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Overlapping Phenotypes and Degree of Ventricular Dilatation Are Associated with Severity of Systolic Impairment and Late Gadolinium Enhancement in Non-Ischemic Cardiomyopathies

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Background: Dilatation and other infrastructural rearrangements of the left ventricle are connected with poor prognosis. The aim of our study was to analyze the overlapping phenotypes and dilatation of the ventricle on impairment of systolic function and existence of late gadolinium enhancement (LGE).

Material/Methods: Consecutive sample of cases with dilated left ventricle due to non-ischemic cardiomyopathy and healthy controls were included from our cardiac magnetic resonance imaging (CMR) database for a period of 3 years (n=1551 exams).

Results: The study included 127 patients; 30 (23.6%) with dilated cardiomyopathy (DCM); 30 (23.6%) with left ventricular non-compaction (LVNC); 13 (10.2%) with hypertrophic cardiomyopathy (HCM), and 50 (39.4%) controls. Overlapping phenotypes were found in 48 (37.8%) of the studied cases. Odds for impairment of systolic function in connection with overlapping phenotypes were estimated at 7.8 (95%-CI: 3.4–17.6), (p<0.001). There were significant differences in geometric parameters for patients with overlapping phenotypes *vs.* controls, as follows: left ventricle end-diastolic dimension(LVEDD)=6.6±0.8 *vs.* 5.6±1.0 cm (p<0.001); left ventricular ejection fraction (LVEF)=39.3±14.0 *vs.* 52.1±16.1 (p<0.001); and existence of LGE 36 (75.0%) *vs.* 21 (26.6%), (p<0.001), respectively. Overlapping phenotypes correlated with LVEDD (Spearman's-Rho-CC)=0.521, p<0.001; LVEF (Rho-CC)=–0.447, p<0.001 and LGE (Rho-CC)=0.472, p<0.001.

Conclusions: This study found there are many patients with overlapping phenotypes among NICMPs with dilated left ventricles. Overlapping phenotype was associated with greater LVEDD, lesser systolic function, and commonly existing LGE, which all impose increased cardiovascular risk. Linear midventricular LGE stripe was the most powerfully connected with loss of systolic function.

MeSH Keywords: **Cardiomyopathy, Dilated • Gadolinium DTPA • Heart Failure • Magnetic Resonance Imaging • Ventricular Remodeling • Cardiomyopathy, Hypertrophic • Genes, Overlapping**

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Background

Non-ischemic cardiomyopathies (NICMPs) are diseases of heart muscle connected with many poor prognostic outcomes [1]. These are caused by various mechanisms, which eventually lead to development of arrhythmia, heart failure, and sudden cardiac death. Dilated cardiomyopathy (DCM) is the most common cause of heart transplantation in developed Western countries [2]. Dilated left ventricle is a prominent characteristic of several NICMPs, which is associated with a critical point in the progress of multiple undesirable prognostic outcomes. One of the most prominent landmarks of imminent or developed heart failure is dilatation of the left ventricle [3,4]. The later was shown to be an important prognostic parameter in various heart diseases [5]. It is associated with the development of arrhythmias and can be in part ameliorated using resynchronization therapy [6]. The prevalence of sudden cardiac death was also found to be related with increased dimension of the left ventricle [7]. Ventricular dimension, as one of the most important diagnostic sign of DCM, also has prognostic implications [8]. In addition, dimension of the left ventricle was shown to be a superior prognostic sign compared with systolic function of the ventricle, when used prior to heart transplantation in children with dilated cardiomyopathy [9]. Dilatation of the ventricle in patients with hypertrophic cardiomyopathy (HCM) was found to be connected with perfusion defects, vasodilatory flow reserve, and myocardial mass [10]. Long-term prognostic significance of ventricular dimension was also shown in patients with left ventricular non-compaction (LVNC) [11,12].

However, there is limited knowledge about imaging of NICPMs that express elements of more than 1 cardiomyopathy [13]. Combinations of elements of dilated and hypertrophic cardiomyopathy or LVNC in a single patient are common. Prevalence, hemodynamic relations, existence of prognostic imaging parameters, and clinical impact of those effects are still largely unknown. However, genetic studies have shown overlapping types of cardiomyopathies. A large study of truncated filamin C gene in dilated and arrhythmogenic cardiomyopathies found connections with dilatation of the ventricle, loss of systolic function, and increased myocardial fibrosis, which were associated with sudden cardiac death [14].

In recent decades cardiac magnetic resonance (CMR) has become an important diagnostic tool in patients with NICMPs [15], and is the reference method for non-invasive analyzes of geometry, volume, and function of the left ventricle. Additional advantages include availability of tissue analyses and contrast imbibition of the malfunctional myocardium, detecting areas of fibrosis, which can be identified on imaging even prior to the development of overt heart failure [16]. The latter, in terms of late gadolinium enhancement (LGE), also brings prognostically-relevant information, particularly about prevalence of arrhythmia, heart failure, and cardiac death [17,18]. Remarkably, despite the wide range of etiologies, highly complex mechanisms of origin, and different phenotypes, imaging with late gadolinium enhancement was proven to provide prognostically-relevant information on all types of NICMPs [19,20].

The aim of the present study was to systematically analyze effects of overlapping phenotypes of NICMP in patients with dilated left ventricle and healthy controls, as well as to subanalyze the degree of ventricle dilatation with functional and previously mentioned prognostic parameters.

Material and Methods

This study adhered to the Declaration of Helsinki and good clinical practice guidelines. Patients signed informed consent prior to data acquisition. There was no funding, compensation, or other sources of financing. There were no additional reimbursements or in-kind compensations. The study was approved by the Hospital Ethics Board.

Imaging data and reports on patients were obtained from the computerized CMR data base for a 3-year period (n=1551 CMR exams). Patients with dilatation of the left ventricle caused by non-ischemic cardiomyopathy were consecutively included. Guidelines-based criteria were used to determine the primary type of cardiomyopathy, while combined characteristics of several cardiomyopathies types were classified as secondarily overlapping phenotype [21]. Diagnosis of LVNC was based on presence of thinned solid myocardium ≤0.5 cm, NC/C ratio ≥2.3: 1, and proportion of non-compact myocardium being greater than 20%, as we previously described [22]. Marginal cases with NC ≥15% but with NC/C ≥2.3: 1 and those with HCM and end-diastolic thickness ≥1.40 cm were included in the group of overlapping phenotypes. Left ventricle dilatation was diagnosed based on left ventricular end-diastolic dimension (LVEDD) ≥6.0 cm, with further study of severity using supplementary LVEDD cutoff points set at ≥6.5 cm and ≥7.0 cm. The control group was a sex-matched sample of consecutive patients from the same time period with no structural heart disease. We excluded patients with significant chest wall deformities, cardiac tumors, sarcoidosis, congenital heart disease, previous heart surgery, and ischemic heart disease (known coronary artery disease; non-negative adenosine stress testing or with existent ischemic type of late gadolinium enhancement). Most of the patients were referred to our center from other institutions around the country for CMR diagnosis, since at the time we were the only large-volume center. For this reason, many patients in this population had cardiac problems, with initial diagnostic workup mostly performed at tertiary medical centers.

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Patient studies were performed on a 1.5 T Magnetom Avanto, Siemens® device (Erlangen, Germany), using Body Matrix chest and spine coils, and sequences were recorded under ECG gating and respiratory control. Imaging protocol consisted of setting localizers, Half-Fourier Acquisition Single-shot Turbo spin Echo (HASTE) sequences, steady-state free precession (SSFP) of standard heart 2, 4, 3, chamber planes and 6-mm stack of short axial slices, and optional adding of right ventricle and its outflow tract in case of clinical question. Those were followed by short tau inversion-recovery (STIR) or turbo spin echo (TSE) T1, and in cases with concordant clinical question, the dark blood T2 sequences followed by fat saturation sequences. Gadolinium-based contrast was administered in a dose of 0.2 mL/kg (0.1 mmol/kg). Initially, we used an intravenous bolus of Omniscan® (Gadodiamide) or Dotarem® (gadoterate meglumine), prior acquisition of inversion time recovery scout sequence, using phase-sensitive inversion-recovery (PSIR) and STIR late gadolinium enhancement (LGE) sequences, within 20–30 min after contrast application. Postprocessing analyzes were done on standard software Siemens AG- NUMARIS/4, Syngo MR B17® (Erlangen, Germany) and volumetric measurements using Siemens AG- Syngo Console VA 30 Argus®, by 2 high-throughput cardiologists (over 400 exams per year) and radiologist. Diagnostic reports included clinical question of referring cardiologist, interpretation of entire set of planes, sequences, tissue analyzes, volumetric, semiquantitative analyzes of valvular function, late gadolinium enhancement, and conclusion of exam, with final interpretation of results consistent with available up-to-date guidelines and standardized 17-level myocardial segmentation.

We used the Kolmogorov-Smirnov test to assess normality of distribution. Groups of numeric data were scrutinized using descriptive statistic and are presented as means combined with standard deviations. Group data are presented as numbers and percentages, while analyses were performed using the chi-square test. Numeric variables were analyzed for differences by Mann-Whitney U test and in testing of geometry and volumetric to studied NICMPs etiologies of controls by Kruskal-Wallis test. Correlations of CMR parameters with clinical data were done by Spearman Rho. Diagnostic value of investigated parameters for detection of systolic impairment was defined by left ventricle ejection fraction (LVEF) cutoff point set at <50% using receiver operating curve (ROC) analyses. Binomial regression analysis was used for quantification of odds between overlapping phenotypes and systolic impairment. P values less than 0.05 were regarded as significant. Statistical analyses were done by an experienced statistician using Statistica 10® for Windows (StatSoft inc, Tulsa, OK); MedCalc v. 12.2® for Windows (MedCalc software co, Belgium) and IBM-SPSS12® v 20 (IBM co, Chicago, IL).

Results

Studied sample

This study included 127 cases referred to CMR. Average age was 49.1±15.9 years (range 15.2–78.3), male-to-female ratio 98 (77.2%) to 29 (22.8%). Impairment of systolic function was found in 58 (45.7%), LGE existed in 57 (44.9%), and overlapping phenotype was found in 48 (37.8%) cases. LGE was significantly correlated with impairment of left ventricle systolic function (Rho-CC=0.635; p<0.001) and overlapping phenotypes (Rho-CC=0.472; p<0.001). There were 77 (60.6%) consecutive patients with left ventricular dilatation due to non-ischemic cardiomyopathy, as follows: 13 (10.2%) with hypertrophic cardiomyopathy, 30 (23.6%) with dilated cardiomyopathy, and 30 (23.6%) with left ventricular non-compaction. The control group consisted of 50 (39.4%) matched consecutive cases from the same period with no structural heart disease. For the group of patients with overlapping phenotype, the most common associated diagnostic elements were the combination of DCM and LVNC in 34 (26.8%) of patients, followed by DCM and HCM in 13 (10.2%), and there was a single case of DCM and HCM and LVNC (0.8%) (Figure 1).

Main characteristics of geometry, volumes, and systolic function of the left ventricle in studied patients depending on the NICMP diagnosis shown in the Table 1.

Infrastructural changes of the left ventricle

Effects of left ventricle dilatation severity were studied for different degrees of end-diastolic dimensions, and separately for existence of overlapping morphology, and the latter was considered for cases that expressed elements of more than 1 NICMP. Existence and morphologic type of LGE was analyzed for studied groups. Detailed data on differences and correlations are shown in Tables 2 and 3.

In binomial regression analyze model, odds of overlapping phenotypes for impairment of systolic function were estimated at 7.8 (95%CI: 3.4–17.6), b=2.1, Wald=24; p<0.001.

ROC analyses of ventricular dilatation, systolic dysfunction, overlapping phenotype, and LGE

In ROC analyzes, the degree of dilatation was assessed over the rate of systolic function; LVEDD ≥6 cm had critical point of LVEF at ≤55.3% with sensitivity of 93.5 (85.5–97.9), specificity 90.0 (78.2–96.7), +LR 9.4 (8.4–10.4) and –LR 0.07 (0.02–0.2), AUC 0.953 (0.900–0.983), p<0.001. LVEDD ≥6.5cm had critical point of LVEF set at ≤49.6% with sensitivity of 86.5 (71.2–95.5), specificity 73.3 (63.0–82.1), +LR 3.2 (2.7–3.9) and –LR 0.2 (0.08–0.4), and AUC 0.866 (0.795–0.920), p<0.001. The most severe grade of ventricular dilatation in our study – LVEDD

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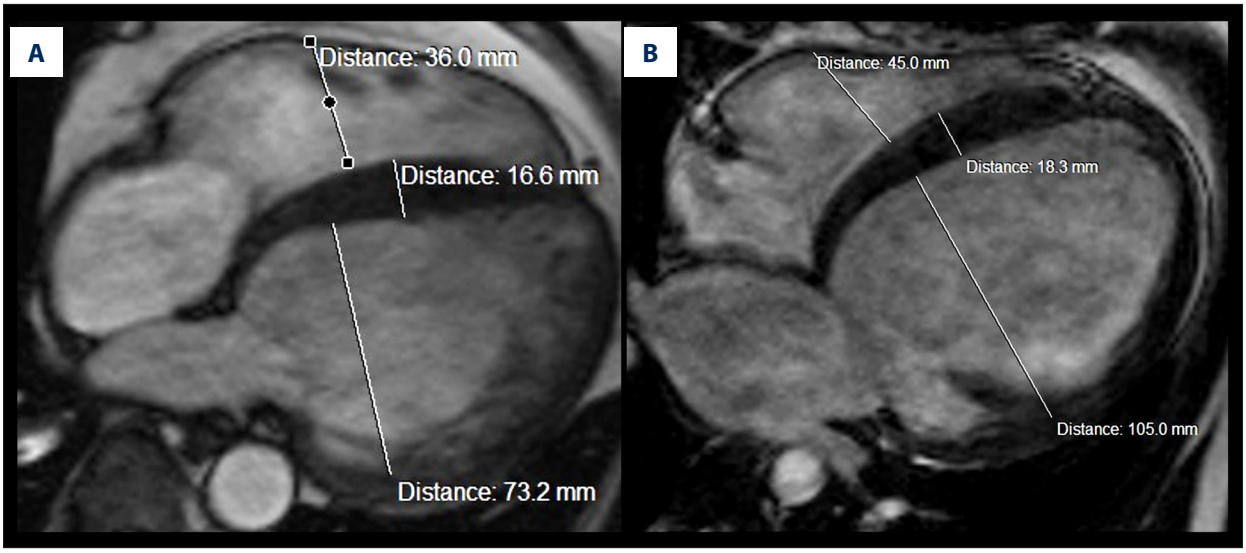

Figure 1. Examples of patients with overlapping phenotypes. Four-chamber view, Cine SSFP sequence at end-diastole: (**A**) Case of 50-year-old male patient with dominant morphotype of left ventricular non-compaction, associated with hypertrophy of interventricular septum and dilated left ventricle, LVEF=45%; NC/C=4.7; NC=35.3% of the left ventricle. White lines showing measurements: LVEDD=73.2 mm=7.32 cm; IVS=16.6 mm=1.66 cm and RVEDD=36 mm=3.6 cm. (**B**) Case of 22-year-old male patient with dominant morphotype of dilated cardiomyopathy, associated with hypertrophy of interventricular septum, with arrhythmogenic artefacts, LVEF=12%. White lines showing measurements: LVEDD=105.0 mm=10.5 cm; IVS=18.3 mm=1.83 and RVEDD=45 mm=4.5 cm. SSFP – steady-state free precession; NC – non-compact myocardial thickness at end-diastole; C – compact myocardial thickness at end-diastole; LVEDD – left ventricular end-diastolic dimension; IVS – interventricular septum thickness at end-diastole; RVEDD – right ventricle end-diastolic dimension.

≥7 cm – had critical point of LVEF set at ≤30.0% with sensitivity 82.4 (56.6–96.2), specificity 90.0 (82.8–94.9), +LR 8.2 (6.6–10.4) and –LR 0.2 (0.06–0.6), and AUC 0.928 (0.869–0.967), p<0.001.

In regard to systolic impairment *per se* (LVEF<50%), critical value of LVEDD being >6 cm had sensitivity 96.6 (88.1–99.6), specificity 75.4 (63.5–84.9), +LR 3.9 (3.4–4.5) and –LR 0.05 (0.01–0.2), and AUC 0.903 (0.838–0.949), p<0.001.

Overlapping phenotype was found with LVEEF of ≤55% having sensitivity 95.8 (85.7–99.5), specificity 62.0 (50.4–72.7), +LR 2.5 (2.1–3.0) and –LR 0.1 (0.02–0.3), and AUC 0.766 (0.683–0.837), p<0.001. On the other hand, overlapping phenotype was found with LVEDD of >5.99 cm having sensitivity 100.0 (92.6–100.0), specificity 63.3 (51.7–73.9), +LR 2.7 (2.3–3.2) and –LR 0.06 (0.02–0.3), and AUC 0.810 (0.731–0.874), p<0.001.

With respect to late gadolinium enhancement existence, a critical value to the LVEF ≤52% had sensitivity 87.7 (76.3–94.9), specificity 80.0 (68.7–88.6), +LR 4.4 (3.8–5.1) and –LR 0.2 (0.1–0.4), and AUC 0.887 (0.819–0.936), p<0.001. Additional analyses were performed in regard to linear type of LGE imbibition, where a critical value of LVEF ≤45% had sensitivity 85.7 (69.7–95.2), specificity 78.3 (68.4–88.2), +LR 3.9 (3.3–4.7) and –LR 0.2 (0.07–0.4), and AUC 0.880 (0.810–0.931), p<0.001. Focal type of LGE imbibition in the model of ROC analysis was not statistically significant (p=0.198). Diffuse type of LGE imbibition had a critical value to the LVEF ≤52% with sensitivity of 100.0 (54.1–100.0), specificity 52.1 (42.8–61.2), +LR 2.1 (1.8–2.5) and –LR 0.3 (0.05–1.9), and AUC 0.720 (0.633–0.796), p=0.003. Existence of LGE was found with LVEDD of >6 cm having sensitivity 94.7 (85.4–98.9), specificity 72.9 (60.9–82.8), +LR 3.5 (3.0–4.1) and –LR 0.1 (0.02–0.2), and AUC 0.883 (0.814–0.933), p<0.001.

Discussion

Infrastructural and functional changes in the failing heart by means of ventricular dilatation, loss of systolic function, and late gadolinium enhancement are known prognostic parameters of complications associated with non-ischemic cardiomyopathies [23,24]. This study first systematically analyzed the effects of overlapping morphologies, which combine elements of several types of non-ischemic cardiomyopathies and functional impact of ventricular dilatation, as well as connections existing with late gadolinium imbibition and systolic impairment [25].

In this study, elements of several types of non-ischemic cardiomyopathies (e.g., overlapping phenotype) were found in 37.8% of individual patients. The most common combination of DCM and LVNC was found in 70% of overlapping cases, similar to a previous report [26]. Although this report found no connections of coexisting trabeculations that fit within NC/C ratio criteria in DCM with clinical points, it only could be partially

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Table 1. Studied sample of patients grouped by NICMP dominant morphotype.

	OK	DCM	HCM	LVNC	Kruskal-Wallis
	N (%)	N (%)	N (%)	N (%)	
Male	40 (74.1%)	25 (83.3%)	13 (100.0%)	20 (66.7%)	0.085
Female	14 (25.9%)	5 (16.7%)	0 (0.0%)	10 (33.3%)	
LVEF ≤50%	1 (1.9%)	27 (90.0%)	9 (69.2%)	21 (70.0%)	**<0.001**
Overlap	0 (0.0%)	7 (23.3%)	12 (92.3%)	29 (96.7%)	**<0.001**
Existing LGE	2 (3.7%)	23 (76.7%)	12 (92.3%)	20 (66.7%)	**<0.001**
No LGE	52 (96.3%)	7 (23.3%)	1 (7.7%)	10 (33.3%)	
Focal LGE	2 (3.7%)	2 (6.7%)	10 (76.9%)	2 (6.7%)	**<0.001**
Linear LGE	0 (0.0%)	18 (60.0%)	2 (15.4%)	15 (50.0%)	
Diffuse LGE	0 (0.0%)	3 (10.0%)	0 (0.0%)	3 (10.0%)	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Kruskal-Wallis**
Age (years)	45.2±15.8	54.7±14.4	54.1±15.4+8	48.2±16.2	**0.033**
LVEDD (cm)	5.1±0.6	7.0±1.0	6.4±0.4	6.4±0.3	**<0.001**
IVS (cm)	1.0±0.2	1.1±0.2	2.0±0.6	1.0±0.2	**<0.001**
RV (cm)	3.8±0.6	4.0±1.0	3.8±0.5	3.6±0.8	0.527
LA (cm^2)	25.2±5.9	36.3±10.6	36.4±7.5	29.0±6.0	**<0.001**
RA (cm^2)	23.9±7.9	29.3±9.0	28.5±7.0	26.6±7.7	**0.029**
LVEF (%)	61.1±5.1	31.3±13.9	44.3±15.6	39.7±12.7	**<0.001**
EDV (mL)	142.9±39.7	269.7±128.7	185.1±25.2	212.0±52.1	**<0.001**
ESV (mL)	58.0±25.5	192.3±129.3	107.2±44.4	129.5±47.4	**<0.001**
SV (mL)	87.7±21.2	75.0±28.7	77.7±22.2	82.6±31.0	0.065
MM (gram)	112.0±30.5	170.6±65.3	178.1±55.8	128.3±31.4	**<0.001**

OK – no structural heart disease; DCM – dilated cardiomyopathy; HCM – hypertrophic cardiomyopathy; LVNC – left ventricular non-compaction; LVEF – left ventricle ejection fraction; Overlap – overlapping NICMP morphology; LGE – late gadolinium enhancement; LVEDD (cm) – left ventricle end diastolic dimension in 4 chamber view; IVS (cm) – interventricular septum thickness in 4 chamber view; RV (cm) – right ventricle end diastolic dimension in 4 chamber view; LA & RA (cm^2) – left and right atrial area in square centimeters in 4 chamber view; EDV (mL) – end diastolic volume; ESV (mL) – end systolic volume; SV (mL) – stroke volume; MM (gram) – myocardial mass in end-diastole. Data shown as numeric and percentages or means and standard deviations (SD). Statistically significant values ($p<0.05$) presented in bolded text.

compared to the present study and our previous study due to using triple criteria of thinning of the compact myocardium, NC/C ratio, and sufficient share of non-compact myocardium in total mass of the left ventricle [27]. The second most common combination, DCM/HCM, was found in nearly one-third of our overlapping patients, but this combination could be even more powerfully connected with undesirable prognosis due to partially shared gene basics [28,29]. The least frequent combination in our settings was the DCM/HCM/LVNC, with only a single case in the monitored period, which was also previously described in a large registry with clinical endpoints, which reported a greater incidence of cardiovascular adverse events [30]. Since overlapping phenotypes could be common on imaging studies, additional cooperation between imaging and clinical genetics would be necessary to gain more objective insight about prognostic-related challenges [31]. In recent years, even the role of immunology has been recognized as being to some extent responsible for development of heart failure in genetic cardiomyopathies, which could also be a productive area for the field of overlapping phenotypes of NICMPs [32].

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Table 2. Studied sample of cases grouped by overlapping phenotype and grade of dilatation of the left ventricle.

	Overlapping phenotype		Sig.	LVEDD ≥6.0		Sig.	LVEDD ≥6.5		Sig.	LVEDD ≥7.0		Sig.
	No	Yes		No	Yes		No	Yes	N (%)	No	Yes	
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)		N (%)		
Male	60 (75.9%)	38 (79.2%)	0.675*	36 (72.0%)	62 (80.5%)	0.264*	69 (76.7%)	29 (78.4%)	0.835*	87 (79.1%)	11 (64.7%)	0.189*
Female	19 (24.1%)	10 (20.8%)		14 (28.0%)	15 (19.5%)		21 (23.3%)	8 (21.6%)		23 (20.9%)	6 (35.3%)	
LVEF ≤50%	22 (27.8%)	36 (75.0%)	**<0.001***	1 (2.0%)	57 (74.0%)	**<0.001***	26 (28.9%)	32 (86.5%)	**<0.001***	41 (37.3%)	17 (100.0%)	**<0.001***
Overlap	0 (0.0%)	48 (100.0%)	N/A	0 (0.0%)	48 (62.3%)	**<0.001***	26 (28.9%)	22 (59.5%)	**0.001***	39 (35.5%)	9 (52.9%)	0.166*
Existing LGE	21 (26.6%)	36 (75.0%)	**<0.001***	2 (4.0%)	55 (71.4%)	**<0.001***	26 (28.9%)	31 (83.8%)	**<0.001***	41 (37.3%)	16 (94.1%)	**<0.001***
No LGE	58 (73.4%)	12 (25.0%)		48 (96.0%)	22 (28.6%)		64 (71.1%)	6 (16.2%)		69 (62.7%)	1 (5.9%)	
Focal LGE	4 (5.1%)	12 (25.0%)	**<0.001#**	2 (4.0%)	14 (18.2%)	**<0.001#**	11 (12.2%)	5 (13.5%)	**<0.001#**	13 (11.8%)	3 (17.6%)	**<0.001#**
Linear LGE	14 (17.7%)	21 (43.8%)		0 (0.0%)	35 (45.5%)		12 (13.3%)	23 (62.2%)		23 (20.9%)	12 (70.6%)	
Diffuse LGE	3 (3.8%)	3 (6.3%)		0 (0.0%)	6 (7.8%)		3 (3.3%)	3 (8.1%)		5 (4.5%)	1 (5.9%)	
	n=79 (62.2%)	**n=48 (37.8%)**	**Sig.**	**n=50 (39.4%)**	**n=77 (60.6%)**	**Sig.**	**n=90 (70.9%)**	**n=37 (29.1%)**	**Sig.**	**n=110 (86.6%)**	**n=17 (13.4%)**	**Sig.**
	Mean ±SD	**Mean ±SD**		**Mean ±SD**	**Mean ±SD**		**Mean ±SD**	**Mean ±SD**		**Mean ±SD**	**Mean ±SD**	
Age (years)	48.5 ±16.0	50.0 ±16.0	**0.579$**	45.7 ±16.4	51.2 ±15.3	0.070$	47.6 ±16.1	52.6 ±15.3	0.111$	47.3 ±15.6	60.5 ±13.4	**0.001$**
LVEDD (cm)	5.6 ±1.0	6.6 ±0.8	**<0.001$**	5.0 ±0.5	6.7 ±0.7	**<0.001$**	5.6 ±0.7	7.1 ±0.8	**<0.001$**	5.8 ±0.8	7.6 ±1.0	**<0.001$**
IVS (cm)	1.0 ±0.2	1.3 ±0.5	**0.007$**	1.0 ±0.2	1.2 ±0.5	**0.005$**	1.1 ±0.4	1.1 ±0.3	0.937$	1.1 ±0.4	1.2 ±0.4	0.645$
RV (cm)	3.9 ±0.8	3.6 ±0.8	0.088$	3.8 ±0.6	3.8 ±0.9	0.721$	3.8 ±0.7	3.7 ±1.0	0.665$	3.9 ±0.7	3.3 ±1.0	**0.025$**
LA (cm^2)	28.7 ±9.5	31.8 ±7.3	**0.004$**	25.0 ±6.0	33.0 ±9.0	**<0.001$**	28.1 ±7.7	34.2 ±10.1	**0.001$**	28.8 ±7.9	36.8 ±11.5	**0.004$**
RA (cm^2)	25.8 ±8.3	27.1 ±8.1	0.314$	23.6 ±8.0	28.1 ±7.9	**0.001$**	25.2 ±7.8	29.0 ±8.7	**0.044$**	25.9 ±7.8	28.7 ±10.8	0.540$
LVEF (%)	52.1 ±16.1	39.3 ±14.0	**<0.001$**	61.6 ±5.0	38.0 ±14.7	**<0.001$**	53.5 ±12.8	32.2 ±14.7	**<0.001$**	51.1 ±13.7	22.8 ±11.5	**<0.001$**
EDV (mL)	175.5 ±73.7	223.0 ±101.3	**<0.001$**	140.2 ±35.1	228.1 ±94.5	**<0.001$**	161.5 ±45.1	271.3 ±115.0	**<0.001$**	172.7 ±51.1	328.0 ±144.5	**<0.001$**
ESV (mL)	93.3 ±73.8	141.8 ±100.3	**<0.001$**	53.4 ±17.4	149.5 ±94.1	**<0.001$**	79.2 ±40.3	190.7 ±117.5	**<0.001$**	88.9 ±46.0	258.8 ±139.8	**<0.001$**
SV (mL)	83.2 ±24.4	81.2 ±28.6	0.689$	85.8 ±20.3	80.3 ±29.1	0.124$	83.9 ±23.2	78.9 ±31.9	0.193$	85.1 ±25.4	65.3 ±23.4	**0.006$**
MM (gram)	127.4 ±42.0	151.3 ±61.1	**0.012$**	110.4 ±30.0	153.4 ±55.1	**<0.001$**	123.5 ±39.4	168.0 ±62.4	**<0.001$**	126.2 ±38.2	202.7 ±73.3	**<0.001$**

OK – no structural heart disease; DCM – dilated cardiomyopathy; HCM – hypertrophic cardiomyopathy; LVNC – left ventricular non-compaction; LVEF – left ventricle ejection fraction; Overlap – overlapping NICMP morphology; LGE – late gadolinium enhancement; LVEDD (cm) – left ventricle end diastolic dimension in 4 chamber view; IVS (cm) – interventricular septum thickness in 4 chamber view; RV (cm) – right ventricle end diastolic dimension in 4 chamber view; LA & RA (cm^2) – left and right atrial area in square centimeters in 4 chamber view; EDV (mL) – end diastolic volume; ESV (mL) – end systolic volume; SV (mL) – stroke volume; MM (gram) – myocardial mass in end-diastole; * Chi Square; # Kruskal-Wallis; $ Mann-Whitney; SD – data shown as numeric and percentages or means and standard deviations. Statistically significant values ($p<0.05$) presented in bolded text.

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Table 3. Correlations of studied parameters.

		Overlap	LVEDD ≥6.0 cm	LVEDD ≥6.5 cm	LVEDD ≥7.0 cm	Existing LGE
Gender	Rho CC	–0.037	–0.099	–0.019	0.117	–0.038
	Sig. (2-tailed)	0.678	0.267	0.836	0.191	0.669
Age (years)	Rho CC	0.050	0.162	0.142	**0.295**	**0.193**
	Sig. (2-tailed)	0.580	0.069	0.111	**0.001**	**0.029**
Existing LGE	Rho CC	**0.472**	**0.662**	**0.501**	**0.389**	N/A
	Sig. (2-tailed)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	N/A
LVEDD (cm)	Rho CC	**0.521**	**0.846**	**0.787**	**0.589**	**0.659**
	Sig. (2-tailed)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
IVS (cm)	Rho CC	**0.242**	**0.248**	0.007	0.041	**0.252**
	Sig. (2-tailed)	**0.006**	**0.005**	0.935	0.644	**0.004**
RV (cm)	Rho CC	–0.152	0.032	–0.039	**–0.200**	–0.080
	Sig. (2-tailed)	0.088	0.720	0.665	**0.024**	0.372
LA (cm^2)	Rho CC	**0.255**	**0.483**	**0.303**	**0.255**	**0.435**
	Sig. (2-tailed)	**0.004**	**<0.001**	**0.001**	**0.004**	**<0.001**
RA (cm^2)	Rho CC	0.090	**0.299**	**0.180**	0.055	**0.241**
	Sig. (2-tailed)	0.314	**0.001**	**0.043**	0.539	**0.006**
LVEF (%)	Rho CC	**–0.447**	**–0.767**	**–0.577**	**–0.505**	**–0.667**
	Sig. (2-tailed)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
EDV (mL)	Rho CC	**0.352**	**0.664**	**0.608**	**0.500**	**0.524**
	Sig. (2-tailed)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
ESV (mL)	Rho CC	**0.433**	**0.786**	**0.616**	**0.524**	**0.618**
	Sig. (2-tailed)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
SV (mL)	Rho CC	–0.036	–0.137	–0.116	**–0.247**	**–0.273**
	Sig. (2-tailed)	0.689	0.124	0.193	**0.005**	**0.002**
MM (gr)	Rho CC	**0.225**	**0.460**	**0.386**	**0.426**	**0.386**
	Sig. (2-tailed)	**0.011**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Rho CC – Spearman Rho correlation coefficient; sig-significance; LVEDD (cm) – left ventricle end diastolic dimension in 4 chamber view; LGE – late gadolinium enhancement; IVS (cm) – interventricular septum thickness in 4 chamber view; RV (cm) – right ventricle end diastolic dimension in 4 chamber view; LA & RA (cm^2) – left and right atrial area in square centimeters in 4 chamber view; EDV (mL) – end diastolic volume; ESV (mL) – end systolic volume; SV (mL) – stroke volume; MM (gram) – myocardial mass in end-diastole. Statistically significant values ($p<0.05$) presented in bolded text.

Our cases with overlapping phenotype were dominantly males in their 50s, with significantly impaired mean systolic function of 39.3±14.0%, as well as high proportion of systolic dysfunction (LVEF <50%), recorded in a remarkable 75% of this group. In addition, late gadolinium enhancement, an independent supplementary negative prognostic sign, was found in 75% of patients in the overlapping phenotypes group [33]. The most common morphotype of LGE was linear, followed by focal, and the least common was the diffuse type; the latter particularly points toward increased risk of long-term adverse cardiovascular events [34]. The reason for such a distribution could be the greater prevalence of DCM and LVNC among patients with dilated left ventricles. Conversely, the most common cardiomyopathy in the general population HCM was less frequently represented in our settings due to study inclusion criteria [35]. When supplementary analyses of LGE morphology were performed, the linear midventricular type of imbibition was associated with LVEF ≤45%, while the general existence of LGE and the diffuse type of LGE imbibition were both estimated at LVEF ≤52%. This result is in line with a study that

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assessed effects of linear midventricular stripe on prognosis of DCM, taking into account the need for ventricular assist device, heart transplantation, or cardiac death [36]. Similarly, the diffuse type of ventricular fibrosis was previously reported to increase prevalence of arrhythmias in patients with HCM, as opposed to focal type of inhibition, which occasionally was not connected with adverse cardiovascular events [37]. Nevertheless, it is worth noting that the morphology of LGE, in addition to its existence, conceals more meaningful prognostic value, and should be further investigated.

Patients with overlapping phenotype also had significant difference in left ventricle dimension than controls: 6.6±0.8 *vs.* 5.6±1.0 cm, respectively. This result represents an additional negative prognostic landmark of increased wall stress [38]. Furthermore, significant correlations of overlapping phenotype were found in connection with most of the geometric or volumetric measurements, including positive effects on rise of overall myocardial mass and left atrial size, as well as intermediate- to high-grade inverse correlations with systolic function. Of all the parameters studied, only stroke volume was not significantly changed or correlated to controls, which could be explained by compensation mechanisms of the Frank-Starlings' curve, in which the preservation of ejected volume is maintained for a relatively long time due to the rise in wall stress, chamber size, and end-diastolic volume [39]. Taking into account changes in nearly all parameters of geometry, volume, and function, the rather common existence of LGE, and particularly the malignant linear midventricular LGE type, patients with overlapping phenotypes of NICMPs could be well classified as high-risk patients.

Left ventricular end-diastolic dimension *per se* was also closely connected with diagnostic and prognostic parameters. Different degrees of ventricular dilatation were positively correlated with parameters that indirectly characterize wall stress, existence of LGE, and of intermediate- to high-grade negative correlations with systolic function [40]. These relations were not straightforward correlations, probably due to gradual exhausting of compensating mechanisms, as the dilatation of the ventricle was of greater dimensions, as well as alternations in myocardial tissue and function at cellular and subcellular levels [41].

Patients with the most severe-grade dilatation (LVEDD ≥7.0 cm) paradoxically had lower correlations than groups of intermediate- and mild-grade dilatations. The former is most likely explained by the effects of gradually decreasing marginal loss of ejection fraction, due to exhaustion of compensatory mechanisms (i.e., due to decrease of functional reserve), which is gradually less and less. From all studied levels of ventricular dilatations, only this particular group displayed mild- to intermediate-grade negative correlations with stroke volume. The latter is undeniably clinically important, because it represents the terminal grade of systolic dysfunction, and incapability of the failing heart for further compensations of ejection volume on behalf of increased wall stress or chamber sizes. It is valuable to note that this was also the only group that had positive correlations with age, with mean age of 60 years, which is still within the range for transplantation; however, due to standard deviations of ±13 years, part of this group might be still treated using other resources like ventricular assist devices. The group of patients with the most severe grade of ventricular dilatation in our study also had an astonishingly high 94% prevalence of LGE imbibition, which in two-thirds of those cases was in the form of more malignant linear midventricular stripe.

Limitations of our study include characteristics inherent in retrospective case-control settings. The population size was rather limited, and the selection of control cases with sex-matching procedure might conceal potential for bias. Additional potential for risk in regard to reproducibility could be due to inclusion criteria, the population of sub-selected cases, referred from mostly tertiary centers, and potential challenge that some cases due to external procedural reasons (that we are not aware of; like transportation difficulties, waiting lists, age related issues or else) could not be able to attend appointments. Another potential limitation lays in the current diagnostic guidelines for some entities, like LVNC. Further studies with prospective validation are warranted in order to improve reproducibility.

Conclusions

In conclusion, this study analyzed cardiac morphology and functions in patients with dilated left ventricle due to non-ischemic cardiomyopathies. We found that overlapping type of non-ischemic cardiomyopathy was highly prevalent. Studied patients with overlapping type of NICMPs had significantly greater dilatation of left ventricle, coexistent systolic impairment, and fairly common presence of LGE imbibition, which are all well-established prognostic parameters. Higher grades of ventricular dilatation were connected with greater changes in structural, geometric, volumetric, and functional data, imposing higher overall risk of unwanted major cardiovascular events in the long term. Morphological type of LGE was found to meaningfully influence prognostic-related parameters, which could be at least similarly important, or supplementary to binomial assessment of LGE-(non)existence. This study also reaffirmed the important position of CMR for diagnosis, follow-up, and potential to modify therapeutic-based interventions in patients with NICMPs with(out) heart failure.

Conflicts of interest

None.

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