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ORIGINAL ARTICLE

Evaluation of genetic, clinical features, and prognosis in pediatric patients diagnosed with cardiomyopathy.

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Abstract

BACKGROUND: Pediatric cardiomyopathy (PCM) comprises a genetically heterogeneous, high risk group of myocardial disorders and is a leading cause of pediatric heart failure and transplantation. Genotype–phenotype correlations and outcome data remain limited, particularly in populations with high consanguinity.
METHODS: We conducted a retrospective cohort study of 53 children with cardiomyopathy classified as hypertrophic (HCM), dilated (DCM), left ventricular noncompaction (LVNC), or restrictive cardiomyopathy (RCM). We analyzed demographics, consanguinity, echocardiographic parameters, genetic testing results (available in 26/53 patients, 49.1%), device therapy, transplantation, and mortality.
RESULTS: The cohort included 20 HCM (37.7%), 17 DCM (32.1%), 13 LVNC (24.5%), and 3 RCM (5.7%) patients, with a median age at diagnosis of 6.5 years (interquartile range [IQR] 2.0–10.0). Consanguinity was documented in 24 of 53 patients (45.3%). A pathogenic or likely pathogenic (P/LP) variant was identified in 9 of 26 tested patients (34.6%), corresponding to 17.0% of the total cohort (9/53). When variants of uncertain significance (VUS) are included, 20 of 26 tested patients (76.9%) harbored at least one rare variant; however, 11 of these 20 findings (42.3% of tested patients) were VUS, which are not counted toward diagnostic yield and remain subject to reclassification. Baseline ejection fraction was markedly reduced in DCM (median 35%, IQR 28–37%), whereas HCM and RCM had preserved systolic function at diagnosis. During a median follow up of 3.0 years, 15 patients (28.3%) underwent implantable cardioverter defibrillator implantation, 6 (11.3%) underwent heart transplantation, and 18 (34.0%) died; mortality was highest in DCM (58.8%) and RCM (66.7%).

CONCLUSION: Among the 26 of 53 patients who underwent genetic testing, PCM in this cohort showed a P/LP diagnostic yield of 34.6% (9/26) and substantial mortality, particularly in DCM and RCM phenotypes. High consanguinity was associated with a notable P/LP yield and a frequent VUS burden; whether consanguinity contributes to earlier or more severe disease requires confirmation in larger, prospective studies. These findings support offering comprehensive genetic testing to pediatric cardiomyopathy patients, especially in high consanguinity settings, to enable molecular diagnosis and structured family counseling. In this cohort, a substantial proportion of tested patients had P/LP variants, and many others carried VUS that will require ongoing re evaluation. Future prospective studies should assess how specific genetic findings, combined with imaging and functional parameters, can be incorporated into validated risk stratification and management algorithms.

INTRODUCTION

Cardiomyopathies represent a diverse collection of myocardial disorders that compromise cardiac function, leading to potential heart failure, arrhythmias, and sudden cardiac death, particularly in the pediatric population where they are associated with poorer outcomes despite their rarity (Alakhfash *et al.* 2024). These conditions can be inherited or arise de novo, necessitating comprehensive genetic and clinical evaluation (Lee *et al.* 2025; Popa-Fotea *et al.* 2020). The intricate genetic landscape underlying pediatric cardiomyopathies often involves a wide array of genes, with mutations in TNNI3 and MYH7 frequently implicated in restrictive and hypertrophic cardiomyopathy, respectively (Yuan *et al.* 2024). Given that nearly 40% of symptomatic pediatric cardiomyopathy patients face heart transplantation or mortality within two years post-diagnosis, understanding the genetic underpinnings is critical for early intervention and improved prognostic assessment (Lipshultz *et al.* 2019).

Pediatric cardiomyopathy is the third leading cause of cardiac death in children in the United States, accounting for 20–35% of cases, with etiologies spanning inherited sarcomeric mutations, cytoskeletal defects, and acquired triggers such as viral myocarditis and neurometabolic disorders (Rosamilia *et al.* 2023; Chung *et al.* 2017). Despite advances in genetic testing that have improved genotype–phenotype characterization, outcome data from high-consanguinity populations — where autosomal recessive and syndromic forms may predominate — remain scarce (Lipshultz *et al.* 2019; Westphal *et al.* 2022).

This study aimed to characterize the genetic diagnostic yield, genotype–phenotype correlations, arrhythmia burden, and clinical outcomes — including transplantation and mortality — across four cardiomyopathy subtypes (HCM, DCM, LVNC, RCM) in a single-center pediatric cohort with a high prevalence of consanguinity, and to evaluate whether consanguinity and genetic positivity are associated with adverse outcomes.

MATERIALS AND METHODS

Study design and population

We conducted a retrospective review of 53 pediatric patients diagnosed with cardiomyopathy between 2014 and 2025. Transthoracic echocardiography (TTE) was used for initial diagnosis and follow-up in all patients. Cardiac MRI, diagnostic catheter angiography, and endomyocardial biopsy were performed in selected cases (n = 12 for CMR; n = 4 for biopsy); however, given the limited and non-uniform availability of these data across the cohort, their findings are not systematically reported and were not incorporated into outcome modelling. ICD implantation was performed according to institutional protocols based on current pediatric heart failure and arrhythmia guidelines, with indications including sustained ventricular tachycardia or fibrillation (secondary prevention), severely reduced ejection fraction with high-risk morphological features, or syncope with high-risk genotype (primary prevention). The specific indication for each patient is not individually reported due to the retrospective design. Genetic testing was performed in 26 of 53 patients (49.1%). Testing modalities included cardiomyopathy gene panels and, in later years, exome-based assays. All tests were conducted in accredited clinical laboratories. Variants were classified as pathogenic, likely pathogenic, or of uncertain significance according to contemporary ACMG/AMP criteria, based on population frequency, in silico prediction, segregation (when available), functional data, and published literature. For this analysis, 'diagnostic yield' was defined strictly as the proportion of tested patients with at least one P/LP variant; VUS were reported separately and were not counted as diagnostic. Special attention was given to family history to identify inherited patterns of cardiomyopathy. Consanguinity was defined as a known union between first- or second-degree relatives and was ascertained by structured parental interview or chart documentation. Cardiomyopathy subtypes were classified according to the American Heart Association scientific statement (Lipshultz *et al.* 2019). Given the retrospective chart review design, individual informed consent was waived by the Institutional Review Board (KA 26/06).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation or median (interquartile range), depending on distribution. Categorical variables were presented as frequencies

and percentages. Given the retrospective design and limited sample size, analyses were primarily descriptive in nature. Comparisons among cardiomyopathy subtypes were intended using one-way analysis of variance (ANOVA) for normally distributed continuous variables and the Kruskal–Wallis test for non-normally distributed variables; however, given the small and unequal subgroup sizes — particularly RCM (n = 3) — formal between-group p-values were not computed and all subtype comparisons in this report are descriptive only. These analyses are planned for a prospective follow-up study with adequate power.

Ethics

The study was approved by the Başkent University Institutional Review Board (Project No: KA 26/06). The study was conducted in accordance with institutional policies for retrospective chart reviews.

RESULTS

A total of 53 pediatric patients with cardiomyopathy were included in the cohort. The distribution by subtype is detailed in Table 1; HCM was most common (n = 20, 37.7%), followed by DCM (n = 17, 32.1%), LVNC (n = 13, 24.5%), and RCM (n = 3, 5.7%).

The median age at diagnosis for the overall cohort was 6.5 years (IQR 2.0-10.0), and the median follow-up duration was 3.0 years (IQR 2.0-7.0). Age at diagnosis varied by subtype, with earlier presentation in LVNC and RCM [2.0 (0.1-6.0) and 1.0 (0.7-3.0) years, respectively], compared with HCM and DCM [8.0 (3.2-10.0) and 10.0 (7.0-12.0) years, respectively]. Between-subtype differences in age at presentation and ejection fraction are illustrated in Figure 1.

Baseline left ventricular ejection fraction (EF) was lowest in the DCM group (35.0%, IQR 28.0-37.0) and highest in the HCM and RCM groups. In the overall cohort, median EF increased from 51.0% (IQR 35.0-69.0) at diagnosis to 61.0% (IQR 47.5-68.0) at last follow-up. Improvement in EF was most apparent descriptively in the DCM and LVNC subgroups, whereas EF remained relatively stable in HCM.

Consanguinity was documented in 24 of 53 patients (45.3%); because some patients belong to the same families, this percentage refers to patient-level consanguinity rather than independent families. A history of an affected sibling was present in 15 of 53 patients (28.3%). Consanguinity was most frequently recorded in HCM (55.0%) and RCM (66.7%), although the RCM subgroup comprised only three patients and these proportions should be interpreted with caution.

Genetic testing data showed substantial heterogeneity. Genetic testing results were available for 26 of 53 patients (49.1%). Among tested patients (n = 26): 9 (34.6%) carried P/LP variants, 11 (42.3%) carried VUS, and 6 (23.1%) had negative results. The P/LP diagnostic yield was 9/53 (17.0%) of the full cohort; including

Tab. 1. Baseline and follow-up clinical characteristics of 53 pediatric patients with cardiomyopathy, stratified by subtype. Continuous variables are presented as median (interquartile range); categorical variables as n (%). The column "Genetic positive/variant" includes patients with pathogenic, likely pathogenic, or variants of uncertain significance (VUS) identified on completed genetic testing; patients with testing not performed, pending, or unrecorded are not included in this count. EF at last follow-up reflects the most recent available echocardiographic assessment prior to death, transplantation, or end of follow-up. No formal between-group statistical comparisons are presented; subgroup differences are descriptive only.

Subtype	n	Age at diagnosis, y	Follow-up, y	Baseline EF, %	Last EF, %	Consanguinity, n (%)	Consanguinity, n (%)	P/LP variant, n (%)	VUS, n (%)	ICD, n (%)	Transplant, n (%)	Deaths, n (%)
Overall	53	6.5 (2.0-10.0)	3.0 (2.0-7.0)	51.0 (35.0-69.0)	61.0 (47.0-68.0)	24 (45.3)	15 (28.3)	9 (17.0)	11 (20.8)	15 (28.3)	6 (11.3)	18 (34.0)
HCM	20	8.0 (3.2-10.0)	5.5 (2.8-11.2)	70.0 (59.5-76.0)	68.0 (62.0-75.0)	11 (55.0)	7 (35.0)	5 (25.0)	4 (20.0)	8 (40.0)	0 (0.0)	4 (20.0)
DCM	17	10.0 (7.0-12.0)	2.0 (0.3-6.0)	35.0 (28.0-37.0)	42.0 (32.0-56.0)	6 (35.3)	4 (23.5)	2 (11.8)	1 (5.9)	6 (35.3)	3 (17.6)	10 (58.8)
LVNC	13	2.0 (0.1-6.0)	2.0 (2.0-4.0)	47.0 (42.0-56.0)	60.0 (53.0-63.0)	5 (38.5)	2 (15.4)	2 (15.4)	5 (38.5)	1 (7.7)	1 (7.7)	2 (15.4)
RCM	3	1.0 (0.7-3.0)	2.0 (1.1-2.0)	70.0 (64.0-71.5)	68.0 (62.5-69.0)	2 (66.7)	2 (66.7)	0 (0.0)	1 (33.3)	0 (0.0)	2 (66.7)	2 (66.7)

Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; LVNC, left ventricular noncompaction; RCM, restrictive cardiomyopathy; EF, left ventricular ejection fraction (%); ICD, implantable cardioverter defibrillator; IQR, interquartile range; n, number of patients.

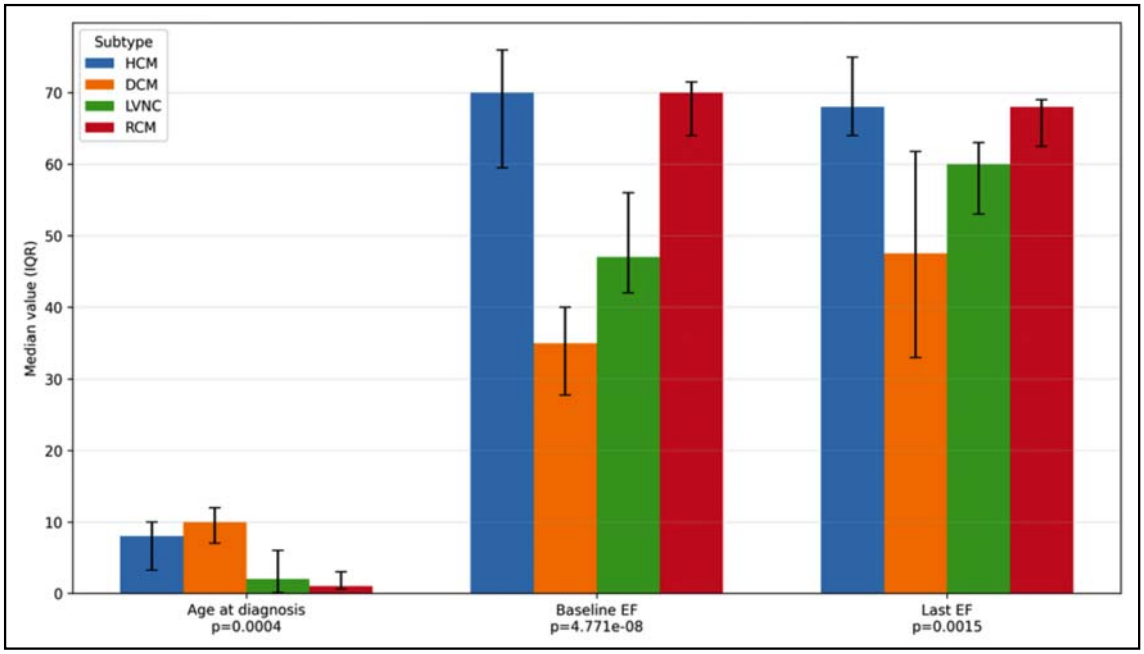

Fig. 1. Between-subtype comparison of continuous clinical variables in pediatric cardiomyopathy (n = 53). Grouped bar chart displaying median values with interquartile range (IQR) error bars for three variables — age at diagnosis (years), baseline left ventricular ejection fraction (EF, %), and last recorded EF (%) — stratified by cardiomyopathy subtype. *Abbreviations:* DCM, dilated cardiomyopathy; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; LVNC, left ventricular noncompaction; RCM, restrictive cardiomyopathy

VUS, the broader yield was 20/26 (76.9%) among those tested. Recurrent findings included MYBPC3, TTN, PTPN11, and DSP variants (Table 2).

Fifteen of 53 patients (28.3%) underwent ICD implantation according to institutional protocols (Table 1). The specific arrhythmia indication per patient is not individually reported; documentation of VT/VF was noted across subtypes, particularly in HCM (8/20, 40.0% with ICD) and DCM (6/17, 35.3% with ICD). Heart transplantation was performed in 6/53 patients (11.3%), most frequently in RCM (2/3, 66.7%) and DCM (3/17, 17.6%).

At last follow-up, 35/53 patients (66.0%) were alive and 18/53 (34.0%) had died. Mortality was highest in the DCM subgroup (10/17, 58.8%) and RCM subgroup (2/3, 66.7%), while lower mortality was observed in HCM (20.0%) and LVNC (15.4%). In exploratory univariate logistic regression analyses, DCM subtype and baseline EF <40% were associated with higher odds of mortality. Compared with other subtypes, DCM was associated with an approximate five-fold increase in mortality (odds ratio 4.99; 95% CI 1.40–17.8; $p = 0.013$), and baseline EF <40% was associated with an odds ratio of 4.50 (95% CI 1.20–16.9; $p = 0.026$). Other candidate predictors did not reach statistical significance in this small cohort (Figure 2). No multivariable models were constructed, given the limited number of events relative to predictors.

Pharmacological therapy data were not systematically extracted in this retrospective review; treatment regimens varied by subtype, era, and referring center and are not individually reported.

DISCUSSION

In this single-center retrospective pediatric cardiomyopathy cohort, we observed a substantial genetic burden, high consanguinity rates, and persistently elevated mortality, particularly among children with dilated and restrictive phenotypes. These findings are consistent with the paradigm that pediatric cardiomyopathy is not merely a phenotypic classification of myocardial dysfunction, but rather a genetically driven, molecularly heterogeneous disease spectrum with significant prognostic implications, though the descriptive and single-center nature of the present analysis limits the strength of this reinforcement. These results highlight the critical need for standardized protocols in genetic testing and counseling to ensure equal access and consistent diagnostic accuracy for pediatric patients. The underrepresentation of diverse ancestries in genetic reference databases may affect variant interpretation in populations such as ours; the majority of this cohort is of Middle Eastern/Turkish origin with high consanguinity, a demographic rarely represented in large cardiomyopathy sequencing datasets, which may explain part of the high VUS rate observed here (11/26 tested patients, 42.3%).

Descriptive patterns in our cohort suggest an association between genetic positivity and phenotype severity: HCM patients had the highest rate of genetic

Tab. 2. Genetic variants identified in 20 pediatric patients with available positive or variant-of-uncertain-significance (VUS) genetic testing results, out of 53 total patients in the cohort. Six patients with negative genetic testing results are not displayed. Variant nomenclature follows HGVS (Human Genome Variation Society) standards. Variant classification follows ACMG/AMP 2015 five-tier criteria: Pathogenic, Likely Pathogenic, or Variant of Uncertain Significance (VUS). VUS were not counted toward diagnostic yield. Where multiple variants are listed for a single Case ID, all variants were identified in the same patient. Inheritance pattern reflects the established mode for the reported gene, not confirmed segregation in the proband's family.

Case ID	Subtype	GENE	Inheritance	Variant	Zygosity	Variant Classification
1	HCM	PTPN11	AD	c.836A>G p.Y279C	Heterozygous	Pathogenic
2	HCM	PTPN11	AD	c.836A>G p.Y279C	Heterozygous	Pathogenic
3	LVNC	RYR2	AD	c.848+1G>A (p.Met2827Ile)	Heterozygous	Pathogenic
4	DCM	MYBPC3	AD, AR	c.2504G>T p.R835L	Heterozygous	Likely Pathogenic
				c.785C>T p.T262I	Heterozygous	Variant Of Uncertain Significance
5	LVNC	KCNH2	AD	c.2908G>A p.G970R	Heterozygous	Variant Of Uncertain Significance
6	HCM	PRKAG2	AD	c.617C>T p.P206L	Heterozygous	Variant Of Uncertain Significance
		MYBPC3	AD, AR	c.814C>T p.R272C	Heterozygous	Variant Of Uncertain Significance
7	LVNC	ABCC9	AD, AR	c.497G>A p.R166H	Heterozygous	Variant Of Uncertain Significance
8	DCM	DSP	AD, AR	c.5269C>T p.Q1757*	Homozygous	Pathogenic
9	DCM	TTN	AD, AR	c.40056A>C p.K13352N	Heterozygous	Variant Of Uncertain Significance
10	LVNC	TTN	AD, AR	c.34849A>G p.R11617G	Heterozygous	Variant Of Uncertain Significance
		VCL	AD	c.2914T> A p.S972T	Heterozygous	Variant Of Uncertain Significance
11	LVNC	MIB1	AD	c.2239delG p.A747Qfs*20	Heterozygous	Likely Pathogenic
12	HCM	MYBPC3	AD, AR	c.2234A>G p.D745G	Homozygous	Variant Of Uncertain Significance
13	HCM	MYBPC3	AD, AR	c.1765C>G p.R589G	Homozygous	Variant Of Uncertain Significance
14	HCM	MYBPC3	AD, AR	c.1765C>G p.R589G	Homozygous	Variant Of Uncertain Significance
15	HCM	TPM1	AD	c.842T>C p.M281T	Heterozygous	Pathogenic
16	LVNC	MYOM1	AR	c.991C>T	Homozygous	Variant Of Uncertain Significance
17	RCM	TAF1A	AD	c.1021G>A p.G341R	Homozygous	Variant Of Uncertain Significance
		LMOD2	AR	c.1147G>A p.G383R	Homozygous	Variant Of Uncertain Significance
18	LVNC	DES	AD	c.1286G>A p.R429Q	Heterozygous	Variant Of Uncertain Significance
		CDH2	AD	c.2027A>T p.Y676F	Heterozygous	Variant Of Uncertain Significance
19	HCM	MYBPC3	AD, AR	c.1504C>T p.R502W	Heterozygous	Likely Pathogenic
			AD, AR	c.1321G>A p.E441K	Heterozygous	Variant Of Uncertain Significance
		MYH7	AD	Exon 15-40 duplication	Heterozygous	Likely Pathogenic
		MYH6	AD	Exon 1-14 duplication	Heterozygous	Likely Pathogenic
20	HCM	MYBPC3	AD, AR	c.2234A>G p.D745G	Heterozygous	Likely Pathogenic

Abbreviations: ACMG, American College of Medical Genetics and Genomics; AD, autosomal dominant; AMP, Association for Molecular Pathology; AR, autosomal recessive; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HGVS, Human Genome Variation Society; LVNC, left ventricular noncompaction; RCM, restrictive cardiomyopathy; VUS, variant of uncertain significance;;.

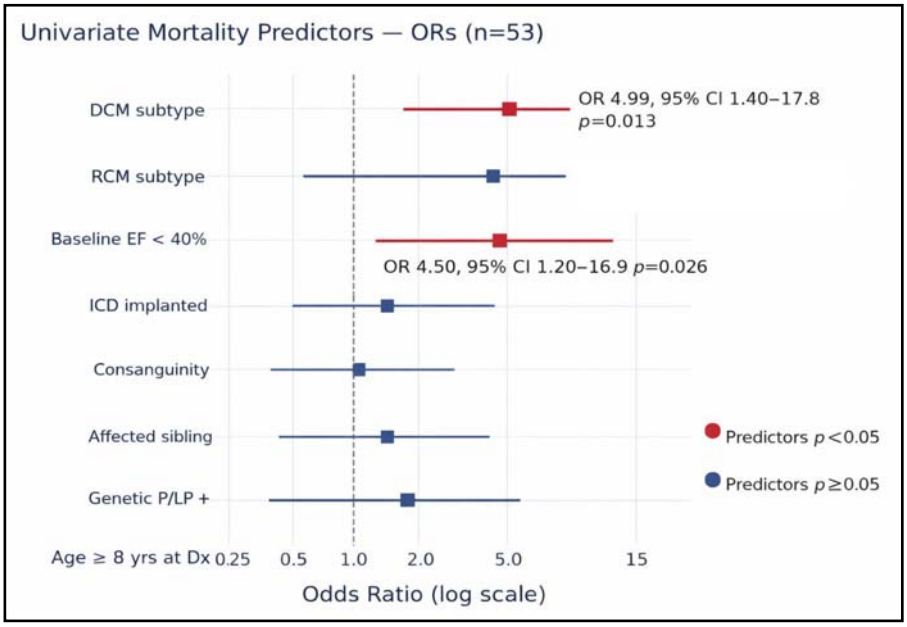

Fig. 2. Univariate odds ratios for all-cause mortality in pediatric cardiomyopathy (n = 53). Forest plot displaying odds ratios (OR) with 95% confidence intervals (CI) on a log scale for eight candidate mortality predictors. Red markers indicate predictors reaching nominal significance ($p < 0.05$): DCM subtype (OR 4.99, 95% CI 1.40–17.8, $p = 0.013$) and baseline ejection fraction below 40% (OR 4.50, 95% CI 1.20–16.9, $p = 0.026$). Blue markers indicate non-significant predictors. The vertical dashed reference line denotes OR = 1 (no effect).
Abbreviations: CI, confidence interval; DCM, dilated cardiomyopathy; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; OR, odds ratio; P/LP, pathogenic or likely pathogenic variant; RCM, restrictive cardiomyopathy.

findings (60.0% with P/LP or VUS among tested patients, Table 1), with predominantly sarcomeric variants (MYBPC3, TPM1, MYH7 — Table 2), while DCM patients showed lower genetic positivity (23.5%). LVNC patients demonstrated intermediate genetic positivity (53.8%) with a strikingly heterogeneous variant profile spanning ion channel (KCNH2, RYR2), sarcomeric (MIB1), cytoskeletal (TTN, VCL, DES), and adhesion (CDH2) genes (Table 2), consistent with the current understanding of LVNC as a phenotypic endpoint of multiple genetic pathways rather than a single disease entity (Brescia *et al.* 2013, Pugh *et al.* 2014, McNally *et al.* 2017). These observations are hypothesis-generating but were not formally tested with correlation or regression analyses in the current study. The identified variants — predominantly in sarcomeric genes (MYBPC3, TPM1), cytoskeletal genes (DSP, TTN, VCL), and signaling pathway genes (PTPN11, PRKAG2) — illustrate the broad genetic heterogeneity of PCM in a high-consanguinity population. LVNC patients in our cohort carried the most genetically diverse variant profile (RYR2, KCNH2, TTN, VCL, ABCC9, MIB1, DES, CDH2, MYOM1 — Table 2), consistent with published observations that LVNC represents a phenotypic trait shared across multiple genetic backgrounds rather than a single-gene disorder (Arbustini *et al.* 2014; Probst *et al.* 2011). Two HCM patients (cases 1 and 2) carried the identical PTPN11 c.836A>G (p.Y279C) pathogenic variant, associated with Noonan syndrome — a RASopathy in which spontaneous regression may occur in infancy yet late progression and sudden death risk differ from sarcomeric HCM, warranting dedicated surveillance protocols (Prendiville *et al.* 2014, Tartaglia *et al.* 2001).

Case 17 additionally harbored a homozygous variant in TAF1A (c.1021G>A, p.G341R), a gene not currently established as a cardiomyopathy disease gene. This finding is reported as a candidate variant of uncertain clinical significance and requires independent functional validation before disease attribution. Genetic testing resources and clinical practice patterns, however, exhibit considerable variability across pediatric cardiomyopathy programs, impacting the consistency of variant interpretation and the availability of genetic counseling (Godown *et al.* 2024).

The genetic yield in our cohort — 34.6% P/LP among tested patients (9/26) and 76.9% including VUS (20/26) — is consistent with published exome-based pediatric series and clinically meaningful; the broader yield when VUS are included was 76.9% of patients tested (20/26); however, 11 of these 20 findings were VUS (42.3% of tested patients), which do not constitute diagnostic yield and should not be interpreted as confirmed pathogenic variants pending; all yield figures in this report use the tested cohort (n = 26) as denominator unless otherwise stated. This rate aligns with published pediatric series and reinforces the clinical utility of genetic testing in this population, particularly in high-consanguinity settings where recessive variants may be enriched. The higher genetic positivity observed in hypertrophic cardiomyopathy compared to dilated forms corroborates the established dominance of sarcomere gene mutations in HCM. However, the genetic heterogeneity in DCM observed in our cohort further highlights the involvement of cytoskeletal, mitochondrial, and signaling pathways, underscoring the complexity of genotype–phenotype correlations in childhood disease. In particular, case 8 — a homozygous DSP truncating variant (p.Q1757) — represents desmoplakin cardiomyopathy, increasingly recognized as a fibrotic, arrhythmia-prone entity distinct from typical DCM, with implications for ICD candidacy and

immunosuppressive management (Smith *et al.* 2020). The high rate of parental consanguinity (45.3%) in our study likely contributes to the enrichment of rare, potentially recessive variants and partly explains the high proportions of both P/LP variants and VUS observed. Whether consanguinity is independently associated with earlier onset or a more aggressive clinical course could not be formally assessed in this small, retrospective cohort and remains an important question for larger, prospective studies. This is illustrated by the three homozygous MYBPC3 cases in our cohort (cases 12, 13, 14 — Table 2); homozygous MYBPC3 mutations have been associated with particularly severe infantile-onset HCM in other high-consanguinity populations, with earlier presentation and higher mortality than heterozygous carriers (Xin *et al.* 2007, Zahka *et al.* 2008). This observation has important implications for regions with similar demographic patterns, suggesting that autosomal recessive and syndromic forms may be under recognized contributors to pediatric cardiomyopathy globally. These data advocate for systematic family screening strategies and genetic counseling infrastructure tailored to high-consanguinity populations. Mortality in our cohort (34%) is substantial and reflects the advanced disease stage of referred patients; DCM and RCM accounted for 10/18 and 2/18 deaths, respectively. This finding should be interpreted in the context of our unit's role as a tertiary heart transplant center; the majority of these patients were referred from outside institutions specifically for transplant evaluation, reflecting a highly selected population with advanced, treatment-refractory disease. Notably, the DCM subgroup had a follow-up IQR lower bound of 0.3 years, indicating that a proportion of deaths occurred within months of diagnosis — a pattern consistent with acute decompensated heart failure at referral rather than chronic disease progression, which further limits the generalizability of subgroup mortality estimates. The markedly reduced baseline ejection fraction in DCM and the severe clinical course observed in RCM highlight the ongoing vulnerability of these subgroups despite contemporary medical therapy (Webber *et al.* 2012). These findings highlight that DCM and RCM patients in this referral cohort had the highest mortality (58.8% and 66.7%, respectively) and transplantation rates, suggesting that timely recognition and referral for advanced heart failure therapies warrants further prospective study. In summary, this single-center cohort underscores three points. First, children with DCM and RCM in this referral population experienced high mortality, and simple clinical markers such as subtype and baseline EF <40% may help identify those at highest risk. Second, comprehensive genetic testing in a high-consanguinity setting yielded P/LP variants in a substantial minority of tested patients but also revealed a large VUS burden, highlighting the need for better representation of such populations in genetic reference databases. Third, future multicenter, prospective studies integrating genotype, myocardial imaging, and functional parameters are needed to validate risk-prediction models and move toward truly individualized management in pediatric cardiomyopathy. Genetic positivity should not be viewed solely as diagnostic confirmation but as a potential prognostic modifier (Ellepola *et al.* 2017). Emerging evidence suggests that specific gene variants, sarcomere mutation status, and even variant burden may influence arrhythmic risk, progression, and transplant-free survival (Nakano *et al.* 2018). Our findings provide further rationale for incorporating genetic stratification into therapeutic decision-making algorithms. A combined framework incorporating genetic architecture, myocardial fibrosis burden, and functional parameters may enable true precision-based management in pediatric cardiomyopathy.

LIMITATIONS

This study has several important limitations. First, it represents a single-center, retrospective cohort from a tertiary heart transplant referral center, where many DCM and RCM patients were referred with advanced, treatment-refractory disease. This referral bias likely inflates the observed mortality rates relative to unselected population-based cohorts and limits generalizability to community or early-stage presentations. Second, genetic testing was not performed uniformly: only about half of patients were tested, different modalities were used over time, and variant interpretation may change with ongoing reclassification. These factors may have influenced the observed diagnostic yield and VUS burden. Additionally, a small number of variants were identified in genes not currently established as cardiomyopathy disease genes (e.g., TAF1A in Case 17); these represent candidate findings of uncertain significance and are not counted toward diagnostic yield. Third, cardiovascular magnetic resonance data and quantitative fibrosis burden were not systematically incorporated into outcome modeling. Fourth, subgroup sizes were small, particularly for RCM (n = 3), limiting statistical power for phenotype-specific conclusions. Fifth, longitudinal genotype-specific survival analyses were not performed and warrant prospective evaluation. Sixth, pharmacological treatment data — including beta-blockers, ACE inhibitors, diuretics, and antiarrhythmic agents — were not systematically collected, representing a significant unmeasured confounder for both ejection fraction trajectory and survival outcomes. CMR with fibrosis quantification was available in only 12 of 53 patients and was not incorporated into outcome modelling; future studies integrating fibrosis burden with genetic architecture may refine prognostic modelling in this population.

CONCLUSION

Dilated and restrictive cardiomyopathies remain associated with poor prognosis, particularly in the presence of severe systolic dysfunction. The high prevalence of pathogenic variants and consanguinity underscores the critical importance of comprehensive genetic evaluation and structured family screening. Our findings indicate that pediatric cardiomyopathy in this referred cohort is characterized by a substantial P/LP yield among tested patients (34.6%, 9/26), considerable mortality risk, and phenotype-dependent outcome variability, with mortality ranging from 15.4% in LVNC to 66.7% in RCM. The presence of multiple variants in a single patient — such as Case 19, who carried four variants across MYBPC3, MYH7, and MYH6 (Table 2) — raises the hypothesis that cumulative variant burden may modify phenotype severity. Emerging evidence supports the concept that multi-hit genetic architecture, rather than single pathogenic variants, may underlie the most severe pediatric cardiomyopathy phenotypes (Mazzarotto *et al.* 2021). This observation warrants prospective investigation with formal polygenic frameworks, which are beyond the scope of the current descriptive analysis.

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ETHICS APPROVAL: Ethical approval was granted by the Başkent University Institutional Review Board (Project No: KA 26/06).

CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

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