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Effects of Systolic Dysfunction on Clinical and Diagnostic Parameters in Pediatric Patients with Isolated Left Ventricular Non-compaction

İzole Sol Ventrikül Non-Kompaksiyon Tanılı Pediatrik Hastalarda Sistolik Disfonksiyonun Klinik ve Tanısal Parametreler Üzerindeki Etkileri

ABSTRACT

Objective: Left ventricular non-compaction is a rare cardiomyopathy following an early arrest in endomyocardial morphogenesis. This study aimed to present the clinical and electrocardiographic characteristics, diagnostic features, treatment strategies, effects of systolic dysfunction on clinical and diagnostic parameters, and follow-up of pediatric patients diagnosed with left ventricular non-compaction.

Methods: We retrospectively reviewed children with isolated left ventricular non-compaction at Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital from January 2010 to June 2020.

Results: Fifty-five children were diagnosed with left ventricular non-compaction. Thirty-two patients (58.2%) were male, and the median age of presentation was 8.5 years (1 month-17.9 years). The median follow-up of the study was 19 months (1-121 months). Fourteen (25.5%) presented with systolic dysfunction (ejection fraction < 45%), and 2 presented with resuscitated/aborted cardiac arrest. Electrocardiographic abnormalities were present in 78.2%. Fragmented QRS was observed in 6 patients, and QTc duration was 450 milliseconds and above in 17 patients (30.9%). Electrocardiographic abnormalities, low QRS voltage, fragmented QRS, and thrombus were common in patients with ejection fraction < 45% group. Atrial and ventricular arrhythmias (including ventricular fibrillation-VF) were found with similar frequency in both ejection fraction < 45% and ≥45% groups. One patient with a complete atrioventricular block and 1 with long QT syndrome and severe bradycardia underwent permanent pacemaker implantation. Five (9.1%) patients died.

Conclusions: Left ventricular non-compaction has heterogeneous clinical findings in childhood. It is essential to follow-up with the patients closely for the development of ventricular dysfunction or arrhythmias due to the progressive course of the disease. Further studies are needed since life-threatening ventricular arrhythmias can be seen, even in patients with preserved ejection fraction.

Keywords: Arrhythmias, cardiomyopathies, children, left ventricular non-compaction

ÖZET

Amaç: Sol ventrikül nonkompaksiyonu (SVNC), endomiyokardiyal morfogenezin erken dönemde duraklaması sonucu görülen nadir bir kardiyomiyopatidir. Bu çalışmada, SVNC tanısı alan pediatrik hastaların klinik, elektrokardiyografik ve ekokardiyografik özelliklerini, tedavi stratejilerinin, sistolik disfonksiyonun klinik ve tanısal parametreler üzerindeki etkisinin değerlendirilmesi ve izlemi amaçlandı.

Yöntemler: Ocak 2010 ile Haziran 2020 tarihleri arasında Mehmet Akif Ersoy Göğüs Kalp ve Damar Cerrahisi Eğitim ve Araştırma Hastanesi'ne başvuran izole SVNC tanılı hastaları geriye dönük olarak inceledik.

Bulgular: Elli beş çocuğa sol ventrikül nonkompaksiyonu tanısı konuldu. Hastaların otuz ikisi (%58,2) erkekti ve ortanca başvuru yaşı 8,5 (1 ay-17,9 yıl) idi. Çalışmanın ortanca takip süresi 19 aydı (1-121 ay). Hastaların on dördü (%25,5) sistolik disfonksiyon (EF < %45) ve ikisi resüsite edilmiş kardiyak arrest ile başvurdu. EKG anormallikleri hastaların %78,2'de mevcuttu. Altı hastanın EKG'sinde fragmante QRS (fQRS) saptandı, 17 hastada (%30,9) QTc süresi 450 ms ve üzerinde idi. EF < %45 grubundaki hastalarda EKG anormallikleri, düşük QRS voltajı, fQRS ve trombüs daha sık olduğu görüldü. Atriyal ve ventriküler aritmiler (VF dahil) hem EF < %45 hem de ≥%45 gruplarında benzer sıklıkta bulundu. Tam AV bloğu olan bir hastaya ve Long QT sendromu ve şiddetli bradikardisi olan bir hastaya kalıcı kalp pili implantasyonu uygulandı. Beş (%9,1) hasta kaybedildi.

ORIGINAL ARTICLE
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Sonuç: Sol ventrikül nonkompaksiyonu çocukluk çağında heterojen klinik bulgulara sahiptir. Hastalığın ilerleyici seyrine bağlı olarak ventrikül disfonksiyonu veya aritmi gelişimi açısından hastaların yakından takip edilmesi esastır. Korunmuş EF'li hastalarda da yaşamı tehdit eden ventriküler aritmiler görülebileceğinden bu konuda ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Aritmi, kardiyomiyopati, çocuk, sol ventrikül nonkompaksiyonu

Left ventricular non-compaction (LVNC) is a rare cardiomyopathy (CMP) thought to be the result of an arrest in endomyocardial morphogenesis and is characterized by the presence of a bilayered myocardium with prominent trabeculations and deep recesses.[1] Although this condition was classified as primary cardiomyopathy by the American Heart Association in 2006,[2] LVNC remains unclassified by the European Society of Cardiology.[3] The disease typically affects the left ventricular (LV); however, the right ventricular can also be involved.[4] In this disease, where pediatric experience is still limited, clinical manifestations are heterogeneous in both child and adult patients, ranging from no symptoms to a progressive deterioration of systolic and diastolic functions that results in heart failure, thromboembolic events, arrhythmias, and sudden cardiac death (SCD).[1,4]

This study, the most extensive study of the pediatric population with LVNC in our country, aimed to define the clinical and electrocardiographic (ECG) characteristics, diagnostic features, treatment strategies, effects of systolic dysfunction on clinical and diagnostic parameters, and follow-up of pediatric patients diagnosed with LVNC.

Materials and Methods

Patient Selection

In this study, we included 55 patients between 1 month and 18 years diagnosed with LVNC between January 2010 and July 2020. Left ventricular non-compaction diagnosis was based on the following echocardiographic criteria[5]:

- the absence of coexisting cardiac anomalies;
- the presence of prominent trabeculations and deep intertrabecular recesses filled with blood shown by the color Doppler echo;
- the end-systolic ratio of thicker non-compacted (NC)/thinner compacted (C) myocardium >2.

ABBREVIATIONS

AF	Atrial flutter
AVB	Atrioventricular block
CMM	Compacted myocardial mass
ECG	Electrocardiography
ICD	Implantable cardioverter-defibrillator
IQR	Interquartile range
LBBB	Left bundle branch block
LVEDv	Left ventricular end-diastolic volume
LVESv	Left ventricular end-systolic volume
LVNC	Left ventricular non-compaction
NCMA	Non-compacted myocardial area
PAC	Premature atrial contraction
PVC	Premature ventricular contraction
SCD	Sudden cardiac death
SVT	Supraventricular tachycardia
VT	Ventricular tachycardia

The patients' demographic data, symptoms at admission, familial history, 12-lead ECG, transthoracic echocardiography, 24-hour Holter monitoring, exercise testing, cardiac magnetic resonance imaging (MRI), management modalities, and follow-up data were evaluated retrospectively. Patients with congenital heart disease, metabolic illnesses, systemic diseases, and neuromuscular diseases were excluded from the study.

Twelve-Lead Electrocardiograms and Holter Electrocardiography Monitoring

Twelve-Lead ECGs of the patients were recorded with 10 mm/mV and 25 mm/s paper speed. Electrocardiograms were evaluated to determine the ECG findings of LVNC, and all Holter recordings were reviewed for evaluating arrhythmias. The P-wave duration, P-wave height, PR interval, QRS duration, and QTc interval were calculated using standard methodology (Bazett's formula for QTc). R wave amplitude is greater than normal in V5 and V6, S wave amplitude is deeper than normal in V1 and V2, R/S ratio is smaller than normal in V1 and V2, and Q waves deeper than 5 mm for age in V5 and V6 were considered as a left ventricular hypertrophy criterion on ECG. The Holter recordings were evaluated for premature atrial contraction (PAC), supraventricular tachycardia (SVT), atrial flutter (AF), premature ventricular contraction (PVC), ventricular tachycardia (VT), and atrioventricular block (AVB).

Transthoracic Echocardiography

Transthoracic echocardiographies were performed using an iE33 ultrasound system (Philips Healthcare, Andover, Mass, USA) and an EPIQ 7 ultrasound system (Philips Healthcare, Andover, Mass, USA) with an appropriate transducer. Two-dimensional imaging, M-mode sonography, and color-flow Doppler echocardiography were evaluated according to the guidelines of the American Echocardiography Association.[6] The LV wall thickness, LV end-diastolic diameter (LVEDd), and LV end-systolic diameter (LVESd) were measured in the parasternal long-axis view by M-mode sonography. Trabeculations and deep intertrabecular recesses in the LV were assessed in the parasternal, apical, and short-axis views. The LVEDd and LVESd >2 *z* scores for age and body surface were defined as left ventricular dilatation. The LV ejection fraction (LVEF) (%) was measured using Simpson's method.

We defined the patients according to the LVNC type as isolated (with normal LV size, thickness, and function), hypertrophic (with LV hypertrophy ± depressed systolic function), and dilated (with LV dilation ± depressed systolic function) type.

Cardiac Magnetic Resonance Imaging

Cardiac MRI was performed on a 1.5 Tesla MRI scanner (Magnetom Aera; Siemens Healthcare, Erlangen, Germany). During cardiac MRI examination, the myocardium was divided into 16 segments. Patients whose non-compacted myocardium layer-compacted myocardium layer ratio at the end of diastole was more than 2.3 were diagnosed with LVNC.[7] To analyze whether there is any

relationship between ventricular performance and morphological features, different measures, including compacted myocardial mass (CMM), non-compacted myocardial area (NCMA), distribution of LVNC, left ventricular end-diastolic volume (LVEDv), and left ventricular end-systolic volume (LVESv), and assessment of ventricular wall motion abnormalities were evaluated.

Treatment

The treatments patients received were determined as medications, pacemaker therapy, electrophysiological study ± radiofrequency ablation, and implantable cardioverter-defibrillator (ICD) implantation. An ICD was placed on the patients according to the indications in the current guidelines regarding the treatment of ventricular arrhythmias and the prevention of sudden cardiac death.[8]

Follow-Up

Patients were followed-up in our pediatric echocardiography and arrhythmia outpatient clinics at regular intervals of 3 or 6 months. The ECG was performed on each admission, and Holter monitoring was performed every 6-12 months. Follow-up was defined from the presentation time to the time of the last clinical follow-up or death. In this study, our two primary objectives were;

- to evaluate the features and characteristics of LV non-compaction patients; and
- to determine the effects of low EF (EF < 45%, n=14) on clinical and diagnostic parameters.

The study was planned in accordance with the Declaration of Helsinki after obtaining the required approval from the Ethics Committee of Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, University of Health Sciences (March 2022/2022.03.20).

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences 25 software (SPSS Inc., Chicago, Ill, USA). The study population was divided into 2 groups based on the LV ejection fraction (EF) as EF ≥ 45%, (n=41) and EF < 45% (n=14). One-sample Kolmogorov-Smirnov test was used to test for the normality of the distribution of each continuous variable. Normally distributed variables are expressed as mean ± standard deviation (SD), while non-normally distributed variables were performed using the Mann–Whitney U test and are expressed as median value [interquartile range (IQR)]. The categorical variables are expressed in frequencies and percentages. Pearson's chi-square test and Fisher's exact test were used to compare categorical variables. The cumulative survival curves for all-cause mortality according to the EF group were constructed using the Kaplan–Meier method. A *P*-value < 0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the patients are presented in Table 1.

A total of 55 patients with isolated LVNC were evaluated; 32 patients (58.2%) were male, the median age at

Table 1. The Demographic and Clinical Characteristics of the Patients with LVNC

Clinical Category	All Patients	LV Ejection Fraction ≥ 45%	LV Ejection Fraction <45%	*P*
Number of patients, n (%)	55 (100)	41 (74.5)	14 (25.5)	
Median age (IQR), years	8.5 (0.08-17.9)	8.5 (0.04-17.9)	7.4 (0.08-17.3)	0.678
Median weight (IQR), kg	90 (3-92)	30 (3-92)	26.5 (3.5-65)	0.772
Male gender, n (%)	32 (58.2)	26 (63.4)	6 (42.9)	0.178
Left ventricular non-compaction type				
Isolated, n (%)	32 (58.2)	32 (78)	0	
Dilated, n (%)	20 (36.4)	7 (17.1)	13 (92.9)	**<0.001**
Hypertrophic, n (%)	3 (5.4)	2 (4.9)	1 (7.2)	0.594
Referral symptoms				
None, n (%)	22 (40)	21 (51.2)	1 (7.2)	**0.004**
Palpitation, n (%)	10 (18.2)	9 (22)	1 (7.2)	0.709
Syncope, n (%)	4 (7.3)	4 (9.7)	0	
Cardiac arrest, n (%)	2 (3.6)	2 (4.9)	0	
Fatigue/heart failure, n (%)	16 (29.1)	4 (9.7)	12 (85.7)	**<0.001**
Chest pain, n (%)	1 (1.8)	1 (2.4)	0	
Family history	8 (14.5)	7 (17.1)	1 (7.2)	0.176
Sudden deaths at a young age, n (%)	2 (3.6)	2 (4.8)	0	
Dilated cardiomyopathy, n (%)	5 (9.1)	4 (9.7)	1 (7.2)	0.623
Hypertrophic cardiomyopathy, n (%)	1 (1.8)	1 (2.4)	0	

LVNC, left ventricular non-compaction. Statistically significant parameters are indicated in bold.

presentation was 8.5 years (range, 1 month to 17.9 years), and 13 patients (23.6%) were admitted under the age of 1 year. The median follow-up of the study was 19 months (range, 1-121 months). The main presentation was congestive heart failure in 16 (29%) patients. The EF < 45% group had the highest rate of hospital admission with heart failure symptoms. Palpitation was the second most common initial symptom (n=10, 18.2%) and was seen entirely in children at the age of > 7 years. Two patients presented with resuscitated/aborted cardiac arrest. There was a statistically significant difference between the 2 clinical groups in terms of the LVNC types and having congestive heart failure symptoms at admission (all $P < 0.05$). A total of 22 patients (40%) had no symptoms at admission, and there was a statistically significant difference between the clinical groups. Asymptomatic patients are identified incidentally by echocardiography after referral because of a murmur or familial screening.

Table 2. The Electrocardiographic Characteristics of the Patients with LVNC

Clinical Category	All Patients (n=55)	LV EF ≥ 45%	LV EF <45%	*P*
Electrocardiographic abnormalities, n (%)	43 (78.2)	29 (70)	14 (100)	**0.025**
Right atrial enlargement, n (%)	5 (9.1)	2 (4.8)	3 (21.4)	0.098
P amplitude (mV), mean ± SD	1.6 ± 0.6	1.5 ± 0.5	2.1 ± 0.7	**0.002**
Left atrial enlargement, n (%)	13 (23.6)	5 (12.2)	8 (57.1)	**0.002**
P-wave duration (ms), mean ± SD	78.7 ± 22.4	72.4 ± 20.2	95.8 ± 19.6	**<0.001**
PR duration (ms), mean ± SD (IQR)	138.1 ± 31.9 (80-248)	135.7 ± 31.1 (80-248)	144.7 ± 34.8 (106-214)	0.370
Low QRS voltage, n (%)	6 (10.9)	2 (4.8)	4 (28.6)	**0.031**
Interventricular conduction delay, n (%)	14 (25.5)	9 (21.9)	5 (35.7)	0.313
Fragmented QRS (fQRS), n (%)	6 (10.9)	2 (4.8)	4 (28.6)	**0.031**
Left ventricular hypertrophy, n (%)	12 (21.8)	7 (17.1)	5 (35.7)	0.259
Biventricular hypertrophy, n (%)	1 (1.8)	1 (2.4)	0	
Incomplete right bundle branch block, n (%)	6 (10.9)	3 (7.3)	3 (21.4)	0.165
Left bundle branch block, n (%)	2 (3.6)	1 (2.4)	1 (7.1)	0.448
QRS duration (ms), mean ± SD (IQR)	84.3 ± 20.5 (54-152)	81 ± 16.5 (54-130)	94.3 ± 27.7 (60-152)	0.110
QRS axis, mean ± SD	53.2 ± 41.2	49.2 ± 36.8	65 ± 51.9	0.220
Long QTc interval, n (%)	17 (30.9)	10 (24.4)	7 (50)	0.098
QTc interval (ms), mean ± SD (IQR)	435.6 ± 32.1 (380-530)	432.6 ± 33.9 (380-530)	444.5 ± 25.1 (393-474)	0.234
ST-T changes, n (%)	15 (27.3)	8 (19.5)	7 (50)	0.152
Atrial arrhythmias				
Premature atrial contractions, n (%)	7 (12.7)	6 (14.6)	1 (7.2)	0.624
Sustained atrial tachycardia, n (%)	2 (3.6)	2 (4.9)	0	
Focal atrial tachycardia, n (%)	1 (1.8)	1 (2.4)	0	
Ventricular arrhythmias				
Premature ventricular complexes (PVCs), n (%)	10 (10.8)	7 (17.1)	3 (21.4)	0.355
Polymorphic PVCs, n (%)	3 (5.5)	3 (7.3)	0	
Non-sustained ventricular tachycardia, n (%)	1 (1.8)	1 (2.4)	0	0.329
Sustained ventricular tachycardia, n (%)	8 (14.5)	5 (12.2)	3 (21.4)	
Ventricular fibrillation, n (%)	4 (7.3)	2 (4.9)	2 (14.3)	0.145
Wolff-Parkinson-White (WPW) pattern, n (%)	2 (3.6)	2 (4.9)	0	
Sinus node dysfunction, n (%)	2 (3.6)	2 (4.9)	0	
Heart block				
First-degree atrioventricular block, n (%)	8 (14.5)	4 (9.7)	4 (28.6)	0.181
Second-degree atrioventricular block, n (%)	1 (1.8)	1 (2.4)	0	
Complete atrioventricular block, n (%)	1 (1.8)	1 (2.4)	0	

LVNC, left ventricular non-compaction; PVCs, premature ventricular contractions; SD, standard deviation. Statistically significant parameters are indicated in bold.

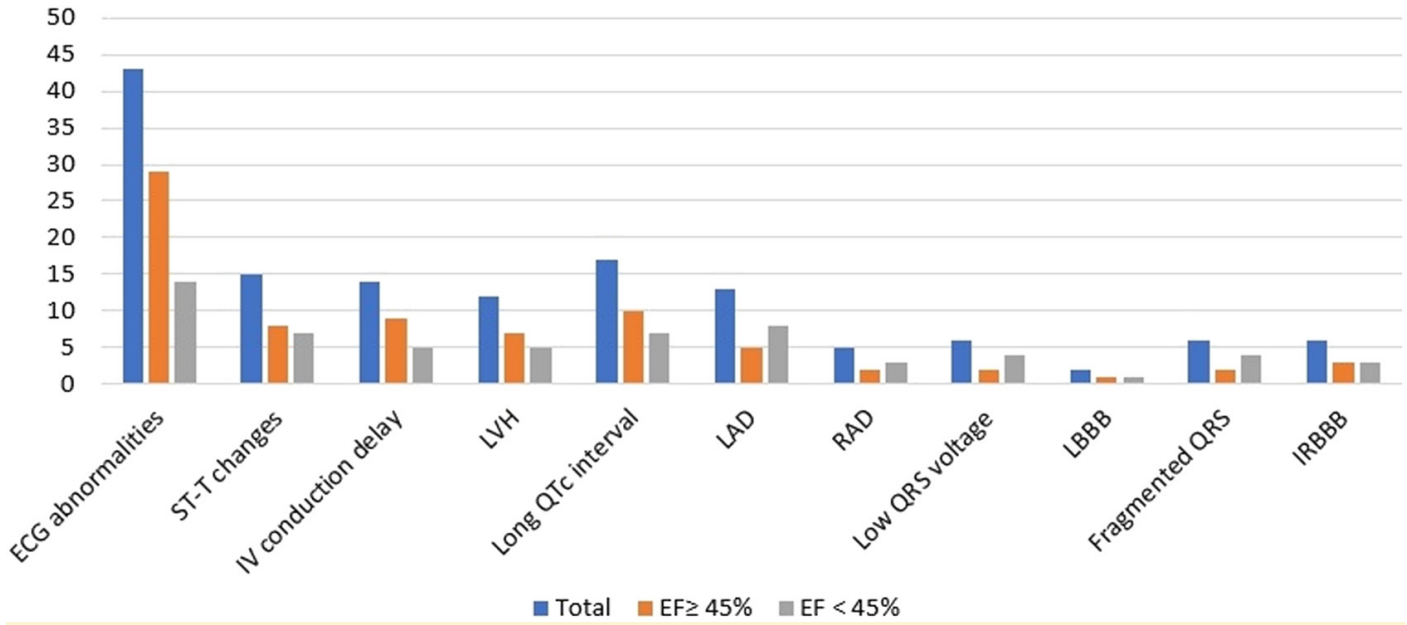

Figure 1. ECG findings of LVNC patients on admission. ECG, electrocardiography; EF, ejection fraction; IRBBB, incomplete right bundle branch block; IV, interventricular; LAD, left atrial dilatation; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; LVNC, left ventricular non-compaction; RAD, right atrial dilatation.

Family History and Diagnostic Evaluation

A review of familial history revealed that 6 patients had sudden cardiac deaths in their families at a young age, and 5 patients had dilated CMPs. Three patients with a family history of sudden death presented with syncope, 1 with palpitation, and 2 were asymptomatic.

Medical records revealed that 32 patients underwent cardiac MRI. The patients' diagnostic tests (echocardiographic and cardiac MRI findings) are presented in Table 2.

Electrocardiographic Findings

Table 2 and Figure 1 present the ECG characteristics and arrhythmias of the patients with LVNC. Forty-three out of the 55 (78.2%) patients with LVNC showed ECG abnormalities at diagnosis. The most frequent findings were T-wave flattening or negative T-waves, ST depression in the inferior and lateral leads, interventricular conduction delay, and LV hypertrophy. Low QRS voltage was detected in 6 patients, left bundle branch block (LBBB) in 2 patients, the Wolff-Parkinson-White (WPW) pattern in 2 patients, and sinus node dysfunction in 1 patient. Fragmented QRS was observed in the ECGs of 6 patients, and the QTc duration was 450 milliseconds and above in 17 patients (30.9%). The mean QTc duration was 435.6 ± 32.1 milliseconds. Eight patients had a first-degree AVB, 1 had a second-degree AVB, and 1 had a complete AVB. On the 24-hour Holter ECG, PACs were observed in 4 patients, supraventricular tachycardia (SVT) in 2, and focal atrial tachycardia in 1 patient. Premature ventricular contractions (PVCs) were observed in 10 patients (polymorphic, n=3), non-sustained VT in 1, and sustained VT in 8 patients on ECG and Holter monitoring. Ventricular fibrillation developed in half of the 8 patients with sustained VT. Standard ECG and Holter ECG findings were normal in 12 (21.8%) patients at diagnosis. The P-wave duration (mm), left atrial enlargement (LAE), P-wave amplitude (mm), low QRS voltage (%), and fragmented QRS (%) were found to be statistically different among the 2 clinical groups (all $P < 0.05$). No statistically significant correlations were found between the other ECG findings or arrhythmias (all $P > 0.05$). Figure 2A and Figure 2B show examples of ECG and Holter recording.

Echocardiographic and Cardiac Magnetic Resonance Imaging Findings

The echocardiographic and cardiac MR findings of the patients with LVNC are presented in Table 3. Excessive left ventricular trabeculation and deep intertrabecular recesses were detected with echocardiography in all of the patients (Figures 2c and 2d). Both ventricles were involved in 1 patient, and none of the patients had RV involvement without LV. Non-compaction was more evident in the LV apex and free wall myocardium. Ten patients (18.2%) had LV dysfunction (EF < 45%) at admission, and in 4 patients' EF progressively decreased during follow-up. The mean end-systolic LV ratio of non-compacted to compacted myocardium was 2.5 (2.1-5.5), and the mean EF was 58.8% (28%-78%). Echocardiographic parameters (*z* scores of the LVEDd and LVESd) were identified to have increased in the EF < 45% group. There was a significant difference between the 2 groups according to the echocardiographic findings [LVEDd (*z* score), LVESd (mm), LVESd (*z* score), EF (%)] (all $P < 0.05$). Although ECG abnormalities were more common in the EF < 45% group, atrial and ventricular arrhythmias (including VF) were found in similar frequencies in both groups. Intracardiac thrombus was detected in 4 patients with LVEDd *z* scores >2 (3 of them were in the EF < 45% group) during follow-up; however, no embolic event developed in any of them.

The functional and morphological cardiac MRI findings are demonstrated in Tables 3 and 4. The median EF was 57.5%

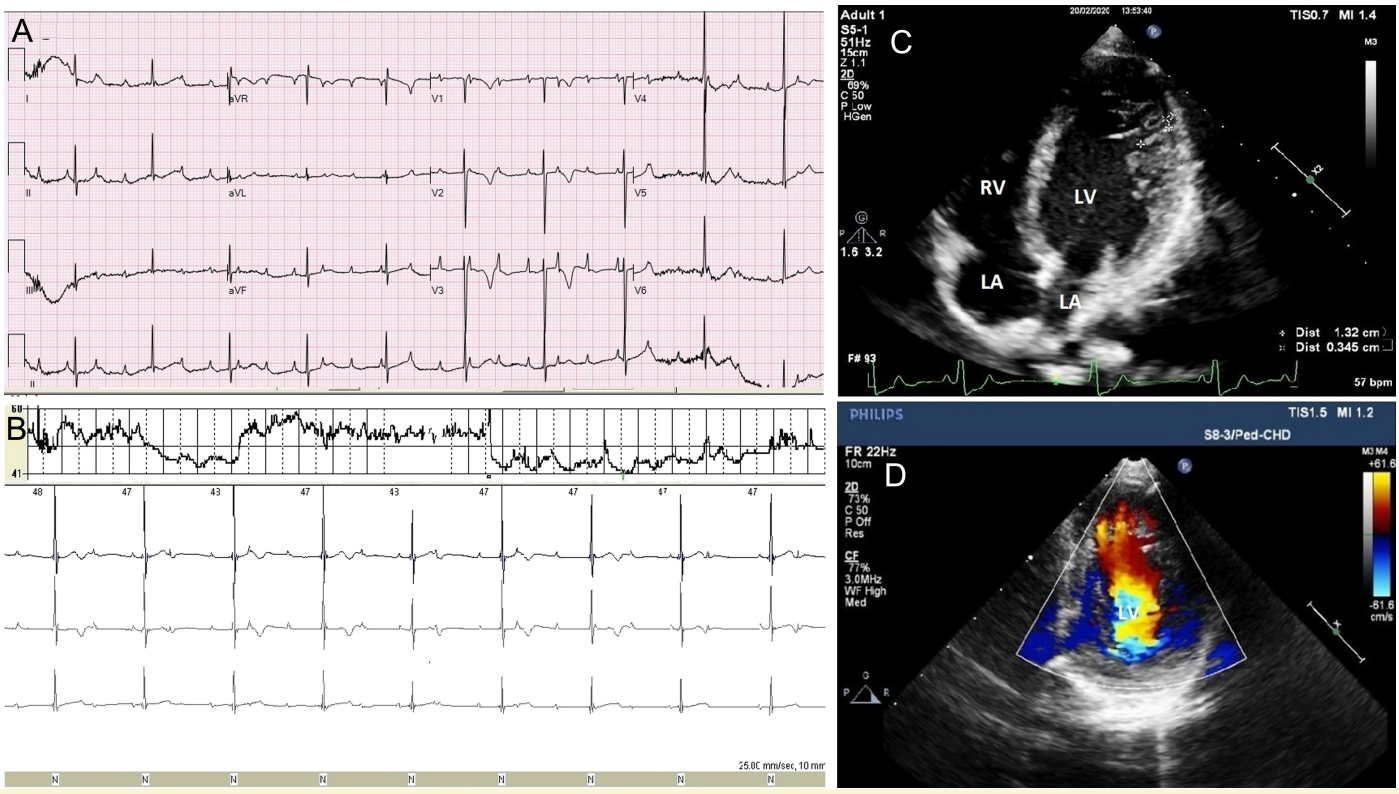

Figure 2. (A) The surface ECG image of a patient with LVNC and complete AVB. (B) The 24-h Holter image of the patient with LVNC and complete AVB. (C) Echocardiographic image of a patient with left ventricular non-compaction. (D) Echocardiographic image of a patient with prominent trabeculations and deep intertrabecular recesses filled with blood. AVB, atrioventricular block; ECG, electrocardiography; LA, left atrium; LV, left ventricular; LVNC, left ventricular non-compaction; RA, right atrium; RV, right ventricular.

(ranging from 38% to 78%), and only 5 patients had a decreased EF (<53%). Only one patient had late gadolinium enhancement (LGE), and one had wall motion abnormalities.

Genetic Testing

In this study, genetic testing was possible in 10 patients. Pathological mutations were detected in 4 patients as Alström syndrome (n=2), long QT syndrome (n=1), ACTN2, and LAMA4 gene mutation (n=1). Genetic result of one patient has not yet been obtained and was reported as normal in 5 patients.

Management and Follow-Up

The treatment strategies of the patients are summarized in Table 3. Antiaggregant doses of acetylsalicylic acid and anticongestive therapy were given to patients with left ventricular dilatation. Of the 55 patients with LVNC, 12 patients (21.8%) received antiarrhythmic drug (AAD) therapy and 3 patients received combined AAD therapy with 2 drugs. Anticongestive, acetylsalicylic acid, and amiodarone usage were higher in the EF < 45% group. Four patients underwent an electrophysiological study (EPS). One patient underwent WPW accessory pathway ablation, 1 of them had VT ablation, 1 had Purkinje fiber RF ablation, and 1 underwent focal atrial tachycardia ablation. Implantable cardioverter-defibrillators were placed in a total of 6 patients to prevent sudden cardiac death, and 4 patients received the device for primary prevention. One patient with a complete AVB and 1 patient with long QT syndrome and severe bradycardia underwent permanent pacemaker implantation.

The overall mortality of pediatric LVNC was 9.1% (n=5). Four of the patients in the EF < 45% group died of heart failure, and 1 patient in the EF ≥ 45% group who had long QT syndrome died suddenly at another center. The Kaplan–Meier curve for long-term all-cause mortality according to the EF group (EF ≥ 45%, EF < 45%) in the entire population of patients is shown in Figure 3 (P=0.001). Mortality data are shown in Figure 2. The death ratio was observed to be higher in the dilated CM type. There was a significant difference in mortality among these groups (P=.012).

Discussion

The results of this study describe the clinical characteristics, ECG, and echocardiographic findings of 55 pediatric patients with isolated LVNC from a tertiary cardiac center. To the best of our knowledge, although there are some studies on LVNC,[4,9-11] this is the most extensive study to report about pediatric LVNC evaluated with clinical groups from our country.

Left ventricular non-compaction has a heterogeneous clinical presentation ranging from asymptomatic to arrhythmias and sudden cardiac death. Brescia et al[12] reported that 60 patients (25%) presented with symptoms of congestive heart failure,

Table 3. The Diagnostic Tests and Treatment Strategies of the Patients with LVNC

	Total (n=55)	LV EF ≥ 45% (n=41)	LV EF <45% (n=14)	*P*
Echocardiographic findings				
LVEDd (mm), mean ± SD	41.7 ± 10.7	40 ± 9.3	46.8 ± 13.1	0.089
LVEDd (*z* score), mean ± SD	1.3 ± 2.1	0.5 ± 1.3	3.6 ± 2.3	**<0.001**
LVESd (mm), mean ± SD	28 ± 10	25.1 ± 7.6	36.6 ± 11.5	**0.003**
LVESd (z score), mean ± SD	1.6 ± 2.2	0.6 ± 1.4	4.3 ± 2.1	**<0.001**
LV EF (%), mean ± SD	58.8 ± 15.5	65.8 ± 10.8	38.2 ± 4.9	**<0.001**
NC/C ratio, mean ± SD	2.5 ± 0.7	2.5 ± 0.7	2.4 ± 0.4	0.600
Left atrial dilatation, n (%)	21 (38.2)	7 (17.1)	14 (100)	**<0.001**
Left ventricular dilatation, n (%)	23 (41.8)	9 (21.9)	14 (100)	**<0.001**
Left ventricular hypertrophy, n (%)	4 (7.3)	3 (7.3)	1 (7.2)	
Biventricular hypertrophy, n (%)	1 (1.8)	1 (2.4)	0	
NC localization				
LV apex, n (%)	4 (7.3)	3 (7.3)	1 (7.1)	0.735
LV free wall, n (%)	18 (32.7)	13 (31.7)	5 (35.7)	0.514
LV apex+free wall, n (%)	33(60)	25 (60.9)	8 (57.1)	0.800
Biventricular, n (%)	1 (1.8)	1 (2.4)	0	
Thrombus, n (%)	4 (7.3)	1 (2.4)	3 (21.4)	**0.047**
Cardiac MRI, n (%)	16 (29.1)	14 (34.1)	2 (14.3)	
LVEDv, mL/m^2	76.5 (58-145)	76.5 (66-95)	101.5 (58-145)	
LVESv, mL/m^2	32 (19-90)	32 (19-45)	59 (28-90)	
LV EF (%), median (IQR)	56.5 (30-78)	57.5 (50-78)	44.5 (38-51)	
NC/C ratio, median (IQR)	3.5 (2.5-6.2)	3.4 (2.5-4.3)	5.6 (5-6.2)	
CMM, g/m^2	42 (25.3-126)	42 (25.3-69.8)	76.3 (26.7-126)	
NCMA, cm^2/m^2	39.6 (12.5-75)	39.6 (17.6-75)	40.2 (12.5-68)	
Wall motion abnormalities, n (%)	1 (6.2)	1 (7.1)	0	
LGE, n (%)	1 (6.2)	1 (7.1)	0	
Treatment				
Medications, n (%)	35 (63.6)	21 (51.2)	14 (100)	**0.001**
Acetylsalicylic acid, n (%)	31(56.4)	18 (43.9)	13 (92.9)	**0.001**
Anticongestive, n (%)	21 (38.2)	7 (17.1)	14 (100)	**<0.001**
Beta blocker, n (%)	6 (10.9)	6 (14.6)	0	
Amiodarone, n (%)	4 (7.3)	1 (2.4)	3 (21.4)	**0.047**
Amiodarone+ mexiletine, n (%)	2 (3.6)	1 (2.4)	1 (7.1)	0.448
Flecainide, n (%)	1 (1.8)	1 (2.4)	0	
Flecainide+propafenone, n (%)	1 (1.8)	1 (2.4)	0	
Pacemaker, n (%)	2 (3.6)	2 (4.9)	0	
ICD, n (%)	6 (11)	4 (9.8)	2 (14.3)	0.638
EPS, n (%)	4 (7.3)	4 (9.8)	0	
Death, n (%)	5 (9.1)	1 (2.4)	4 (28.6)	**0.012**
Median follow-up period (months), median (IQR)	19 (1-121)	24 (1-121)	10 (1-56)	**0.038**

CMM, compacted myocardial mass; EF, ejection fraction; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVEDd, left ventricular end-diastolic diameter; LVEDv, left ventricular end-diastolic volume; LVESd, left ventricular end-systolic diameter; LVESv, left ventricular end-systolic volume; LVNC, left ventricular non-compaction; NC/C, non-compacted myocardium layer-compacted myocardium layer ratio; NCMA, non-compacted myocardial area; SD, standard deviation.
Statistically significant parameters are indicated in bold.

Table 4. Morphological and Cardiac Functional Findings of Patients with LVNC on Cardiac MRI

Patients	EF (%)	EF < 53%	LGE	NC/C	Wall Motion Abnormalities	Number of Segments with NC
1	67	No	Negative	4.3	No	10
2	56	No	Negative	3.4	No	8
3	70	No	Negative	2.6	No	9
4	54	No	Negative	2.5	No	10
5	57	No	Negative	3.2	No	8
6	56	No	Negative	3.4	No	12
7	50	**Yes**	Negative	3.8	No	12
8	52	**Yes**	Negative	4.3	No	8
9	52	**Yes**	**Positive**	2.7	No	7
10	63	No	Negative	3.9	No	6
11	68	No	Negative	3.6	No	6
12	58	No	Negative	3.2	No	10
13	78	No	Negative	4.3	No	11
14	38	**Yes**	Negative	5	No	5
15	51	**Yes**	Negative	6.2	No	10
16	66	No	Negative	3.3	**Yes**	10

EF, ejection fraction; LGE, late gadolinium enhancement; NC/C, non-compacted myocardium layer-compacted myocardium layer ratio.
Statistically significant parameters are indicated in bold.

5 presented with aborted sudden death, and an additional 12 were referred for evaluation of unexplained syncope. In our study, 16 patients (29%) presented primarily with signs and symptoms of congestive heart failure, and palpitations were the second most common initial symptom (n=10, 18.2%). Besides this, 4 patients were admitted with syncope and 2 with resuscitated/aborted cardiac arrest. Because it is characterized by excessive trabeculae, deep intertrabecular recesses, and thickening of the myocardium in 2 layers as compacted and non-compacted, the left ventricular may demonstrate impaired systolic function, with or without dilatation.[13] Pignatelli et al[1] reported an LVEF value of 30% at admission. Brescia et al[12] identified ventricular systolic dysfunction in 62% (n=150) of LVNC patients. In the present study, 14 patients' EF was < 45%, and 41 patients' was ≥ 45%.

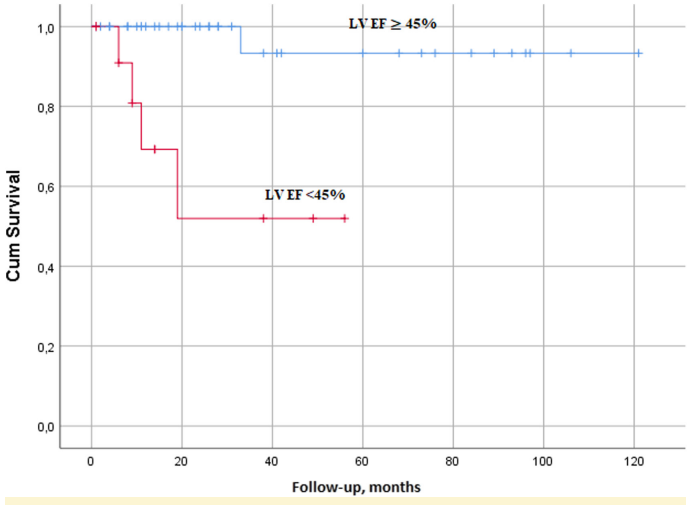

Figure 3. The Kaplan–Meier curve for long-term all-cause mortality. EF, ejection fraction.

A variety of ECG abnormalities and arrhythmias have been reported in patients with LVNC, and the frequency of ECG abnormalities was reported as 75%-100%.[1,4,12] Our study found it to be 78.2% (n=43). Ergul et al[4] demonstrated that the most frequent ECG finding was ST-T wave changes and T-wave inversion as in our study (27.3%, n=17). Left ventricular non-compaction can also be present with bundle branch blocks, arrhythmias, WPW syndrome, and atrioventricular conduction defects such as complete AVB. In the present study, patients had prolonged PR intervals (n=10) and slightly wide QRS (n=16) on their ECGs. Howard et al[14] described that WPW syndrome was found in 10% of patients with LVNC, and patients with associated LVNC and WPW had a higher risk of cardiac dysfunction. In our study, 2 patients (3.6%) had WPW syndrome and normal cardiac functions. Ventricular tachycardia and ventricular fibrillation, potentially fatal arrhythmias, are critical features of the disease. The pediatric study by Chin et al[13] showed the VT rate to be up to 38%, Brescia et al[12] reported 42 patients (17%) had VT, and Ozgur et al[10] detected one patient (3%) with VT. In a study by Stanton et al.[15] VT (sustained or non-sustained) was noted in 4 (13.3%) patients. In our study, the incidence of ventricular arrhythmias was 23.6% (n=13), the sustained VT frequency rate was 14.5% (n=8), and the non-sustained VT rate was 1.8% (n=1). It was observed that the frequency of ventricular arrhythmias was independent of reduced EF. Therefore, we suggest that the first presentation in LVNC patients may be with arrhythmias, and there might be an electrical phase of the disease before EF decreases. Six patients (10.9%) had fragmented QRS, a marker of depolarization abnormality. fQRS is related to myocardial fibrosis or dysfunction in patients with coronary artery

disease, dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy, and some congenital heart diseases such as tetralogy of Fallot.[16-20] Regions of myocardial fibrosis may produce slow and disorganized conduction, and the QRS morphology in the leads overlying fibrotic area may be altered. An increased risk of sudden cardiac death associated with fQRS has been documented in patients with hypertrophic cardiomyopathy (HCM) and tetralogy of Fallot.[19-21] Debonnaire et al[21] reported that both fQRS and QTc duration are associated with SCD in HCM patients, incremental to conventional SCD risk factors. The correlation between fQRS and tetralogy of Fallot or HCM may also be present in LNVC patients. Fragmented QRS in LVNC might be a result of subendocardial ischemia and fibrosis.[22] In Ning et al's[22] study, they conclude that the existence of fQRS on a 12-lead ECG in LVNC patients was associated with a decreased time to death. Care should be taken regarding ventricular tachyarrhythmias and SCD development in these patients.

Prolongation of the QT interval on the surface ECG results from transmural myocardial repolarization dispersion with action potential prolongation in the medial layer.[23] It can be caused by several possible genetic defects of the cardiac ion channels or in response to various drugs. Prolongation of the QT interval can also accompany underlying heart diseases such as HCM, DCM, LVNC, or heart failure. Manoach et al[24] suggested that the prolongation of the QT interval might result from delayed or incomplete differentiation of myocardial cells. Fein et al[25] demonstrated a correlation between the persistence of undifferentiated myoblasts and the prolonged QT interval in the electrocardiogram of mice and rats. The interlayer differentiation (2 distinct layers consisting of compacted and non-compacted myocardial tissue) is well known in LVNC. Disease-mediated reduction in the repolarizing current of cardiac cells can lead to prolongation of the QT interval,[23] and prolongation of the QT interval is associated with a high risk of ventricular tachyarrhythmias. We can suppose that layer alterations in LVNC also have an effect on the pathogenesis of QT prolongation. Concomitant QT prolongation has been reported in patients with LVNC.[26-29] In the present study, 17 patients (30.9%) had prolonged QTc intervals on their ECGs, which is a common ECG abnormality in LVNC patients.

Nascimento et al[30] described a patient with a complete AVB requiring placement of a permanent pacemaker as a first manifestation of LVNC. Similarly, a case of a patient diagnosed with non-compaction after the occurrence of a complete AVB with syncope was described by Jackson et al.[31] We detected a complete AVB in 1 patient (1.8%).

Although echocardiography provides good acoustic windows in children, CMR should be performed to confirm the diagnosis of LVNC in pediatric patients. Magnetic resonance imaging allows for a comprehensive assessment of the heart, including accurate measurement of cardiac function, cardiac volumes, CMM, NCMM, and more detailed visualization and analysis of all segments of the ventricles, which may be difficult using echocardiography. Furthermore, MRI allows us to perform myocardial viability, which is not possible with echocardiography. However, it is not clear that all these data benefit us on the prognosis of the disease. Although in the adult population it has been found that the NC/C ratio and NCMA are well correlated with systolic dysfunction, these relations have not been established in children. Unfortunately, our data are not sufficient to connect MRI findings and prognosis.[32]

Recent articles reported that sudden death rates of patients with LVNC were in the range of 1-22%.[1,9,10,12,13,33] Pignatelli et al[1] reported a death rate of 22% for a follow-up period of an average of 3.2 years. In Brescia et al's[12] report, 242 patients were evaluated, and the death rate was identified as 12.8%. In our study, the death rate was determined as 9.1%, similar to the previously reported results.

Study Limitations

This study had several limitations. Our analysis was performed in a tertiary center and evaluated the patients with LVNC through retrospective reviews. Over the years, our awareness of this disease was heightened. Additionally, as a developing country, since cardiac MRI could not be performed routinely in our clinic before 2015, the patients who were diagnosed before do not have MRI results. Moreover, genetic screening could not be performed in most patients.

Conclusion

Left ventricular non-compaction has heterogeneous clinical findings in childhood, ranging from asymptomatic to sudden death. Ventricular arrhythmias or cardiac dysfunction are associated with increased mortality. Arrhythmias can be seen frequently in different types at every stage of the disease. Congestive heart failure clinic may develop in patients during follow-up. It is essential to follow-up with the patients closely for the development of ventricular dysfunction or arrhythmias due to the progressive course of the disease. Further studies are needed since life-threatening ventricular arrhythmias can be seen, also in patients with preserved EF.

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