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Molecular Findings, Clinical Severity, and Transplant-Free Survival in Pediatric Cardiomyopathy: A Prospective Indian Cohort

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Research Article

Keywords:

Posted Date: November 4th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11438528/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

The relationship between molecular findings, clinical disease severity, and heart failure (HF) outcomes in pediatric cardiomyopathy remains uncertain.

Objectives

To evaluate genetic diagnostic yield and the relative associations of clinical severity, biomarkers, and multimodality imaging with death or heart transplantation in children with cardiomyopathy.

Methods

This prospective single-center study included 235 children younger than 18 years at a South Indian referral center. Genetic testing, HF functional class, biomarkers, echocardiography, cardiac magnetic resonance (CMR), and longitudinal outcomes were evaluated. Transplant-free survival was assessed using Kaplan–Meier analysis and Cox regression. Hierarchical models evaluated incremental prognostic discrimination using Harrell's C-index.

Results

Genetic testing was performed in 112 children (47.7%), of whom 54 (48.2%) had reported pathogenic or likely pathogenic (P/LP) variants. During a median follow-up of 15 months, 63 children (26.8%) died or underwent heart transplantation. Transplant-free survival did not differ significantly between P/LP-positive and genetic-negative groups (log-rank P = 0.058). Reduced ventricular function and late gadolinium enhancement were associated with adverse outcomes in univariable analyses. Among complete cases, the apparent C-index increased from 0.527 for demographics and cardiomyopathy phenotype to 0.813 after adding HF functional class and 0.842 after biomarkers, with limited additional discrimination from imaging measures.

Conclusions

Genetic testing demonstrated substantial laboratory-reported P/LP yield, although its effects on clinical management, family screening, and costs were not evaluated. HF functional severity and biomarkers provided the greatest apparent prognostic discrimination for death or transplantation, supporting an integrated clinical approach to pediatric cardiomyopathy assessment.

Introduction

Pediatric cardiomyopathy is a heterogeneous cause of heart failure (HF), death, and heart transplantation. Molecular testing may identify an underlying disorder and, when causality is established, support targeted family evaluation and gene-specific care [1, 5–8]. However, identifying a laboratory-reported pathogenic or likely pathogenic (P/LP) variant is not equivalent to demonstrating a change in management or improvement in survival. Moreover, access to genetic testing is unequal in resource-constrained settings, including India [18, 19]. We evaluated molecular findings alongside clinical severity, biomarkers, echocardiography, and cardiac magnetic resonance (CMR) in a prospective Indian pediatric cardiomyopathy cohort. We aimed to describe the yield of clinically selected testing and examine its association with transplant-free survival, while distinguishing observed prognostic associations from clinical utility that was not directly measured.

Methods

Study Design and Population

From January 2021 through June 30, 2026, this prospective single-center registry enrolled 235 patients younger than 18 years with primary cardiomyopathy at the Narayana Institute of Cardiac Sciences in India, beginning at their first HF clinic visit or hospitalization. Data were collected and managed using the Research Electronic Data Capture (REDCap) platform. The institutional review board approved the study (NHH/AEC-CL-2019-427), and parental or legal-guardian consent with age-appropriate assent was obtained. Patients were classified into four groups: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) using contemporary AHA and ESC definitions [1, 6]. Left ventricular non-compaction cardiomyopathy patients were included under DCM group. Secondary cardiomyopathy attributable to congenital heart disease, chemotherapy, hypertension, endocrine or nutritional disorders, other acquired systemic causes, or resolved myocarditis was excluded.

Clinical, Laboratory, and Imaging Assessment

Demographic, clinical, laboratory, imaging, and outcome data were prospectively recorded. HF severity was graded by NYHA or age-appropriate Ross class. Baseline laboratory measures included blood urea nitrogen, creatinine, and NT-proBNP. Echocardiography followed pediatric recommendations, with prespecified left ventricular ejection fraction (LVEF), LV internal diameter in diastole (LVIDd), and tricuspid annular plane systolic excursion (TAPSE) measurements [20].

CMR was performed when clinically appropriate on a 3-T scanner (Ingenia, Philips Healthcare) using standardized pediatric protocols [21]. Cine imaging provided LVEF and right-ventricular ejection fraction (RVEF), along with LV and RV volumes indexed to body surface area. Late gadolinium enhancement (LGE) was acquired 10 to 15 minutes after 0.2 mmol/kg gadolinium using phase-sensitive inversion recovery and assessed for regional myocardial fibrosis.

Genetic Testing

Genetic testing was performed for clinical etiologic evaluation at MedGenome Labs (Bengaluru, India) using next-generation sequencing cardiomyopathy panels or whole-exome sequencing according to clinical indication. Variants were classified under ACMG/AMP standards as pathogenic, likely pathogenic, variants of uncertain significance (VUS), or negative [22]. P/LP denotes the laboratory-reported classification, not necessarily a confirmed causal diagnosis for the observed cardiomyopathy; gene–disease validity and clinical concordance must be considered. Testing was not protocol-mandated, and financial feasibility influenced uptake. Individual reasons for non-testing, patient-level testing charges, insurance coverage, family cascade testing, and treatment changes following results were not systematically recorded in the available analysis dataset. Therefore, testing uptake and diagnostic yield can be described, but its direct management impact and cost-effectiveness cannot be estimated from this cohort.

Outcome Definition

The primary endpoint was transplant-free survival from the first documented referral-center evaluation to the first occurrence of all-cause death or heart transplantation. The first eligible clinic visits or hospitalization was time zero for Kaplan-Meier and Cox analyses. Patients without an event were censored at their last follow-up on June 30, 2026

Statistical Analysis

Continuous variables are reported as mean ± SD or median (IQR), and categorical variables as n (%). Phenotype comparisons used ANOVA or Kruskal-Wallis and chi-square/Fisher exact tests as appropriate. Kaplan-Meier curves were compared by 2-sided log-rank tests; Cox regression assessed time-to-event associations. NT-proBNP was log-transformed. Imaging variables were evaluated individually because of event constraints. Hierarchical complete-case models included age, sex, and phenotype (Model 1), HF functional class (Model 2), log NT-proBNP and creatinine (Model 3), and echocardiographic LVEF (Model 4). Harrell C-index summarized discrimination and likelihood-ratio tests compared nested models. A separate CMR sequence evaluated RVEF and LGE. Genetic analyses compared P/LP, VUS, and negative groups; VUS and untested patients were excluded from the definitive P/LP-versus-negative comparison. Secondary genetic-burden analyses are detailed in the Supplement. Missing data were handled by complete-case analysis without imputation. Analyses used Python 3.13.5, SciPy 1.17.0, and statsmodels 0.14.6; $P < 0.05$ was significant.

Results

Cohort Characteristics

The pediatric cohort included 235 patients (mean age 7.1 ± 5.5 years; 51.9% male): 161 (68.5%) with DCM, 41 (17.4%) with HCM, 22 (9.4%) with RCM, 10 (4.3%) with ACM/ARVC, and 1 with mixed cardiomyopathy. Among the 234 patients in the 4 major phenotype groups, 157 (67.1%) presented in HF functional class III/IV. Median observed follow-up was 15.0 months (IQR 4.0-30.5), totaling approximately 445 patient-years. All patients had available HF severity assessments and were followed for a minimum of 2 visits and up to 12 visits. Complete clinical, biomarker, and echocardiographic data were available for 191 patients. Genetic testing results were available for 112 patients, and CMR data were available for 102 patients. During follow-up, 51 patients died and 13 underwent heart transplantation; 1 patient had both events recorded, yielding 63 first composite events (death or heart transplantation) (26.8%) (Table 1).

Table 1
Baseline Characteristics and Outcomes by Cardiomyopathy Phenotype

Characteristic	Overall	DCM	HCM	RCM	ACM/ARVC	P value
Age, years	7.1 ± 5.5	6.4 ± 5.4	8.4 ± 6.1	7.7 ± 4.6	11.9 ± 3.9	0.005
Male sex	122 (51.9)	78 (48.4)	22 (53.7)	14 (63.6)	8 (80.0)	0.158
Body surface area, m²	0.8 ± 0.5	0.8 ± 0.4	1.0 ± 0.6	0.8 ± 0.3	1.1 ± 0.3	0.033
HF functional class III/IV, n (%)	157 (67.1)	122 (75.8)	7 (17.1)	22 (100.0)	6 (60.0)	< 0.001
Blood urea nitrogen, mg/dL	14.7 ± 8.3	15.4 ± 8.9	12.5 ± 6.1	12.7 ± 4.9	12.2 ± 4.8	0.248
Creatinine, mg/dL	0.5 ± 0.2	0.5 ± 0.3	0.4 ± 0.2	0.4 ± 0.1	0.4 ± 0.1	0.572
NT-proBNP, pg/mL	6230 (2590–15397)	6560 (2845–16400)	5400 (1450–8565)	6308 (4112–9705)	3630 (1138–5045)	0.253
Echo LVEF, %	35.9 ± 22.4	23.6 ± 9.0	72.8 ± 14.0	55.2 ± 12.8	40.1 ± 21.5	< 0.001
LVIDd, mm	44.9 ± 14.7	50.6 ± 13.2	29.4 ± 7.9	33.5 ± 7.9	44.1 ± 10.5	< 0.001
TAPSE, mm	14.1 ± 4.0	13.6 ± 3.4	18.4 ± 3.6	11.2 ± 2.9	11.8 ± 3.3	< 0.001
CMR performed, n (%)	125 (53.2)	82 (50.9)	22 (53.7)	13 (59.1)	7 (70.0)	—
CMR LVEF, %	31.0 ± 18.9	19.7 ± 8.0	58.1 ± 8.5	55.2 ± 9.7	32.1 ± 18.1	< 0.001
CMR RVEF, %	38.6 ± 18.3	33.2 ± 16.2	61.7 ± 8.0	48.1 ± 13.6	26.4 ± 13.7	< 0.001
LGE present, n/N (%)	67/124 (54.0)	44/82 (53.7)	8/21 (38.1)	7/13 (53.8)	7/7 (100.0)	0.044
Death	51 (21.7)	35 (21.7)	4 (9.8)	8 (36.4)	3 (30.0)	0.082
Heart transplantation	13 (5.5)	11 (6.8)	0 (0.0)	1 (4.5)	1 (10.0)	0.343

[ACM = arrhythmogenic cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; CMR = cardiac magnetic resonance; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; HF = heart failure; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal dimension in diastole; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RCM = restrictive cardiomyopathy; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion.]

Characteristic	Overall	DCM	HCM	RCM	ACM/ARVC	P value
Death or transplantation	63 (26.8)	45 (28.0)	4 (9.8)	9 (40.9)	4 (40.0)	0.025

[ACM = arrhythmogenic cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; CMR = cardiac magnetic resonance; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; HF = heart failure; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal dimension in diastole; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RCM = restrictive cardiomyopathy; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion.]

Genetic Diagnostic Yield and Phenotype Distribution

Genetic testing was performed in 112 patients (47.7%). Laboratory-reported P/LP variants were identified in 54 (48.2%), VUS in 42 (37.5%), and negative results in 16 (14.3%). Among tested patients, P/LP yield was 44.3% in DCM, 63.6% in HCM, 57.1% in RCM, and 25.0% in ACM/ARVC (Table 2). TTN remained the most frequent P/LP gene, followed by MYH7, MYBPC3, FLNC, PTPN11, RAF1, and SLC22A5 (Supplemental Table 1).. The registry summary did not document how many results triggered cascade testing, treatment modification, or altered surveillance; such clinical utility outcomes were therefore not analyzed.

Table 2
Genetic Testing Results by Cardiomyopathy Phenotype

Genetic result	Overall	DCM	HCM	RCM	ACM/ARVC
P/LP	54 (48.2%)	35 (44.3%)	14 (63.6%)	4 (57.1%)	1 (25.0%)
VUS	42 (37.5%)	33 (41.8%)	4 (18.2%)	2 (28.6%)	3 (75.0%)
Negative	16 (14.3%)	11 (13.9%)	4 (18.2%)	1 (14.3%)	0 (0.0%)
Total tested	112	79	22	7	4

[P/LP = pathogenic/likely pathogenic; VUS = variant of uncertain significance]

Genetic Results and Clinical Outcomes

Among patients who underwent genetic testing, composite events occurred in 13 of 54 (24.1%) P/LP-positive children, 16 of 42 (38.1%) with VUS, and 7 of 16 (43.8%) with negative results. Kaplan–Meier curves differed among the three genetic-result groups (log-rank P = 0.035; Fig. 1). In the prespecified definitive-result comparison, P/LP-positive versus genetic-negative transplant-free survival did not reach statistical significance (log-rank P = 0.058). The definitive P/LP-versus-negative curves for the overall cohort and DCM subgroup are provided in Supplemental Fig. 1. Because testing was clinically selected and the negative comparator included only 16 children, these unadjusted group differences

should not be interpreted as evidence of protection from a P/LP variant or of a management benefit from testing.

Multiple-Variant Burden

Secondary genetic-burden analyses are summarized in Supplemental Tables 2 and 3. Seventeen of 112 tested children (15.2%) had variants in ≥ 2 reported genes; multiple-variant burden was not associated with transplant-free survival (log-rank P = 0.916; adjusted HR 0.80, 95% CI 0.31 to 2.11; P = 0.658). Five children carried combined P/LP + VUS findings; they had lower median LVEF than the remaining tested cohort (15% vs 27%; P = 0.017), although the DCM-only comparison was not significant (P = 0.069).

Imaging Associations With Death or Heart Transplantation

Several imaging measures were associated with the composite endpoint on univariable Cox analysis. Each 10% decrement in echocardiographic LVEF was associated with HR 1.25 (95% CI 1.08–1.44; P = 0.002), and each 5-mm decrease in TAPSE with HR 2.50 (95% CI 1.73–3.62; P < 0.001); LVIDd showed a borderline association (HR 1.18 per 10-mm increase, 95% CI 1.00-1.40; P = 0.053). In the CMR subset, each 10% decrease in LVEF was associated with HR 1.31 (95% CI 1.06–1.62; P = 0.012), each 10% decrease in RVEF with HR 1.34 (95% CI 1.11–1.62; P = 0.002), each 10-mL/m² higher RVEDVi with HR 1.04 (95% CI 1.01–1.08; P = 0.021), and LGE with HR 2.27 (95% CI 1.11–4.62; P = 0.024) (Fig. 2).

Genotype-Imaging Associations

Among patients with definitive genetic results, conventional echocardiographic and CMR measures did not differ significantly between P/LP-positive and genetic-negative groups (Supplemental Table 4). Echocardiographic LVEF, LVIDd, TAPSE, CMR LVEF, RVEF, and RVEDVi were similar between groups (all P > 0.05). LGE was numerically more frequent among P/LP-positive patients than among those with negative genetic testing (70.0% vs 50.0%), but the difference was not statistically significant (P = 0.292).

Incremental Prognostic Modeling

Among 191 patients with complete clinical, biomarker, and echocardiographic data (52 events), the base model (Model 1: age, sex, phenotype) had a Harrell C-index of 0.527. Adding HF functional class (Model 2) markedly improved discrimination to 0.813 (likelihood-ratio P < 0.001). Incorporating log NT-proBNP and creatinine (Model 3) further increased the C-index to 0.842 (P < 0.001), whereas adding echocardiographic LVEF (Model 4) produced minimal additional change (C-index 0.843; P = 0.821) (Table 3; Fig. 3). In 102 children with complete clinical and CMR data (34 events), the clinical model C-index was 0.815; adding CMR RVEF yielded 0.811 (P = 0.612), and adding LGE yielded 0.815 (P = 0.174). Thus, HF functional severity provided the largest gain in short-term prognostic discrimination; CMR markers were associated with outcome individually but did not materially improve discrimination beyond the clinical model in the complete CMR subset.

Table 3
Hierarchical Prognostic Models

Model	N	Events	Harrell C-index	Incremental LR P
Model 1: age + sex + phenotype (DCM reference)	191	52	0.527	—
Model 2: + HF functional class	191	52	0.813	< 0.001
Model 3: + log NT-proBNP + creatinine	191	52	0.842	< 0.001
Model 4: + echo LVEF	191	52	0.843	0.821
CMR subset: clinical model	102	34	0.815	—
CMR subset: + CMR RVEF	102	34	0.811	0.612
CMR subset: + CMR RVEF + LGE	102	34	0.815	0.174

[CMR = cardiac magnetic resonance; HF = heart failure; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction.]

Discussion

The principal observation was that clinical HF severity and biomarkers carried the strongest apparent near-term prognostic information, whereas genetic testing yielded laboratory-reported P/LP variants in 48.2% of the selected children tested. Of 235 children, 63 (26.8%) died or underwent heart transplantation. Echo and CMR abnormalities were associated with the composite endpoint, but their additional discrimination after clinical assessment was limited. These findings distinguish molecular characterization from prognosis; they do not demonstrate that genetic testing improved treatment decisions or outcomes. The 3-category genetic survival comparison was significant (P = 0.035), but the P/LP-versus-negative comparison was not (P = 0.058), and selective testing with only 16 negative results makes causal interpretation inappropriate.

The molecular yield is consistent with previous pediatric cardiomyopathy cohorts [2, 4, 9], but the denominator is crucial: only 112 of 235 children were tested. Testing was influenced by financial feasibility, making the tested group unlikely to represent all affected children. Published guidelines describe potential benefits of molecular diagnosis, including evaluation for syndromic or metabolic causes, targeted family testing, and gene-specific surveillance [6–8]. However, the present registry did not capture the number of relatives tested, newly identified affected relatives, or clinical decisions changed by molecular results. We therefore cannot claim those benefits were realized in this cohort. The economic question raised by limited uptake is particularly relevant in India: actual panel/exome charges, out-of-pocket expenditures, financial assistance, and downstream costs were not recorded. Without those data, a cost-effectiveness or value-for-money conclusion would be speculative.

Secondary analyses of reported variant burden did not identify a significant transplant-free survival association, unlike some earlier pediatric studies [24, 25]. The five children with both P/LP and VUS findings had lower median LVEF, but this small subgroup does not establish a gene-burden prognostic effect. Reported variants in genes associated with metabolic, syndromic, or arrhythmia disorders should not automatically be counted as causal cardiomyopathy diagnoses. Systematic review of variant-level reports, inheritance, segregation, and gene–disease validity would strengthen molecular interpretation [22, 28].

Lower echocardiographic LVEF and TAPSE, lower CMR ventricular ejection fractions, increased right ventricular end-diastolic volume index, and late gadolinium enhancement were associated with death or transplantation in univariable models. These findings are compatible with previous pediatric imaging studies [16, 17, 27]. However, imaging was obtained on clinical grounds, and its univariable association does not prove incremental prediction after clinical severity has been considered.

In hierarchical complete-case analyses, adding functional HF class increased the apparent C-index from 0.527 to 0.813; biomarkers increased it to 0.842, with little subsequent gain from echocardiographic LVEF. CMR RVEF and late gadolinium enhancement did not improve discrimination in the smaller CMR subset. The clinical implication is to prioritize careful functional assessment and biomarkers while using imaging and molecular results for complementary phenotypic characterization. These are apparent, internally unvalidated discrimination estimates rather than a ready-to-use clinical prediction tool.

Limitations

This single-center cohort had incomplete, clinically and financially selected genetic testing (47.7%), introducing substantial selection bias. Only 16 tested children had negative results; comparisons by genotype are underpowered and vulnerable to confounding. We did not systematically record reasons for declining testing, the price paid for panels or exomes, payer support, cascade testing, treatment or surveillance changes attributable to results, or downstream economic outcomes. Thus neither management benefit nor cost-effectiveness of genetic testing can be established. Laboratory-reported P/LP variants were not uniformly re-adjudicated for phenotype-specific gene–disease validity; VUS classifications may change [28]. CMR was not universal. Missingness was handled by complete-case analysis, and C-indices were not optimism-corrected or externally validated. Treatment exposures and invasive hemodynamics were not modeled as time-varying covariates.

Conclusions

In this prospective pediatric cardiomyopathy cohort, genetic testing identified laboratory-reported P/LP variants in nearly half of the selected children tested, but the study did not establish incremental clinical-management benefit, cost-effectiveness, or an independent genotype-related survival advantage. HF functional severity and biomarkers provided the strongest apparent near-term discrimination for death or heart transplantation; imaging identified additional markers of disease expression. Future prospective

studies should document testing indications, patient costs, cascade-screening outcomes, and management changes alongside longitudinal events.

Declarations

CRediT Authorship Contribution Statement

Shashi Raj: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing.

Shriprasad R. Deshpande: Validation, Writing – review & editing.

Robert J. Gajarski: Supervision, Writing – review & editing.

Antonio Cabrera: Supervision, Writing – review & editing.

Bibhuti B. Das: Conceptualization, Supervision, Formal analysis, Writing – original draft.

Acknowledgments: We thank Mrs. Vijaya P., RN, BSc, Senior Nursing Lead for the Heart Failure Program at the Narayana Institute of Cardiac Sciences, Bangalore, India, for her contributions to prospective data collection and data stewardship through the REDCap.

Supplementary data: Attached in separate File.

Disclosure of Interest: None

Funding: None

Ethics Approval: Institutional review board (NHH/AEC-CL-2019-427)

Data Availability: Data is stored in REDCap and is available upon request.

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Figures

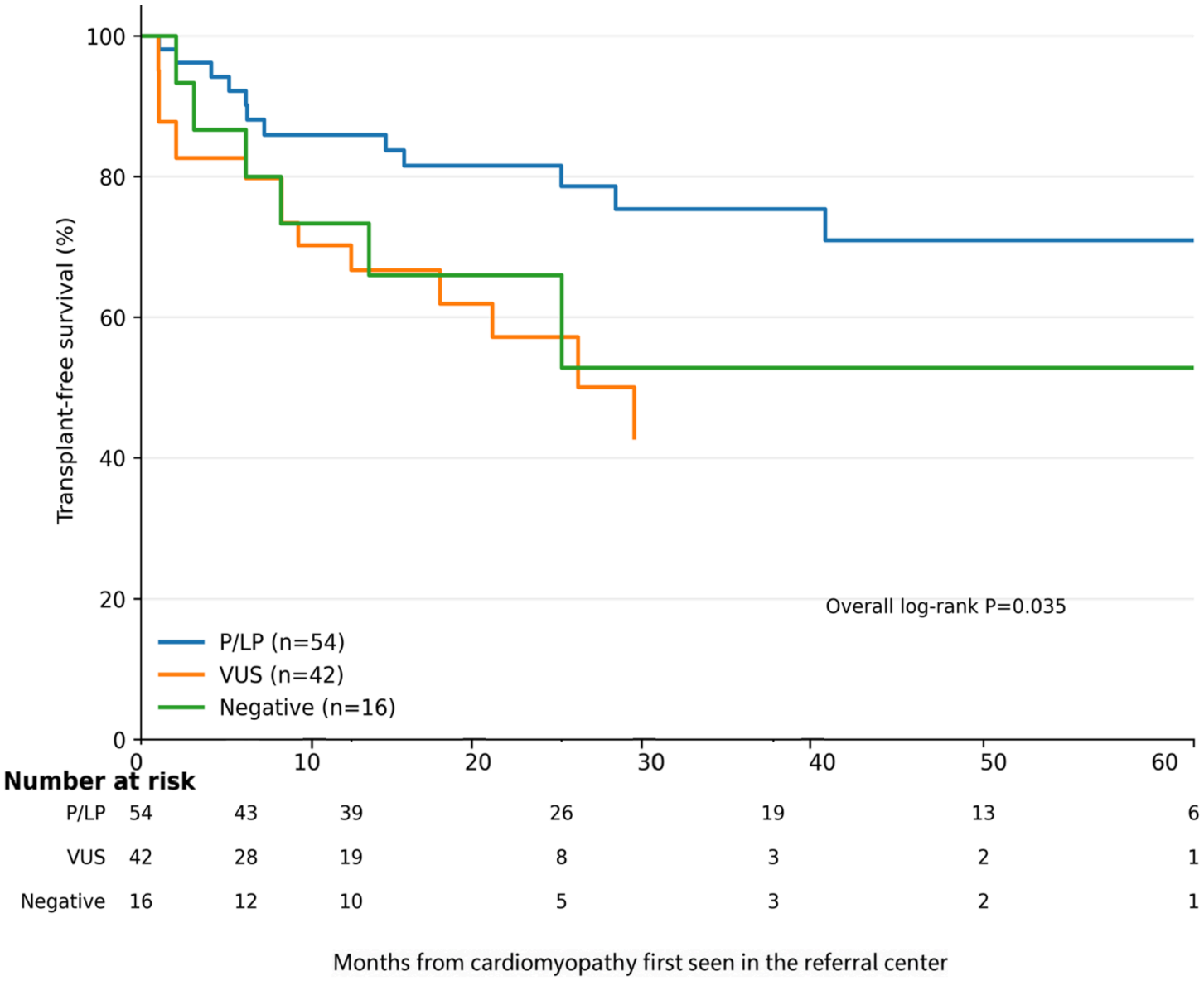


Figure 1

Transplant-free survival according to genetic test result (P/LP, VUS, or negative).

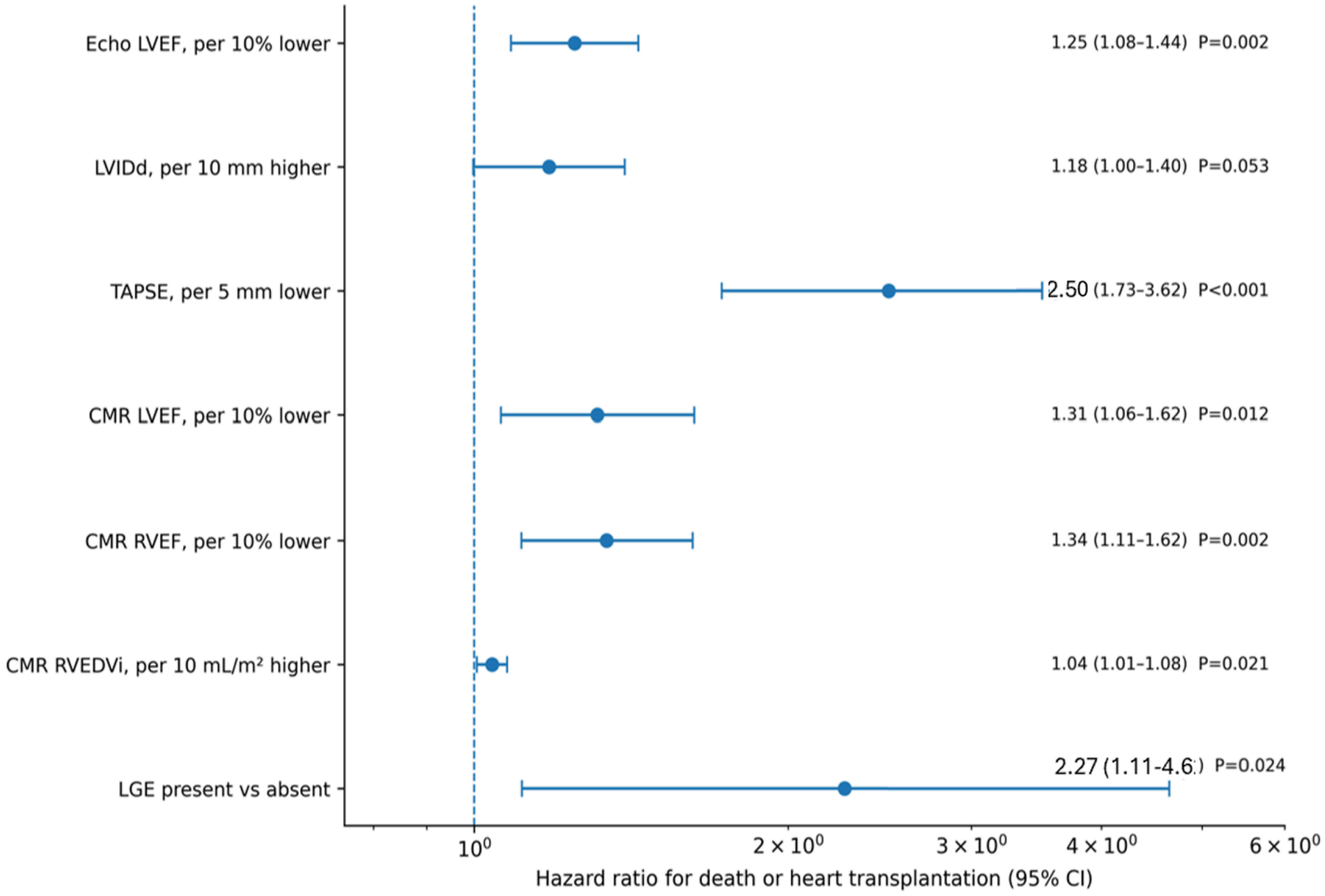


Figure 2

Associations of echocardiographic and CMR measures with death or heart transplantation.

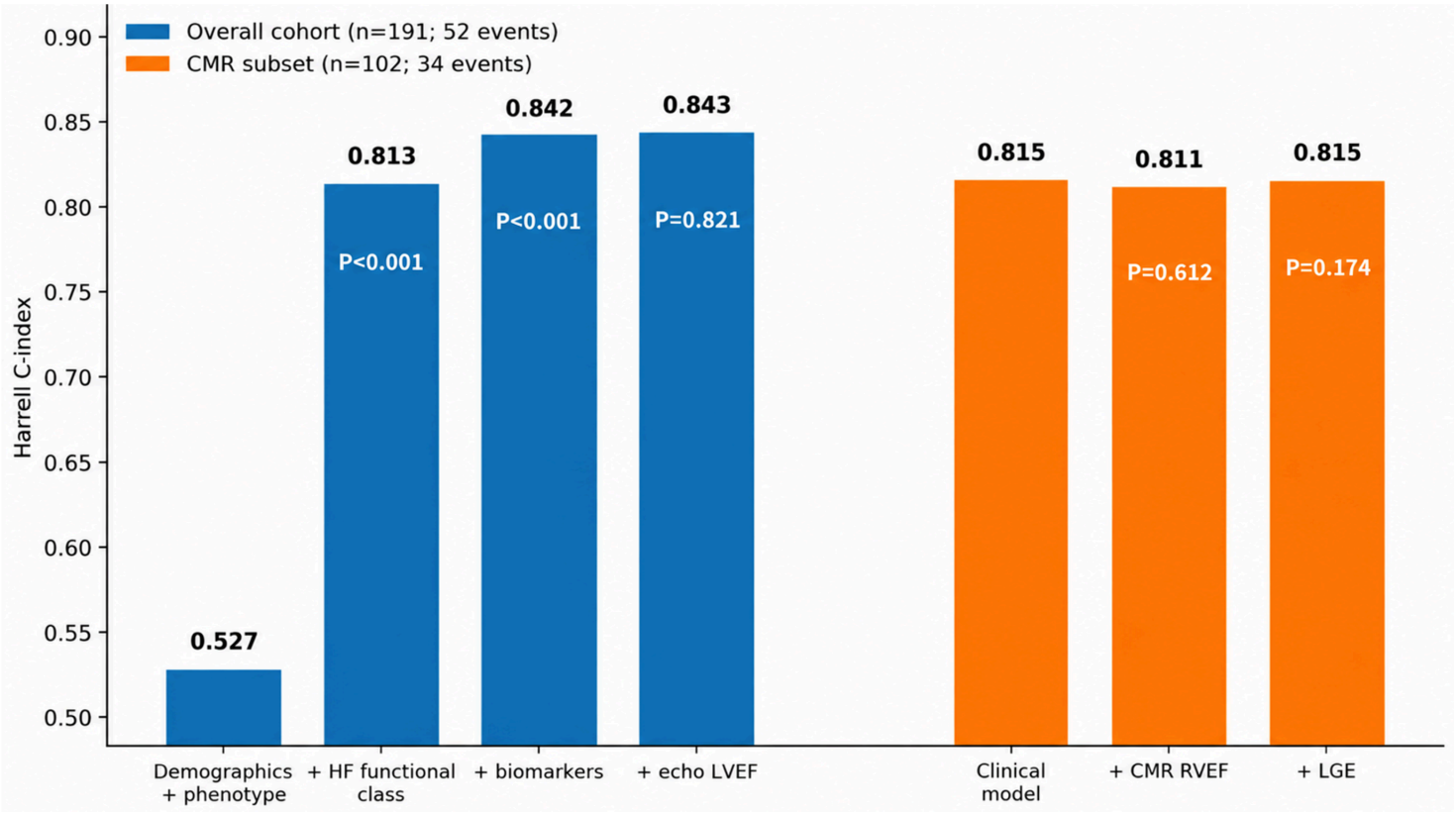


Figure 3

Incremental Prognostic Information From Clinical, Biomarker, Echocardiographic, and CMR Assessment.

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