Mortality and Sudden Death in Pediatric Left Ventricular Noncompaction in a Tertiary Referral Center

Running title: Brescia et al.; Mortality and Pediatric LVNC

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Journal Subject Codes: Etiology:[5] Arrhythmias, clinical electrophysiology, drugs, Heart failure:[11] Other heart failure
Abstract:

Background—Left ventricular noncompaction (LVNC) is a cardiomyopathy characterized by excessive trabeculation of the left ventricle, progressive myocardial dysfunction, and early mortality. LVNC has a heterogeneous clinical presentation including arrhythmia and sudden cardiac death.

Methods and Results—We retrospectively reviewed all children diagnosed with LVNC at Texas Children’s Hospital (TCH) from January 1990 to January 2009. Patients with congenital cardiac lesions were excluded. Two hundred forty two children were diagnosed with isolated LVNC over the study period. Thirty-one (12.8%) died and 13 (5.4%) were transplanted. One-hundred fifty (62%) presented with or developed cardiac dysfunction. The presence of cardiac dysfunction was strongly associated with mortality (HR 11; p<0.001). Electrocardiographic abnormalities were present in 87%, with ventricular hypertrophy and repolarization abnormalities occurring most commonly. Repolarization abnormalities were associated with increased mortality (HR 2.1; p=0.02). Eighty (33.1%) had an arrhythmia, and those with arrhythmias had increased mortality (HR 2.8; p=0.002). Forty-two (17.4%) had ventricular tachycardia (VT) with 5 presenting with resuscitated sudden cardiac death. In total, there were 15 cases of sudden cardiac death in the cohort (6.2%). Nearly all patients with sudden death (14/15) had abnormal cardiac dimensions or cardiac dysfunction. No patient with normal cardiac dimensions and function without preceding arrhythmias died.

Conclusions—LVNC has a high mortality rate and is strongly associated with arrhythmias in children. Preceding cardiac dysfunction or ventricular arrhythmias are associated with increased mortality. Children with normal cardiac dimensions and normal function are at low risk for sudden death.

Key words: cardiomyopathy, heart failure, arrhythmia, death, death, sudden
Introduction

The pathologic description of left ventricular noncompaction (LVNC) was first reported by R. Grant in 1926. Since that time, LVNC has been identified in association with a variety of congenital heart malformations, and more recently, has become recognized in its isolated form as a distinct form of cardiomyopathy.

LVNC was initially thought to be a rare disorder. It has recently become clear, however, that it is more prevalent than previously recognized. Current studies in children estimate that LVNC accounts for approximately 9% of newly diagnosed cardiomyopathies. Ritter et al. reported the prevalence of LVNC in adult echocardiograms to be 0.05%. LVNC commonly presents in infancy with signs and symptoms of congestive heart failure. However, a subset of patients develop symptoms later in life (adolescence and adulthood). There are also individuals with the characteristic findings of LVNC that never develop symptomatic heart failure. There is therefore great interest in characterizing the natural history of this disease to help guide counseling and management of this heterogeneous patient population. Current understanding of the natural history of LVNC is restricted to several case series and small studies. Although arrhythmias and sudden death have been reported, our understanding of mortality profiles in LVNC remains limited. In order to examine the mortality profiles and the incidence of arrhythmias and sudden cardiac death in this patient population, we conducted a retrospective review of all children diagnosed with isolated LVNC at our institution.

Methods

The echocardiogram database of Texas Children's Hospital (TCH) was searched for all children with the diagnosis of LVNC between January 1990 and January 2009. Identified
echocardiograms were then reviewed by two independent pediatric cardiologists (SB, RP) to confirm the diagnosis of LVNC based on previously published criteria: (1) the presence of multiple echocardiographic trabeculations, (2) deep intertrabecular recesses communicating with the ventricular cavity as demonstrated by color Doppler, and (3) a 2-layered structure of the endocardium with a noncompacted to compacted ratio > 2.0.8 Patients were included in the cohort only if both echocardiogram reviewers agreed upon the diagnosis. Patients with LVNC and associated congenital heart disease or known metabolic syndromes (non-isolated LVNC) were excluded. Only patients primarily followed at TCH for LVNC were included; Patients referred for isolated second opinions or only seen for single visits (without longitudinal follow-up) were excluded. This study was approved by the Baylor College of Medicine Institutional Review Board and individual consent was waived. Medical records were reviewed to document clinical presentation and course. Serial echocardiograms were analyzed for measures of systolic function (shortening fraction and ejection fraction), and cardiac dimensions were measured using M-Mode. Ejection fraction (EF) was calculated utilizing the Simpson’s biplane method.

Cardiac systolic dysfunction was defined as an EF less than 55% or, if unavailable, a shortening fraction less than -2 Z-scores for age. Patients were divided into 4 distinct phenotypes of LVNC: dilated, hypertrophic, mixed, and normal dimensions. The dilated phenotype was assigned if the left ventricular end-diastolic dimension (LVEDD) was greater than + 2 Z-scores for age. The hypertrophic phenotype was assigned if septal or posterior wall diastolic measurements were greater than + 2 Z-scores for age. Trabeculated myocardium was not included in the measurement. Patients were classified in the mixed phenotype if there was evidence of both LV dilation and hypertrophy based on M-mode measurements. Patients were classified in the “normal dimension” phenotype if all cardiac dimensions were found to be within normal limits.
(within 2 Z-scores) for body surface area. Holter evaluations and 15-lead electrocardiograms (ECGs) were reviewed by a blinded pediatric electrophysiologist (JK) and examined for abnormalities or the presence of arrhythmias. Ventricular arrhythmias were defined as either ventricular tachycardia or fibrillation. Supraventricular arrhythmias were defined as atrial tachycardia, atrial flutter, junctional tachycardia, or re-entrant SVT. ECG findings were also analyzed and compared with clinical outcomes. Univariate survival data was evaluated with Kaplan-Meier survival analysis utilizing log rank statistics. Time zero for survival analysis was at time of diagnosis / presentation (only factors present at the time of diagnosis were included). COX PH regression analysis with covariates, including both continuous and catagorical data, was used to fit the data. Statistical analysis was performed with SPSS statistical software, version 16.0 (SPSS Inc., Chicago, Illinois).

Results
Cohort Characteristics

Two hundred forty-two (242) patients were diagnosed with isolated LVNC over the 18-year study period and were included in our study. There were an additional 43 patients with prominent trabeculations and presumed LVNC who did not meet proposed diagnostic criteria based on echocardiographic review, and were thus excluded from the study. The diagnosis of LVNC did become more common over time with 25 patients being diagnosed over the 1st 9 years of the study, and 217 patients being diagnosed over the last 9 years. However, the frequency of diagnosis did stabilize over time with no significant change in the incidence of diagnosis over the last 8 years of the study (p=NS). One hundred forty five patients (60%) were male and 97 (40%) were female. Ninety-nine patients (41%) were African American, 80 (34%) Caucasian, 52
(21%) Hispanic, 6 (2%) Asian, and 5 (2%) other. The mean age at diagnosis was 7.2 +/- 6.9 years, although 95 patients (39%) presented within the first year of life (infantile LVNC). Fifty-six patients (23%) had a family history of cardiomyopathy in 91 relatives, although only 14/56 (25%) had a family history of LVNC, with the remainder having a family history of dilated cardiomyopathy (27), hypertrophic cardiomyopathy (5), or a combination of cardiomyopathy types (10). One-hundred and eighty-six patients (77%) were de novo presentations. The median duration of follow-up was 4.0 years (range, 1.8 to 15.9 years). Demographic factors are summarized in Table 1.

Clinical Presentation

Sixty patients (25%) presented primarily with signs and symptoms of congestive heart failure. Forty-two patients (17%) presented with arrhythmias or suspected arrhythmias. Of these, 25 patients (10%) presented with documented arrhythmias, 5 patients presented with aborted sudden death, and an additional 12 patients were referred for evaluation of unexplained syncope. Twenty-two patients (9%) presented with a primary complaint of chest pain. Forty-five patients (18%) were referred for evaluation of murmurs or abnormal heart sounds, 24 (10%) were referred for abnormal baseline ECG findings, and 16 (7%) were referred due to cardiomegaly noted on chest radiograph. Thirty-three patients (14%) were found to have LVNC on screening echocardiography due to family history or as an “incidental finding” on echocardiography performed for other reasons (athletic screenings or for screening due to other concomitant medical conditions). In total, eighty-nine patients (37%) were reportedly asymptomatic from a cardiovascular standpoint at the time of presentation. The initial primary presenting symptoms and underlying reasons for referral are summarized in Figure 1.

Echocardiographic Findings
Two-dimensional echocardiography and standard M-mode measurements were reviewed for the entire cohort. Four distinct myocardial phenotypes were identified in patients with LVNC: dilated, hypertrophic, mixed, and normal dimensions. Patients were classified based on presenting echocardiograms as defined in the methods. Sixty-eight patients (28%) had a mixed phenotype with evidence of both dilation and hypertrophy. Sixty-six patients (27%) were hypertrophic and 46 patients (19%) were dilated. Sixty-two patients (26%) had normal M-mode indices. Overall, ventricular systolic dysfunction was noted in 150 patients (62%) of the cohort (EF ranging between 8 and 51%). The majority of these (131 patients; 54%) had systolic dysfunction at presentation. An additional 19 patients (8%) developed systolic dysfunction over follow-up, an average of 47 months after presentation (range 1 month to 175 months). In regards to phenotype and the presence of dysfunction, 41/46 (89%) with dilated phenotype, 28/66 (42%) with hypertrophic phenotype, 59/68 (87%) with mixed phenotype, and 22/62 (35%) with normal dimensions were documented to have depressed systolic function.

**Electrocardiographic Findings**

Two-hundred ten patients (87%) were noted to have an abnormal ECG on presentation. Only 32 patients (13%) had normal ECGs. The most common ECG finding was voltage criteria for ventricular hypertrophy (predominantly left ventricular or biventricular hypertrophy) which was noted in 41% of patients. Some patients had extreme QRS voltage similar to that seen in Pompe’s disease; these were usually in infants or in the setting of ventricular pre-excitation. Other common findings included isolated or diffuse T wave inversion (39%), ST segment abnormalities or strain (34%), atrial enlargement (19%), and left axis deviation (9%). Twenty-two patients (9%) had a prolonged QTc (461-652 msecs), and 20 patients (8%) had manifest pre-excitation consistent with Wolff-Parkinson-White (WPW) syndrome.
Arrhythmias

In total, eighty-one patients (33%) had a documented tachyarrhythmia. Forty-two patients (17%) had ventricular tachycardia (VT), fourteen patients (6%) had atrial tachycardia, and an additional 19 patients (8%) had re-entrant supraventricular tachycardia (SVT). Four patients had atrial flutter, two patients had accelerated junctional rhythm, and one patient had atrial fibrillation. Only 25 out of these 81 patients had documented arrhythmias as a part of their presentation complex. The majority (56/81) developed arrhythmias during the course of their follow-up evaluation, an average of 27 months after presentation (range 1 to 143 months).

Medical Therapy

Outpatients with cardiac dysfunction were typically treated with a combination of beta-blockade and ACE inhibition. Of these patients, 61/150 (41%) were noted to have some improvement in cardiac systolic function with medical therapy over follow-up. Per institutional practice, patients with normal cardiac dimensions and normal function were not placed on medical therapy and were not restricted in any way.

Thirty of the 42 patients with VT were initially treated with beta-blockade alone while 8 patients with associated severely depressed systolic function were started on amiodarone as the initial primary therapy. Patients with recurrent VT while on beta-blockers were transitioned to more aggressive anti-arrhythmic therapy including amiodarone, sotalol, or mexiletene.

Invasive Therapy

Nineteen patients underwent invasive electrophysiologic testing during follow-up. Six patients were found to have re-entrant forms of SVT and 5 underwent successful radiofrequency ablation. One patient with a WPW pattern on her surface ECG was found to be pseudo pre-excited without intracardiac evidence of an accessory pathway. Eleven patients underwent programmed
stimulation to evaluate for inducible ventricular arrhythmias. Four patients had inducible and sustained ventricular arrhythmias and subsequently underwent ICD implantation. Two additional patients with monomorphic VT underwent successful mapping and ablation of a ventricular focus, neither of whom have had recurrent VT to date. In total, eleven patients underwent ICD implantation. Two of these patients have subsequently been transplanted, and there has been one appropriate discharge for ventricular fibrillation over a mean follow-up period of 4.8 +/- 3.4 years. One additional patient had an ICD malfunction and refused a revision procedure and subsequently died suddenly.

**Mortality**

During the study period, 31 patients (12.8%) died and 13 patients (5.4%) underwent cardiac transplantation, thereby resulting in an 18% incidence of death or transplantation in the total cohort. Of the 44 patients that died or were transplanted, 24 of them (55%) presented in the first year of life. Of the 95 patients that presented in the 1st year of life, 20 died while 4 required transplantation. The incidence of death or transplantation in infantile LVNC was thus 25%.

Utilizing COX PH regression with demographic factors as covariates, presentation within the first year of life was associated with increased mortality (HR 2.1; 95% CI 1.0-3.9) (p=0.02) (**Table 2**).

Ventricular systolic dysfunction developed in 150 patients (62%) of the cohort. The presence of cardiac systolic dysfunction was significantly associated with death or transplantation (HR 11; 95% CI 2.6-45)(p<0.001), based on COX PH regression with myocardial phenotype, arrhythmias, and parameters of function as covariates (**Table 2**). The cumulative 5 year survival from death or transplantation for patients with systolic dysfunction was 60%, versus 98% for those with normal cardiac function (**Figure 2**). The patients’ identified
phenotype also bore direct relationship to the risk of death or transplantation based on log rank statistics (p=0.01), with actuarial 5 year survivals of 63% for the dilated phenotype, 64% for the mixed phenotype, 86% for the hypertrophic phenotype, and 98% for the normal dimension phenotype (Figure 3). Patients with a normal dimension phenotype had a significantly decreased risk of mortality (HR 0.44; 95% CI 0.32-0.60)(p=0.01).

Electrocardiographic abnormalities and arrhythmias were also strongly associated with outcomes. T-wave inversion (HR 2.1; 95% CI 1.1-4.2)(p=0.02) and ST segment abnormalities (HR 4.0; 95% CI 1.0-19.9)(p=0.05) were independently associated with death or transplantation (Table 2), based on COX PH regression with ECG findings, arrhythmias, and parameters of function as covariates. Interestingly, of the 32 patients with normal ECGs, none died during the study period. The presence of arrhythmias increased the risk of death or transplantation in this model (HR 2.8; 95% CI 1.4-5.6)(p=0.002), with 30% of these patients dying or being transplanted during the study period. Of the 42 children who had documented VT, 18 (43%) died or were transplanted during follow-up, representing a four-fold increase (95% CI 2.1-9.0)(P<0.001) in this group (Table 2). Seven of these children died suddenly. Seven children presented with depressed systolic function and VT within the first year of life. Five of these children had recalcitrant ventricular arrhythmias and died in follow-up, representing a 12-fold increase (95% CI 2.4-69.2) in the hazard for children presenting with cardiac dysfunction and VT before the age of one when compared with the hazard in children presenting later in life (p=0.002).

Sudden Death

In total, 15 patients (6.2%) experienced sudden cardiac death during the study period. Abnormal M-mode measurements with left ventricular dilation, hypertrophy or a combination of both were
identified in 14/15 patients prior to their event. Preceding systolic dysfunction was identified in 13/15 patients with an average shortening fraction of 15.3 +/- 8.1%. Nine of 15 patients also had a documented arrhythmia prior to cardiac arrest with 8 patients having pre-existing ventricular tachycardia. The hazard of sudden death increased significantly in patients with a preceding arrhythmia (HR 7.6, 95% CI 1.5-37.8)(p=0.01), based on COX PH regression with electrocardiographic abnormalities and arrhythmias as covariates. Both patients who experienced sudden cardiac death that did not have associated cardiac dysfunction had preceding arrhythmias with documented VT in one and WPW and suspected atrial fibrillation in the other. No patient with normal cardiac dimensions and function without preceding arrhythmias died suddenly.

Discussion
In recent years, LVNC has become increasingly recognized as a discrete form of cardiomyopathy with a distinct underlying cause and prognosis. In the developing embryo, the myocardium begins as a loose interwoven mesh of muscle fibers and gradually condenses from epicardium to endocardium, generally resulting in compaction of the endocardial surface between the 5th and 8th weeks of fetal life. This process of trabecular compaction typically progresses from the base of the heart toward the apex and is usually more complete in the LV than in the right ventricle. Arrest in normal endomyocardial morphogenesis is thought to result in LVNC. Although initially thought to be a rare disorder, it has become clear that it is much more prevalent than previously recognized. Indeed, in our cohort, the diagnosis of LVNC has increased over time with the preponderance being diagnosed over the past 10 years. This is likely due to an increased index of suspicion at our institution coupled with the enhanced quality of
echocardiographic images in the current era. Our suspicion is that this pattern of increased recognition is likely mimicked globally, although it may have stabilized in recent years.

This study is the largest report on the natural history of children with LVNC to date and highlights mortality profiles and the incidence of arrhythmias and sudden cardiac death in this patient population. Previous reports on pediatric LVNC have suggested mortality rates of 15-20% in short-term follow-up (2-3 years). Although those reports include patients with associated congenital heart lesions, our cohort had similar findings with an overall mortality rate of 12.8% and a rate of death or transplantation of 18.2%. Our series suggests, as one might expect, that patients with myocardial dysfunction or preceding arrhythmias have a worse prognosis than those with isolated hypertrabeculation. Although this is not unique to LVNC when compared to other forms of cardiomyopathy, it does confirm presumptions. Conversely, the cohort of patients with a diagnosis of LVNC and no signs of functional cardiomyopathy (no myocardial dysfunction, cardiac dilation, or arrhythmias) are distinctive in that they have some phenotypic manifestation of disease (hypertrabeculation) without existing functional abnormalities. Other forms of cardiomyopathy do not typically have a comparative population. In our study, this group of patients seemed to do particularly well, and further long-term evaluation of this cohort is prudent.

Similar to previous studies, mortality in children presenting in the first year of life was significantly higher at 30.4%. The reason for higher mortality in infantile LVNC is not entirely clear, although they are more likely to present with symptomatic heart failure or arrhythmias and this may underscore a more malignant genotype or more global, systemic disease. Although infants with known mitochondrial disease or metabolic syndromes were excluded, it is likely that some of these children escaped diagnosis and harbored the known higher mortality profiles
associated with these syndromes. In our cohort, presentation in the first year of life with ventricular systolic dysfunction and associated ventricular arrhythmias predicted a particularly poor prognosis with a 12-fold increase in the hazard of dying.

Previous studies have described a heterogeneous phenotypic presentation of LVNC.\textsuperscript{9,16} In concordance, we identified 4 phenotypic subtypes of isolated LVNC in children (dilated, hypertrophic, mixed, and normal dimensions). There was a clear discrepancy in prognosis among these groups with those expressing a dilated or mixed phenotype being the most likely to experience death or transplantation. More importantly, children with normal cardiac dimensions (no evidence of hypertrophy or dilation) did well with very low mortality. Specific genetic mutations are possibly responsible for the phenotypic variability; ongoing studies hope to elucidate the cause of this heterogeneity. In addition, consideration should be given to the possibility that our current diagnostic standards for LVNC may be imprecise. Continued follow-up and additional study is necessary to further fine tune diagnostic standards. The inclusion of more advanced imaging modalities and genetic testing may be warranted.

ECG abnormalities should also be considered as an adjunctive diagnostic feature of LVNC. In our cohort, ECG abnormalities were present in 87% of patients and were prevalent in both symptomatic and asymptomatic children. In 5% of cases, an abnormal ECG led to the diagnosis of LVNC by prompting additional evaluation. Characteristic ECG abnormalities included ventricular hypertrophy and repolarization abnormalities such as T-wave inversion and ST segment changes. Similar repolarization abnormalities have been previously reported in children.\textsuperscript{7,9} In our cohort, T-wave inversion and ST segment abnormalities were independently associated with cardiac death while normal ECGs were associated with decreased mortality. We recommend obtaining ECGs in all patients referred for evaluation of possible LVNC and yearly
in patients followed with a diagnosis of LVNC as they appear to harbor diagnostic and prognostic potential. Although early reports suggested that ventricular arrhythmias were uncommon in adults with LVNC, a recent review found the incidence to be as high as 33%. In pediatric patients, ventricular arrhythmias are indeed a relatively common complication of LVNC, affecting 17% of the children in our cohort. Additionally, ventricular arrhythmias continue to be a major cause of mortality, with the onset of VT being an indicator of poor prognosis. In our population, the presence of any arrhythmia was associated with an increased risk of death or transplantation. However, further stratification and survival analysis revealed that the predominant contributing rhythm abnormality was indeed ventricular arrhythmias.

Infants with VT in association with depressed ventricular function appear to do particularly poorly with the majority (71%) dying in the first year of life. This population warrants close observation and early consideration for transplantation.

It is unclear why the noncompacted myocardium is arrhythmogenic. In regards to WPW and re-entrant SVT, it is hypothesized that primitive atrioventricular connections persist due to a generalized arrest in cardiac development. This developmental arrest in the ventricle may also result in increased dispersion of repolarization as is often seen in immature myocardium and predispose to ventricular arrhythmias. Additionally, two separate studies have implicated progressive myocardial ischemia as a potential source for arrhythmogenesis. Myocardial perfusion scans of patients with LVNC demonstrate evidence of microcirculatory dysfunction, and pathologic specimens demonstrate fibroelastosis of affected myocardium. In our cohort, ECG findings consistent with ischemia or strain were associated with increased mortality which may support this hypothesis. Lastly, it has recently been recognized that certain genetic mutations can predispose individuals to both heart failure and arrhythmias by their resultant
functional effects on both sarcomeric structure and ion channels.\textsuperscript{23-25} This may play a role in inherited forms of LVNC. Xq28 chromosomal abnormalities identified in separate families with LVNC have been localized to the G4.5 or tafazzin gene. This region has already been implicated in other cardiomyopathies that are associated with significant arrhythmias including Barth syndrome, myotubular myopathy, and Emery-Dreifuss muscular dystrophy.\textsuperscript{26-28}

There are limited data about the clinical management of children with LVNC and arrhythmias, particularly regarding activity restrictions. Our practice has been to activity restrict any patient with abnormal cardiac dimensions, cardiac dysfunction, or arrhythmias. We do not activity restrict patients with normal cardiac dimensions and function without evidence of arrhythmias. To date, no patient with normal cardiac dimensions and function without preceding arrhythmias has died suddenly, and our data suggest that their risk of sudden death is low. We do recommend, however, continued follow-up, including yearly echocardiograms and Holter evaluations, to monitor for the development of occult abnormalities.

\textbf{Limitations}

This study was a single center retrospective evaluation from a large tertiary referral center and has limitations intrinsic to such an analysis. Although only patients primarily followed at TCH for LVNC were included, it is possible that some patients presented with a presumptive diagnosis of LVNC prior to initial evaluation at our institution. As such, utilization of time of diagnosis for survival analysis may harbor subtle inaccuracies. Findings in this cohort may not be universally applicable to all populations. Also, although not insignificant, there were relatively few sudden death events limiting statistical power to analyze associated risk factors. Follow-up was also limited to 4 years to date. Lastly, due to the retrospective nature of echocardiographic review, diastolic parameters of cardiac function as well as a more detailed
assessment of systolic function could not be extensively analyzed.

Conclusions

Although heterogeneous in its presentation and course, LVNC has a relatively high incidence of cardiac death and is strongly associated with life-threatening arrhythmias in children, particularly in those presenting in the first year of life. ECG abnormalities are prominent and may harbor diagnostic and prognostic potential. Also, preceding cardiac dysfunction or ventricular arrhythmias have a robust association with increased mortality and an increased risk of sudden cardiac death. As such, children with LVNC should have life long monitoring for the development of ventricular dysfunction or arrhythmias. Children with normal cardiac dimensions and normal function without preceding arrhythmias are likely at low risk for sudden death.

Conflict of Interest Disclosures: None.

References:


Table 1. Demographics and Patient Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All Patients (n=242)</th>
<th>Death (n=31)</th>
<th>Transplant (n=13)</th>
<th>Sudden Death (n=15)</th>
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<tbody>
<tr>
<td>Median age, months (IQR)</td>
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<td>6.2 (1-50)</td>
<td>26 (8-135)</td>
<td>48 (7-153.6)</td>
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<td>Male, n (%)</td>
<td>145 (60)</td>
<td>12 (39)</td>
<td>10 (77)</td>
<td>11 (73)</td>
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<td>Race/ethnicity, n (%)</td>
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<td>White</td>
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<td>Black</td>
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<td>10 (32)</td>
<td>2 (15)</td>
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<td>Hispanic</td>
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<td>8 (26)</td>
<td>3 (23)</td>
<td>3 (20)</td>
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<tr>
<td>Other</td>
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<td>1 (8)</td>
<td>0</td>
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<td>Myocardial phenotype, n (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Dilated</td>
<td>46 (19)</td>
<td>10 (32)</td>
<td>1 (8)</td>
<td>5 (33)</td>
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<tr>
<td>Mixed</td>
<td>68 (28)</td>
<td>10 (32)</td>
<td>11 (84)</td>
<td>6 (40)</td>
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<td>Hypertrophic</td>
<td>66 (27)</td>
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<td>3 (20)</td>
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<td>Normal Dimensions</td>
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<td>3 (10)</td>
<td>1 (8)</td>
<td>1 (7)</td>
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<td>Cardiac dysfunction, n (%)</td>
<td>150 (62)</td>
<td>26 (84)</td>
<td>12 (92)</td>
<td>13 (87)</td>
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<td>Arrhythmia, n (%)</td>
<td>81 (33)</td>
<td>15 (48)</td>
<td>9 (69)</td>
<td>9 (60)</td>
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<td>VT/VF, n (%)</td>
<td>42 (17)</td>
<td>11 (35)</td>
<td>7 (54)</td>
<td>7 (47)</td>
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</table>

Table demonstrating the demographic distribution and patient characteristics of the study population, including the distribution of death, sudden death, and cardiac transplantation. Demographic factors and myocardial phenotype as noted at presentation; Cardiac dysfunction and arrhythmias noted at any time during follow-up. (VT = ventricular tachycardia; VF = ventricular fibrillation).

Table 2. Risk Factors for Death or Transplantation

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
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<tr>
<td>Cardiac Dysfunction</td>
<td>11.1</td>
<td>2.6 - 45</td>
<td>&lt; 0.001</td>
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<td>T Wave Inversion</td>
<td>2.1</td>
<td>1.1 – 4.2</td>
<td>0.02</td>
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<tr>
<td>ST Segment abnormalities or Strain</td>
<td>4.0</td>
<td>1.0 – 19.9</td>
<td>0.05</td>
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<td>Any Arrhythmias</td>
<td>2.8</td>
<td>1.4 - 5.6</td>
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<td>Ventricular Arrhythmias</td>
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<td>2.1 – 9.0</td>
<td>&lt; 0.001</td>
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<td>Presentation &lt; 1 year</td>
<td>2.1</td>
<td>1.0 - 3.9</td>
<td>0.02</td>
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<tr>
<td>Presentation &lt; 1 year with ventricular arrhythmias</td>
<td>12.0</td>
<td>2.4 – 68.9</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table demonstrating the significant risk factors for death or cardiac transplantation during follow-up. Separate COXPH models utilized for demographic factors and other risk factors. P values <0.05 considered significant. Only factors found to be statistically significant displayed.
Figure Legends:

**Figure 1.** Clinical Presentation & Symptoms. Chart demonstrating the distribution of primary clinical symptoms at initial presentation and primary reasons for referral. (CHF = Congestive Heart Failure, ECG = electrocardiogram, CXR = Chest X-ray).

**Figure 2.** Kaplan-Meier Survival Curve for Freedom from Death or Transplantation with Cardiac Dysfunction utilizing log rank test. Normal cardiac function (blue). Cardiac dysfunction (green). Follow-up interval in years.

**Figure 3.** Kaplan-Meier Survival Curve for Freedom from Death or Transplantation with Distinct Cardiac Morphologies utilizing log rank test. Normal cardiac morphology (blue). Hypertrophic (purple). Dilated (green). Mixed (red). Follow-up interval in years.
Figure 2
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