillation or flutter was present in 13.6%, and 5.4% had a prior stroke or transient ischaemic attack history. ICD was implanted in 23.2% of patients. DCM patients were older than LVNC patients (45.2 ± 14.3 and 41.2 ± 13.7, *P* = 0.026, respectively).

Table 1 Clinical characteristics of patients and comparison according to NC/C ratios

	Total	NC/C ratio < 2.3	NC/C ratio > 2.3	*P* value	NC/C ratio < 2.57	NC/C ratio > 2.57	*P* value
Age, years	42.8 ± 14	45.2 ± 14.3	41.2 ± 13.7	0.026	44.8 ± 14.1	40.9 ± 13.8	0.017
Male, %	168 (64.1%)	74 (69.1%)	94 (60.6%)	0.19	86 (68.3%)	82 (60.3%)	0.19
BMI, kg/m^2	29.7 ± 6.4	30.6 ± 6.7	29.1 ± 6.1	0.066	30.6 ± 6.4	28.9 ± 6.3	0.037
BSA, m^2	2.0 ± 0.26	2.04 ± 0.28	1.97 ± 0.24	0.037	2.04 ± 0.28	1.96 ± 0.24	0.014
Smoker, *n* (%)	80 (31.5%)	39 (37.9%)	41 (27.2%)	0.075	45 (36.9%)	35 (26.5%)	0.080
Arterial hypertension, *n* (%)	54 (20.9%)	19 (17.9%)	35 (23%)	0.32	21 (16.8%)	33 (24.8%)	0.12
Diabetes mellitus, *n* (%)	44 (17.1%)	17 (16%)	27 (17.8%)	0.74	23 (18.4%)	21 (15.8%)	0.62
Dyslipidaemia, *n* (%)	18 (7.0%)	10 (9.4%)	8 (5.3%)	0.22	10 (8.0%)	8 (6.0%)	0.62
Stroke, *n* (%)	14 (5.3%)	7 (6.6%)	7 (4.6%)	0.58	9 (7.2%)	5 (3.8%)	0.27
COPD, *n* (%)	24 (9.3%)	10 (9.4%)	14 (9.2%)	0.95	11 (9%)	13 (9.9%)	0.80
Renal disease, *n* (%)	7 (2.7%)	2 (1.9%)	5 (3.3%)	0.70	2 (1.6%)	5 (3.8%)	0.29
AF, *n* (%)	33 (12.6%)	19 (18.6%)	14 (10%)	0.060	23 (19.3%)	10 (8.1%)	0.014
Heart rate, beat/min	78 ± 15	79 ± 16	77 ± 15	0.56	78. ± 15	78 ± 15	0.88
Family history of heart failure, *n* (%)	30 (11.5%)	8 (7.5%)	22 (14.2%)	0.11	9 (7.1%)	21 (15.4%)	0.037
ACEi or ARB, *n* (%)	196 (76.3%)	85 (81%)	111 (73%)	0.17	96 (77.4%)	100 (75.2%)	0.76
Beta-blocker, *n* (%)	230 (89.1%)	98 (92.5%)	132 (86.8%)	0.22	113 (90.4%)	117 (88.0%)	0.5
Aldosterone antagonist, *n* (%)	171 (65.3%)	73 (68.3)	98 (63.2%)	0.43	84 (66.7%)	87 (64.0%)	0.69
Loop diuretic, *n* (%)	147 (56.1%)	64 (59.0%)	83 (53.5%)	0.37	74 (58.7%)	73 (53.7%)	0.45
Anticoagulant, *n* (%)	48 (18.3%)	25 (23.4%)	23 (14.8%)	0.10	29 (23.0%)	19 (14.0%)	0.078
Antiplatelet, *n* (%)	83 (31.7%)	29 (27.1%)	54 (34.8%)	0.22	34 (27.0%)	49 (36.0%)	0.14
If channel blocker, *n* (%)	44 (16.8%)	17 (15.9%)	17 (17.4%)	0.86	18 (14.3%)	26 (19.1%)	0.32
ICD, *n* (%)	60 (23.2%)	25 (23.6%)	35 (22.9%)	1.0	27 (21.6%)	33 (24.6%)	0.65

ACEi, angiotensinogen-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; ICD, implanted cardioverter-defibrillator.
Values are mean ± SD or *n* (%), *P* value < 0.05. Comparison of the patients according to non-compacted/compacted myocardial segment ratio. Firstly patients compared with Petersen's criteria. NC/C ratio 2.3 and redefined NC/C ratio 2.57.

Table 2 Echocardiographic parameters and comparison according to NC/C ratios

	Total	NC/C ratio < 2.3	NC/C ratio > 2.3	P value	NC/C ratio < 2.57	NC/C ratio > 2.57	P value
LVEDd, mm	61.4 ± 9.3	60.7 ± 9.3	61.9 ± 9.2	0.36	60.1 ± 9.3	62.6 ± 9.1	0.045
LVESd, mm	50.6 ± 11.7	49.8 ± 11.7	51.2 ± 11.8	0.37	49.3 ± 11.6	52 ± 11.7	0.08
LAd, mm	43.5 ± 7.0	43.1 ± 6.1	43.8 ± 7.5	0.42	43 ± 6.7	44.1 ± 7.2	0.23
LVEF, %	31.1 ± 11.3	31.7 ± 11.1	30.6 ± 11.4	0.45	32.5 ± 11.2	29.7 ± 11.2	0.06
Moderate or severe mitral regurgitation, n (%)	94 (39.5%)	36 (35.6%)	58 (42.3%)	0.20	40 (34.2%)	54 (44.6%)	0.13
Moderate or severe aortic regurgitation, n (%)	10 (4.2%)	3 (2.9%)	7 (5.1%)	0.66	3 (2.6%)	7 (5.8%)	0.43
Moderate or severe tricuspid regurgitation, n (%)	49 (20.6%)	17 (16.8%)	32 (23.3%)	0.46	21 (17.9%)	28 (23.1%)	0.51
TAPSE, mm	18.3 ± 4.9	17.8 ± 4.9	18.6 ± 4.9	0.28	17.9 ± 4.9	18.6 ± 4.9	0.35
TAPSE < 16 mm (RV dysfunction)	59 (29.1%)	30 (34.1%)	29 (25.3%)	0.21	34 (33.7%)	25 (24.5%)	0.16
RVsm (TDI), m/s	11.1 ± 3.69	11.3 ± 4.4	10.9 ± 2.99	0.46	11.2 ± 4.23	10.9 ± 3.0	0.46

LAd, left atrial diameter; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular systolic ejection fraction; LVESd, left ventricular end-systolic diameter; RVsm, right ventricular systolic motion tissue Doppler imaging; TAPSE, tricuspid annular plane systolic excursion.
Values are mean ± SD or n (%), P value < 0.05. Comparison of the patients according to non-compacted/compacted myocardial segment ratio. Firstly patients compared with Petersen's criteria. NC/C ratio 2.3 and redefined NC/C ratio 2.57.

Table 3 Cardiac magnetic resonance imaging parameters and comparison according to NC/C ratios

	Total	NC/C ratio < 2.3	NC/C ratio > 2.3	P value	NC/C ratio < 2.57	NC/C ratio > 2.57	P value
C length, mm	5.3 ± 1.5	6.48 ± 1.62	4.59 ± 0.88	—	6.26 ± 1.62	4.55 ± 0.90	—
NC length, mm	12.2 ± 3.3	9.59 ± 2.13	14.0 ± 2.67	—	9.92 ± 2.21	14.34 ± 2.67	—
NC/C ratio	2.47 ± 0.94	1.53 ± 0.35	3.12 ± 0.65	—	1.67 ± 0.46	3.21 ± 0.61	—
Average wall thickness, mm	9.4 ± 2.0	9.7 ± 1.8	9.13 ± 2.1	0.19	9.7 ± 1.9	9.0 ± 2.1	0.019
Presence RV trabeculations, n (%)	74 (28.7%)	16 (15.2%)	58 (37.9%)	<0.0001	18 (14.9%)	53 (40.2%)	<0.0001
LVEDd, mm	63.2 ± 10.5	62.7 ± 10.0	63.6 ± 10.9	0.49	62.3 ± 9.8	64.1 ± 11.1	0.17
LVESd, mm	54.1 ± 12.3	53.7 ± 11.3	54.4 ± 12.9	0.64	53.1 ± 11.3	55.0 ± 13.1	0.24
LAd, mm	47.6 ± 9.3	46.4 ± 8.5	48.5 ± 9.8	0.064	46.6 ± 8.6	48.6 ± 9.9	0.14
LVEDV(i), mL/m^2	128.7 ± 49.8	116.8 ± 44.6	137.2 ± 51.6	0.002	116.2 ± 43.7	140.5 ± 53.2	<0.0001
LVESV(i), mL/m^2	93.2 ± 47.1	85.9 ± 42.7	98.4 ± 49.5	0.049	84.1 ± 42.0	101.8 ± 50.0	0.005
LV mass(i), g/m^2	78.8 ± 25.6	79.5 ± 23.6	78.2 ± 27	0.71	77.9 ± 23.2	79.7 ± 27.7	0.66
LVEF, %	29.5 ± 11.3	28.6 ± 10.3	30.1 ± 12.0	0.26	29.8 ± 10.7	29.2 ± 11.9	0.87
Cardiac output, L/min	5.34 ± 1.98	4.96 ± 1.83	5.61 ± 2.03	0.010	5.07 ± 1.76	5.60 ± 2.15	0.033
Stroke volume, mL	70.3 ± 27.7	65.1 ± 25.1	73.9 ± 28.8	0.013	66.8 ± 24.8	73.5 ± 30.0	0.053
Cardiac index, L/min/m^2	2.64 ± 0.92	2.37 ± 0.72	2.85 ± 1.0	<0.0001	2.44 ± 0.74	2.84 ± 1.03	0.001
PET, ms	167.6 ± 67.4	161.3 ± 34.7	173 ± 86.2	0.25	166.7 ± 61.8	168.6 ± 74.0	0.84
PFT, ms	516.1 ± 154.5	535.9 ± 168.3	498.9 ± 140.2	0.14	535.3 ± 164.3	492.9 ± 139.5	0.12
LGE distribution, n (%) = 102 (40.9%)							
Sub-endocardial LGE, n (%)	21 (8.4%)	8 (7.8%)	13 (8.9%)	<0.0001	8 (6.7%)	13 (10.1%)	<0.0001
Mid-wall LGE, n (%)	31 (12.4%)	24 (23.3%)	7 (4.8%)		26 (21.7%)	5 (3.9%)	
Sub-epicardial LGE, n (%)	19 (7.6%)	1 (1.0%)	18 (12.3%)		3 (2.5%)	16 (12.4%)	
Focal insertion LGE, n (%)	31 (12.4%)	16 (15.5%)	15 (10.3%)		18 (15.0%)	13 (10.1%)	

C, compacted myocardium; LAd, left atrial diameter; LGE, late gadolinium enhancement; LV mass(i), left ventricular mass index; LVEDd, left ventricular end-diastolic diameter; LVEDV(i), left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; LVESV(i), left ventricular end-systolic volume index; NC, non-compacted myocardium; NC/C ratio, ratio of the non-compacted segment to compacted segment of the myocardium; PET, peak ejection time; PFT, peak filling time.
Values are mean ± SD or n (%), P value < 0.05. Comparison of the patients according to non-compacted/compacted myocardial segment ratio. Firstly patients compared with Petersen's criteria. NC/C ratio 2.3 and redefined NC/C ratio 2.57.

Cardiac magnetic resonance imaging characteristics

Intraobserver and interobserver variability for measuring NC/C ratio was 0.055 (95% CI: −0.06 to 0.17) and −0.016 (95% CI: −0.083 to 0.050), with ICCs of 0.98 (95% CI: 0.98–0.99) and 0.80 (95% CI: 0.76–0.84), respectively (Supporting Information, *Figures S21* and *S22*).

All patients' mean NC/C ratio and LVEF were 2.47 ± 0.94 and 29.5 ± 11.3%, respectively. LVNC and DCM patients' NC/C ratios were 3.12 ± 0.65 and 1.53 ± 0.35, respectively. Neither LVEF nor left ventricular mass index (LV mass(i)) revealed statistical significance. CMR characteristics revealed that LVNC patients had higher LV end-diastolic (137.2 ± 51.6, 116.8 ± 44.6, *P* = 0.002) and systolic volume index (98.4 ± 49.5, 85.9 ± 42.7, *P* = 0.049) than DCM patients. However, associated cardiac haemodynamic variables like cardiac output, stroke volume, and cardiac index were higher in LVNC patients (*Table 3*).

Cardiac magnetic resonance late gadolinium enhancement distribution

A total of 249 of the 262 patient's CMR images were convenient for the LGE analysis. Of all the 249 patients, 102 (40.9%) patients demonstrated any pattern of LGE. The mean age of patients with LGE was 45.1 ± 13, and, by a majority, 75 (73.5%) were men (Supporting Information, *Table S17*).

Late gadolinium enhancement distribution was classified as sub-endocardial in 21 (20.6%) patients, mid-wall in 31 (30.4%) patients, sub-epicardial in 19 (18.6%) patients, and focal insertion in 31 (30.4%) patients. Mid-wall LGE pattern was primarily seen in the DCM patients, 21 (77%), and mid-wall LGE had an estimated HR of 0.88 (95% CI: [0.34–2.24]) compared with non-LGE patients. In contrast to mid-wall LGE distribution, a sub-epicardial LGE pattern was the main finding in 17 (94.4%) LVNC patients. Estimated and adjusted HR for patients with sub-epicardial LGE was 1.69 (95% CI: [0.60–4.80]) compared with non-LGE patients (Graphical Abstract B).

Twelve (11.8%) LGE detected patients experienced death, 1 (1%) patient underwent heart transplantation, and 11 (6.9%) patients had LVAD implantation (Supporting Information, *Table S20*).

There was no difference in the primary endpoint rate regarding LGE-positive and LGE-negative patients (log-rank test *P* = 0.31, HR: 1.34, 95% CI: [0.76–2.36]) (*Figure 2*).

In the univariate analysis, the presence of any LGE was not associated with an increase in the rate of primary endpoint occurrence. Secondary endpoint analysis revealed that the hospitalization rate was higher in the LGE-positive patients. The presence of any pattern of LGE did not impact event-free survival (Supporting Information, *Table S7*).

Survival analysis

The median survival time was 936 [IQR: 422–1827] days. The primary endpoint occurred in 55 (21%) patients and 29 (11.1%) deaths due to cardiovascular aetiology. Six (2.3%) patients underwent heart transplantation, and 20 (7.6%) patients experienced LVAD implantation surgery. Fourteen (5.3%) patients were hospitalized due to acute HF, 4 (1.5%)

Figure 2 MACE-free survival according to cardiac magnetic resonance imaging late gadolinium enhancement. The Kaplan–Meier survival analysis estimates free of major cardiovascular events in the groups of patients' left ventricular cardiac magnetic resonance imaging according to late gadolinium enhancement. CI, confidence interval; CMRI, cardiac magnetic resonance imaging; HR, hazard ratio; LGE, late gadolinium enhancement; LVAD, left ventricular assisted device; MACE, major adverse cardiovascular events.
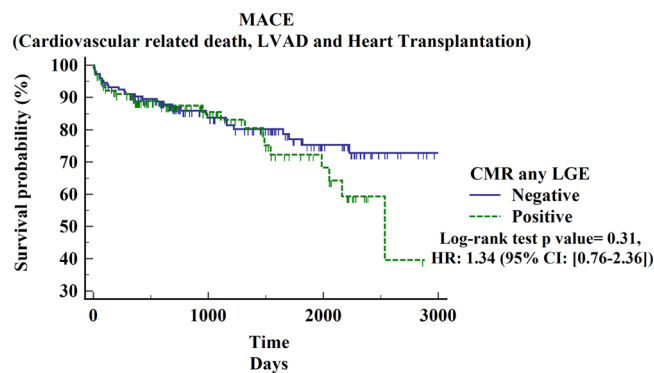
Table 4 Endpoints and comparison according to NC/C ratios

	Total	NC/C ratio < 2.3	NC/C ratio > 2.3	P value	NC/C ratio < 2.57	NC/C ratio > 2.57	P value
Death, n (%)	29 (11.1%)	11 (10.3%)	18 (11.6%)	0.84	12 (9.8%)	17 (12.5%)	0.55
LVAD, n (%)	20 (7.6%)	6 (5.6%)	14 (9.0%)	0.35	6 (4.8%)	14 (10.3%)	0.1
Heart transplantation, n (%)	6 (2.3%)	0	6 (3.9%)	0.08	0	6 (4.5%)	0.03
Hospitalization, n (%)	14 (5.3%)	6 (5.6%)	8 (5.2%)	1.0	7 (5.6%)	7 (5.1%)	1.0
Ventricular arrhythmia, n (%)	10 (3.8%)	4 (3.7%)	6 (3.9%)	1.0	5 (4.0%)	5 (3.7%)	1.0
Cerebrovascular event, n (%)	4 (1.5%)	2 (1.9%)	2 (1.3%)	1.0	3 (2.4%)	1 (0.7%)	0.35
Primary endpoint, n (%)	55 (21%)	17 (15.9%)	38 (24.5%)	0.12	18 (14.3%)	37 (27.2%)	0.015
Follow-up time, days (median–IQRs)	936 (422–1827)	933 (449–1667)	940 (430–1976)	0.95	946 (477–1687)	888 (397–1984)	0.60

IQRs, interquartile ranges; LVAD, left ventricular assisted device.
Values are mean ± SD or n (%), P value < 0.05. Comparison of the patients according to non-compacted/compacted myocardial segment ratio. Firstly patients compared with Petersen's criteria. NC/C ratio criterion 2.3 and redefined NC/C criterion ratio 2.57.

patients experienced ischaemic cerebrovascular events, and 10 (3.8%) patients experienced ventricular arrhythmias or appropriate ICD shocks (*Table 4*).

According to Petersen's CMR LVNC criteria, the Kaplan–Meier survival outcome did not reveal significant differences (log-rank test *P* value = 0.11, HR: 1.53, 95% CI: [0.89–2.63]) (*Figure 3*). Likewise, there were no differences between LVNC and DCM patients for the secondary endpoints.

Receiver operator characteristics analysis

We applied the ROC analysis NC/C ratio to discriminate the primary endpoint of challenging events like cardiovascular-related death, heart transplantation, and LVAD implantation. A higher NC/C ratio of 2.57 was associated with these adverse events. ROC analysis results showed that this higher ratio's sensitivity, specificity, and area under the curve were 67.7%, 52.6%, and 0.600, respectively (*P* value = 0.023)

(Graphical Abstract A). Data was reassessed according to this new NC/C ratio of 2.57. The patients were reclassified; 19 patients who had been included under LVNC were included in the DCM group.

Patients with an NC/C ratio over 2.57 had a higher family history of cardiomyopathy, and atrial fibrillation was more common in patients with a ratio lower than 2.57 (*Tables 1* and *2*). Patients with an NC/C ratio of over 2.57 had higher LV end-diastolic, end-systolic higher volumes, higher cardiac output, and cardiac index. More patients with NC/C ratio over 2.57 reached the primary endpoint, and this was also statistically significant (log-rank *P* value = 0.016, HR: 1.90, 95% CI: [1.22–3.24]) (*Figure 4*).

Cox univariate predictors were assessed for all cardiomyopathy patients with an NC/C ratio of 2.3 and an NC/C ratio of 2.57. Cox univariate predictors listed as baseline characteristics, echocardiography parameters, and CMR imaging parameters. For all cardiomyopathy patients by multivariate analysis, family history, lower tricuspid annular plane systolic

Figure 3 Kaplan Meier survival analysis estimates free of major cardiovascular events in the groups of patients with left ventricular non-compaction cardiomyopathy and dilated cardiomyopathy discriminated according to Petersen et al. CMR criteria. CI, confidence interval; HR, hazard ratio; LVAD, left ventricular assisted device; MACE, major adverse cardiovascular events.
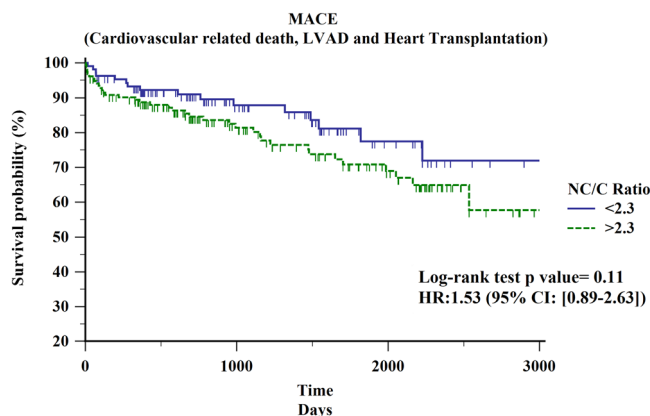
Figure 4 Kaplan Meier survival analysis estimates free of major cardiovascular events in the groups of patients with left ventricular non-compaction cardiomyopathy and dilated cardiomyopathy discriminated according to re-define NC/C ratio 2.57 CMR criteria. CI, confidence interval; HR, hazard ratio; LVAD, left ventricular assisted device; MACE, major adverse cardiovascular events.
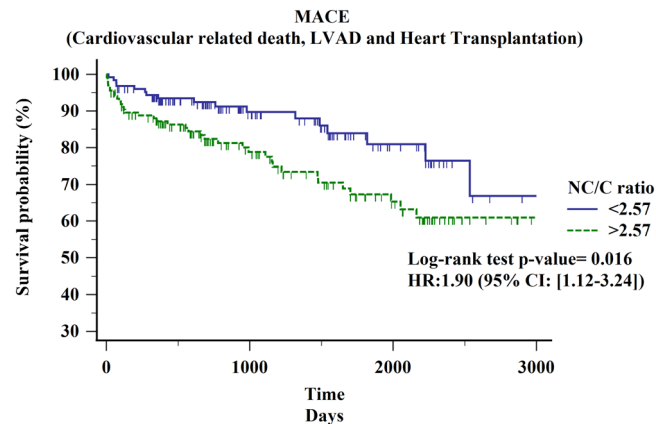
excursion (TAPSE) related to right ventricular systolic dysfunction, and LVEF demonstrated significant primary endpoint-free survival (Supporting Information, *Tables S5–S8*).

In multivariate analysis, DCM patients diagnosed using Petersen's criteria LVEDV(i) was an independent predictor of MACE-free survival. For LVNC patients, TAPSE was an independent predictor for primary endpoint-free survival (Supporting Information, *Tables S9–S12*). By redefined NC/C ratio 2.57 multivariate analysis, the patient's NC/C ratio under 2.57 did not demonstrate significant independent factors for MACE-free survival. For patients with an NC/C ratio over 2.57, TAPSE was again an independent factor for primary endpoint-free survival (Supporting Information, *Tables S13–S16*).

Discussion

Diagnosis

Left ventricular non-compaction cardiomyopathy was considered a rare form of cardiomyopathy resulting from the intra-uterine arrest of the myocardial compaction process resulting in trabeculations with deep myocardial recesses. However, this spongy appearance of the LV is being reported in the adult population with the diagnosis of DCM, valvular, and congenital heart disease. It remains uncertain whether this is a distinct type of cardiomyopathy or whether it is an epiphenomenon or a phenotypic variant of other cardiomyopathies.[12]

Another uncertainty is about the diagnosis of the disease. The definition of LVNC is morphological and is based on the identification of thickened myocardium with echocardiogra-

phy or CMR. The diagnosis is made by demonstrating specific criteria based mainly upon the relative thickness of the compacted myocardial wall and the lace-like mesh of the trabeculated (non-compacted) layer of cardiac muscle. Although there are different proposed criteria for the diagnosis, the one suggested by Petersen has been accepted and used in most studies.[8]

In earlier studies, the diagnostic criteria were based upon the echocardiographic measurement of non-compacted and compacted myocardial layers ratio. Chin *et al.* described the ratio of the two layers, and the 0.5 was an accepted diagnostic criterion for the LVNC. Nonetheless, this criterion was based on eight primarily paediatric patients and eight controls.[3] Jenni *et al.* described LVNC by 2D echocardiographic as end-systolic non-compacted to compacted ratio over 2.0 and with the filling of the intratrabecular recesses with blood in the absence of cardiovascular disease. This ratio was based on seven LVNC patients, with the control composed of 139 hetero-cardiovascular disease patients.[13]

We diagnosed DCM–LVNC patients in this study based on the Petersen criterion, defined as a non-compacted to the compacted myocardial ratio of 2.3 at diastole in the long-axis imaging plane. This ratio was driven from a study that compromised only seven patients evaluated by 2D echocardiography and matched healthy controls. This criterion's specificity and sensitivity were 86% and 99%, respectively.[8] Our cohort was composed of 262 well-selected cardiomyopathy patients, and almost all had LV systolic dysfunction before the CMR examination; the mean LVEF was 29.5 ± 11.3%. A total of 59.2% of the patients met the Petersen criteria. In this study, the diagnosis of LVNC was made by CMR. Evaluation of 262 patients showed that DCM patients were older and had higher body surface area, and there were no differences in echocardiographic variables between the two groups. In LVNC patients, LVs were more dilated and had better haemo-

dynamic parameters measured by CMR. There were no differences regarding primary and secondary endpoints as well. No significant difference was detected in our study cohort when this criterion was used.

There are other data in the literature that conflict with Petersen's criteria. In a study, the myocardial ratio of NC/C of 2.3 was detected 17% of the healthy population. This is also consistent with the findings of the Multi-Ethnic Study of Atherosclerosis study: 44% of 306 healthy patients without cardiac disease met the Petersen criterion of LVNC. At least in one region, the NC/C ratio was over 2.3 in 43% of participants. This study questions the Petersen criteria showing that specificity and pre-test probability were low, and higher cut-off values were required to identify LVNC better.[14] Weir-McCall et al. assessed the cardiovascular disease-free population for the criterion and found nearly 15% met at least one current CMR-derived criteria. These findings led to reviewing the Petersen CMR criteria.[15] Ashrith et al. investigated the severity of LVNC by classifying patients according to an NC/C ratio of 3.0. Patients were not restricted to baseline LVEF. Outcomes were associated with LV systolic function changes, changes in symptom class, the incidence of tachyarrhythmias, and hospitalization. ROC curve analysis identified an NC/C ratio over 3.0 as a predictor of improvement in LVEF, and there was an inverse correlation between change in LVEF and NC/C ratio.[16] Ivanov et al. applied 2D echocardiographic and CMR-based criteria and prospectively enrolled 700 patients without aetiology restriction. For LVNC diagnosis, four CMR LVNC criteria (Petersen, Jacquier, Stacey, and Captur derived) did not demonstrate prognostic significance. They performed ROC curve analysis for each criterion and showed no additional prognostic information, and ROC curves were non-discriminatory for both the primary outcome and mortality.[17]

Vaidya et al. evaluated the largest cohort of 339 LVNC patients for long-term survival. Diagnosis of LVNC was made by Jenni and Petersen's criteria without the restriction of LVEF. The mean follow-up time was 6.3 years. In Cox regression multivariate analysis, age, LVEF, and non-compaction extending apically to mid, basal segments were independent predictors of all-cause mortality. Compared with matched age and gender US population, LVNC patients had reduced survival ($P < 0.001$). The NC/C ratio was a significant predictor of the primary endpoint in Cox regression univariate analysis of all cardiomyopathy patients.[18]

We also applied the ROC analysis for the NC/C ratio for the discrimination of the primary endpoint. A higher NC/C ratio of 2.57 was associated with statistically different demographic, clinical, and CMR data. According to the redefined NC/C ratio, the survival probability difference was statistically significant. When the Petersen criteria were applied, sensitivity and specificity were low (69.0% and 43.4%, respectively). We believe that the NC/C ratio of 2.57 differentiated the two cardiomyopathies better. Atrial fibrillation,

which could have a unique mechanism related to different genotype, was more frequently seen in DCM patients. LVNC patients with more family history of HF may signify a hereditary inclination. In our study, Cox regression multivariate analysis revealed that family history of HF, LVEF, and right ventricular dysfunction were significant prognostic predictors of primary endpoints for all patients. LVNC patients, according to the Petersen and redefined criteria, right ventricular dysfunction was an independent predictor endpoint-free survival.

Cardiac magnetic resonance imaging late gadolinium enhancement distribution

Cardiac magnetic resonance enables better evaluation of tissue-based markers, particularly myocardial fibrosis. Specific CMR LGE distribution patterns have demonstrated the predictive value of HF-related death, advanced HF therapies, and ventricular arrhythmias.[19] Alba et al. assessed the MINICOR registry cohort of 1672 DCM patients. LGE was present in 39% of patients. By multivariate analysis, the presence of LGE increased the risk of the primary outcome (all-cause mortality, LVAD, or heart transplantation). When LGE pattern types assessed primary outcomes, only the existence of sub-endocardial LGE was significantly related to increased primary endpoint events.[20]

Another study presented by Nucifora et al. aimed to evaluate 42 isolated LVNC patients for the extent of LGE and its relation to clinical status and LV systolic function. CMR LGE was observed in 55% of patients and was significantly related to abnormal clinical features. Multivariate analysis revealed that the presence and amount of LGE had an inverse relation with LVEF.[21] Grigoratos et al. published a meta-analysis of four studies, including LVNC patients, on the prognostic role of LGE and LV global systolic impairment for future MACE. A total of 574 LVNC patients and 677 non-LVNC patients were included. The mean follow-up time was 5.2 years. LGE was related to MACE and cardiac death. Neither of the four studies did analyse the LGE patterns and their impact on MACE-free survival. The meta-analysis revealed that the LGE pattern matched for LVEF was not associated with a worse prognosis. This finding means that LV systolic impairment is the determinant of the prognostic impact of LGE and, for this reason, act together.[22]

We analysed the relation of the LGE pattern for patient prognoses in 249 patients. The presence of LGE did not show significant importance for primary endpoint-free survival. As found in the meta-analysis of Grigoratos et al., the presence of LGE and the decrease of LVEF, the collinearity issue is thought to blunt the effect of LGE on the primary endpoint in DCM and LVNC patients. We analysed 102 (40.9%) patients' LGE pattern types and found that none had a significant relationship with primary and secondary endpoints.

However, mid-wall LGE had the lowest HR (0.893; 95% CI: [0.312–2.558]), and sub-epicardial LGE had the highest HR (1.715; 95% CI: [0.709–4.149]). We also showed that the distribution of mid-wall LGE was more common in DCM patients. The distribution of sub-epicardial LGE was more prominent in patients with LVNC. We believe that this finding is new in literature. This information may provide us with the possibility of evaluating sub-epicardial LGE in favour of LVNC in the LGE analysis.

Conclusions

This study evaluated patients diagnosed with CMR using Petersen's criteria of 2.3 and compared the demographic and prognostic data to patients with DCM. There was no difference between the groups regarding prognosis and survival. However, our analysis revealed new criteria of 2.57. Demographic variables and survival analysis showed statistically significant differences when we recategorized the patients with this new criterion. Different demographic data may indicate that there is LVNC cardiomyopathy. It is probable that the criteria used for the diagnosis are far from perfect. We believe that apart from ejection fraction and LGE, the degree of trabeculation is essential for the diagnosis and prognosis of this perhaps distinct entity.

Limitations

Our study compromises one of the largest populations that compared DCM and LVNC patients. However, this study was in retrospective design and represented the single-centre experience. The Jacquier method, based on measuring the non-compact area with CMR, could not be measured with this method due to its impracticality and poor interobserver agreement. Additionally, the regional dispersion of the non-compacted segment was not analysed in the study, which is not a criterion for the diagnosis of non-compaction cardiomyopathy. This study included moderate or severe LV dysfunction HF patients, NC/C ratio over 2.3, and LVEF > 50%; 44 patients did not include the analyses so for evaluating the LV systolic dysfunction developed in patients. Therefore, these results could not be generalized to all patients. The study included patients referred to a tertiary HF centre, and, most likely, LVNC suspected patients performed CMR may cause bias. In addition, all significant parameters in univariate analyses were not included to reduce the effect of overfitting and multicollinearity issues.

Conflict of interest

None.

Funding

None.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information.

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