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ORIGINAL RESEARCH

MYH7 Mutations in Restrictive Cardiomyopathy

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ABSTRACT

BACKGROUND Restrictive cardiomyopathy (RCM) is a rare cardiac disease characterized by impaired ventricular filling and relaxation, with preserved systolic function. This study investigates the genetic basis of RCM and its impact on clinical outcomes, particularly heart transplantation (HTx).

OBJECTIVES The aim of the study was to identify genetic variations associated with RCM and assess their impact on disease progression and HTx necessity.

METHODS A retrospective analysis was conducted on 94 RCM patients from Fuwai Hospital (2003-2021), diagnosed via echocardiography or pathological examination. Whole exome sequencing screened patient samples for variants in key genes associated with RCM, validated via Sanger sequencing. Histopathological analysis of explanted hearts included systematic sampling from ventricles and interventricular septum, with Masson's trichrome staining for fibrosis quantification.

RESULTS Genetic variants were identified in 54% of patients, with a higher prevalence in HTx patients (73%) compared to non-HTx patients (27%). Myosin heavy chain 7 (*MYH7*) mutations were found in 15% of cases, significantly associated with HTx ($P < 0.001$) and atrial fibrillation ($P = 0.025$). Patients with MYH7 mutations exhibited extensive fibrosis in the interventricular septum compared to nonmutation patients ($P < 0.05$). The mean age at diagnosis was 47.8 years, with HTx patients diagnosed at a younger age (mean 36.0 years) and transplanted at a mean age of 37.4 years, compared to non-HTx patients diagnosed at a mean age of 57.9 years. The median follow-up time was 5 years.

CONCLUSIONS Genetic variations, particularly in the *MYH7* gene, are significant risk factors for RCM progression and HTx. Genetic screening may guide early interventions, while fibrosis and MYH7 pathways offer potential therapeutic targets. (JACC Adv. 2025;4:101693) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

HTx = heart transplantation

IVS = interventricular septum

MYH7 = myosin heavy chain 7

OMIM = Online Mendelian Inheritance in Man

RCM = restrictive cardiomyopathy

WES = whole exome sequencing

Restrictive cardiomyopathy (RCM), a rare form of heart muscle disease, is characterized by impaired filling and relaxation of the heart while maintaining normal or near-normal contraction functions.[1] Despite its rarity, the profound impact of RCM on patient survival rates and quality of life—especially in the absence of effective treatment and prognostic strategies—underscores the importance of understanding the factors influencing its prognosis, particularly genetic variations.[2] The investigation into the genetic underpinnings of RCM and their impact on patient outcomes has emerged as a critical area of focus.

Genetic factors play a crucial role in the development of RCM. Approximately 30% of RCM cases are considered a primary disease of genetic origin, but only a few genes have been associated with familial RCM.[3] The application of whole exome sequencing (WES) and other high-throughput genomic technologies has begun to unveil a variety of genetic variations associated with RCM.[4] However, the extent to which genetic variations influence the prognosis of RCM patients remains to be fully elucidated, posing one of the primary challenges in current research.

This study leverages data collected from 94 RCM patients who were diagnosed at the Fuwai Hospital between 2003 and 2021. The study cohort encompasses a wide diagnostic age range (3-88 years), with a nearly balanced male-to-female ratio, all diagnosed through echocardiography or pathological examination, excluding secondary RCM cases. Through WES, this research has identified a series of genetic variations related to RCM and investigated their potential impact on patient prognosis.

The objective of this study is to identify genetic variations associated with RCM and evaluate their impact on clinical outcomes, particularly the necessity for heart transplantation (HTx). Additionally, we aim to explore the relationship between specific genetic mutations and disease progression, including the development of atrial fibrillation (AF) and myocardial fibrosis. By integrating genetic and clinical data, this study seeks to provide insights into the prognostic significance of genetic variations in RCM and to inform personalized treatment strategies.

METHODS

STUDY POPULATION. We retrospectively analyzed all RCM patients with available WES data diagnosed from January 1, 2003, to December 31, 2021, in Fuwai Hospital (documented from January 1, 1982, to December 31, 2021). This study was performed in accordance with the Helsinki Declaration and approved by the local ethics review boards. Informed consent for DNA analysis was obtained from patients in line with local institutional review board requirements at the time of collection. Inclusion criteria for the study were as follows. 1) Patients diagnosed with restrictive cardiomyopathy (RCM) based on echocardiographic findings, including biatrial dilatation, normal or mildly reduced left and right ventricular ejection fraction, and nondilated ventricles. 2) Availability of complete clinical history, imaging studies, and genetic testing results. 3) Presence of primary RCM conditions. Exclusion criteria were as follows. 1) Presence of nongenetic RCM-related conditions, including nonhereditary infiltrative diseases (eg, amyloid light chain amyloidosis, wild-type transthyretin amyloidosis, and sarcoidosis), nongenetic interstitial fibrosis/intrinsic myocyte dysfunction (eg, radiation- or chemotherapy-induced RCM, systemic sclerosis, and diabetic cardiomyopathy), or nongenetic endomyocardial diseases (eg, tropical or nontropical endomyocardial fibrosis, hypereosinophilic syndrome, endocardial fibroelastosis, and carcinoid heart disease). 2) Other systemic or cardiac conditions unrelated to RCM. 3) Inability to provide complete clinical data or follow-up information. 4) Presence of end-stage cardiac disease that precludes clear differentiation of RCM-specific characteristics.[4] Family history was extensively investigated. All familial cases fulfilled the published criteria of 2 or more affected individuals in a single family or unexplained sudden death in a first-degree relative of a cardiomyopathy.

The clinical manifestations and outcomes assessed in this study included symptoms such as dyspnea, chest tightness, weakness, bloating, and jugular vein distention. Medication use was recorded, specifically the administration of angiotensin-converting enzyme (ACE) inhibitors/ARBs, beta-blockers, and diuretics. The presence of familial cardiomyopathy was noted. Key cardiac measurements taken were left atrial diameter, right ventricular diameter, left atrium to aorta ratio (LA/AO), left ventricular end-diastolic diameter, and left ventricular ejection fraction. Detailed methods of echocardiographic assessment are provided in the supplementary materials for reference.

OUTCOME DEFINITIONS AND DATA COLLECTION. The primary outcome was time from the first clinical visit for RCM-related symptoms to HTx. The secondary outcome was implantable cardioverter-defibrillator (ICD) implantation. Data on outcomes were extracted from hospital records, including

procedural notes for ICD. Follow-up commenced at the first documented symptom-based visit and continued until HTx or the last clinical encounter (censoring date). Kaplan-Meier curves analyzed survival free from HTx or ICD implantation stratified by genetic status. The Kaplan-Meier survival curve was corrected using inverse probability weighting, with covariates including sex and diuretic use history. Cox proportional hazards models, adjusted for potential confounders including sex and diuretic use history using the coxph function from the survival package in R, were used to assess the independent impact of different mutation types (myosin heavy chain 7 [MYH7], structural, sarcomeric, metabolic, and others) on outcomes, with no mutation as the reference group to calculate the HRs for each type. Patients without events were censored at their last follow-up date. Symptom and medication data were collected at the time of RCM diagnosis. For adult and adolescent patients, symptoms were documented through direct patient-reported history. For pediatric patients ($\leq$ 18 years), symptoms were assessed based on parental or guardian reports, as younger children may not reliably verbalize their experiences. Pediatric-specific indicators included dyspnea (tachypnea, nasal flaring, and increased work of breathing), chest discomfort (irritability and refusal to lie flat), weakness/fatigue (poor feeding, prolonged feeding time, and reduced activity levels), and bloating (abdominal distension, hepatomegaly, and increased fussiness due to discomfort). Medication use, including beta-blockers, ACE inhibitors/ARBs, and diuretics, was recorded from initial prescription records at diagnosis. Symptoms and clinical signs were separately documented, with clinical signs (eg, jugular vein distention, hepatomegaly, and pulmonary rales) recorded from physician assessments during the initial diagnostic evaluation.

SEQUENCING AND DATA ANALYSIS. Sequencing data were analyzed as previously described.[5] Basically, genomic DNA was extracted from the peripheral blood of each sample, fragmented to an average size of 180 to 280 bp, and DNA libraries were constructed using the established Illumina paired terminal protocol. The Agilent SureSelect Human All Exon V6 Kit (Agilent Technologies) was used for exome capture according to the manufacturer's instructions. The Illumina Novaseq 6,000 platform (Illumina Inc) was used to sequence genomic DNA and generate 150 bp counterpart reads. Minimum coverage of 10$\times$ (average coverage of 100$\times$) for $\sim$99% of the genome. After sequencing, bcl2fastq software (Illumina) was used for basecall file conversion and demultiplexing. The resulting FASTQ data were submitted to in-house quality control software for removing low-quality reads and then were aligned to the reference human genome (hg19) using the Burrows-Wheeler Aligner, and duplicate reads were marked using sambamba tools. Single nucleotide variants (SNVs) and indels were called with samtools to generate genomic variant call format. The raw calls of SNVs and INDELs were further filtered with the following inclusion thresholds: 1) read depth >4; 2) root mean square mapping quality of covering reads >30; 3) the variant quality score >20.

Annotation was performed using annotate variation (June 2019). Annotations included minor allele frequencies from public control data sets as well as deleteriousness and conservation scores enabling further filtering and assessment of the likely pathogenicity of variants.

Filtering of rare variants was performed as follows. 1) Variants with a minor allele frequency <0.01 in 1,000 genomic data (1000g_all), esp6500siv2_all (http://evs.gs.washington.edu/EVS), and gnomAD data (gnomAD_ALL and gnomAD_EAS). 2) Only SNVs occurring in exons or splice sites (splicing junction 10 bp) are further analyzed since we are interested in amino acid changes. 3) Then synonymous SNVs that are not relevant to the amino acid alternation predicted by dbscSNV are discarded; the small fragment nonframeshift (<10 bp) indel in the repeat region defined by RepeatMasker are discarded. 4) Variations are screened according to scores of SIFT, Polyphen, MutationTaster, and CADD softwares. The potentially deleterious variations are reserved if the score of more than half of these 4 softwares support harmfulness of variations. Sites (>2 bp) that did not affect alternative splicing were removed. Detailed methods and additional analyses are provided in the supplementary materials for reference.

GENETIC-BASED CLASSIFICATIONS AND FUNCTIONAL GENE GROUPS. The 19 causative genes analyzed were grouped into functional gene groups as previously described based on similar common gene ontology (GO) functions, involvement in biological processes, localization to subcellular compartments, and other shared properties based on consolidated scientific evidence from the published data and available biological databases. In this way, 19 genes were assigned to one of the following resultant functional gene groups: sarcomeric genes, structural genes, metabolic genes, and other genes. MYH7 (Online Mendelian Inheritance in Man [OMIM]: 160760) was considered as separate groups due to their specific characteristics of frequency and phenotype in RCM. Troponin T2

(*TNNT2*, OMIM: 191045),[6] troponin I3 (*TNNI3*, OMIM: 191044),[7] and troponin C1 (*TNNC1*, OMIM: 191040) were included in the sarcomeric genes group. Each of these genes encodes for components of thick and thin sarcomeric filaments and is involved in sarcomeric contraction, sharing the GO molecular functions of "catalytic activity" and "actin binding motor protein" (GO 0000146; GO 0003824). Desmin (*DES*, OMIM: 125660), titin (*TTN*, OMIM: 188840), vinculin (*VCL*, OMIM: 193065), lamin A/C (*LMNA*, OMIM: 150330), and filamin C (*FLNC*, OMIM: 102565) were included in the structural genes, merging both sarcolemmal and sarcoplasmatic cytoskeletal protein-coding genes. N-Sulfoglucosamine sulfohydrolase (*SGSH*, OMIM: 605270), glucuronidase beta (*GUSB*, OMIM: 611499), galactosidase beta 1 (*GLB1*, OMIM: 611458), glucosidase alpha acid (*GAA*, OMIM: 606800), alanine-glyoxylate aminotransferase (*AGXT*, OMIM: 604285), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*, OMIM: 607786) were included in the metabolic genes group. Patients harboring variants in the remaining screened genes were grouped in an "other genes" group, including Raf-1 proto-oncogene, serine/threonine kinase (*RAF1*, OMIM: 164760), and protein C, inactivator of coagulation factors Va and VIIIa (*PROC*, OMIM: 612283). And patients carrying 2 variants were also classified in "other genes" group, but one patient carrying 2 metabolic-related genes was categorized into metabolic genes group.

PATHOLOGICAL EXAMINATION AND QUANTIFICATION. Gross and microscopic examinations of explanted hearts were performed by 2 pathologists blinded to the clinical and genetic data. A total of 6 specimens were obtained from each explanted heart. Blocks of the left ventricle (LV), including the anterior free wall of the left ventricle, lateral free wall of LV, and posterior free wall of the LV; blocks of the right ventricle (RV) including anterior free wall of RV (right ventricular outflow tract), posterior free wall of the RV (subtricuspid area), and interventricular septum (IVS) were removed systematically for histological study. Samples were fixed in 10% formalin and were processed for histological examination. Tissue samples were stained with Masson's trichrome, and the slides were scanned into a digital image.

Subepicardial adipose tissue, including vessels and pericardium, was removed by Adobe Photoshop CS5 (Adobe Systems) before quantitative analysis. Endocardium was removed from fibrosis analysis when endocardial thickening was detected. The myocardium, fibrosis, and adipose tissue were evaluated using Image-Pro Plus (version 4.0, Media Cybernetics) as previously reported. The proportion of myocardium, fibrosis, and adipose tissue in the LV was the average of the values in the anterior, lateral, and posterior free wall of the LV, and the proportion in the RV was the average of values in the anterior and posterior free wall of the RV. The value for the IVS was directly taken as the IVS proportion.

STATISTICAL ANALYSIS. Clinical and laboratory statistics are reported as mean ± SD, median (IQR), or counts and percentages, as appropriate. The statistical analyses were performed using SPSS version 29.0 and GraphPad Prism 10.

For continuous variables, comparisons between groups were made using the analysis of variance test, with the Brown-Forsythe correction applied when the assumption of equal variances was violated. In cases where data did not meet the assumptions for parametric tests, the nonparametric Mann-Whitney U test was used. For categorical variables, chi-square tests were performed; when expected cell counts were <5, Fisher exact test was used instead.

Kaplan-Meier survival curves were constructed to estimate time from diagnosis to HTx or ICD implantation. The log-rank test was used to compare survival curves between different genetic variant statuses (eg, MYH7 mutations, other variants, and no variants). The Kaplan-Meier analysis was corrected using inverse probability weighting to account for potential confounders, including sex and diuretic use history.

Cox proportional hazards models were fitted to assess the independent impact of different mutation types on the time to HTx or ICD implantation. The Cox regression analysis was adjusted for potential confounders, including sex and diuretic use history, using the coxph function from the survival package in R. HRs and 95% CIs were calculated for each mutation type, with no mutation serving as the reference group. Patients without events were censored at their last follow-up date.

No adjustments for multiple comparisons were made in the statistical analyses due to the exploratory nature of the study, and results were interpreted with caution.

RESULTS

PATIENT CHARACTERISTICS AND BASELINE CLINICAL FEATURES. A total of 102 patients diagnosed with RCM at Fuwai Hospital between 2003 and 2021 (documented from 1982 to 2021) (Supplemental Table 1) were initially identified from the clinical database. Among them, 8 patients were excluded because biological samples could not be obtained due to logistical constraints or insufficient tissue availability. The remaining 94 patients were enrolled in

the study, including 44 heart transplant cases (47%) and 50 nontransplant cases (53%). WES was performed on all 94 patients to identify genetic variants. Based on the WES results, 51 patients were classified as variant-positive and 43 as variant-negative. All enrolled patients were followed up according to standard clinical protocols, and their clinical data were systematically collected and analyzed. For patients who underwent HTx, the date of transplantation was used as the endpoint. For patients who did not undergo HTx, the date of their last clinical visit was recorded as the endpoint, reflecting their final follow-up time. (Supplemental Figure 1). The age at diagnosis ranged from 3 to 88 years (mean 47.8 years), with pediatric patients (≤18 years) comprising a subset of the cohort. Of the total cohort, 54 (57%) were male. The most common presenting symptoms included dyspnea (72%), chest tightness (70%), weakness (35%), and bloating (38%). A total of 61 patients (65%) were prescribed diuretics, 44 (47%) received beta-blockers, and 27 (29%) were on ACE inhibitors or angiotensin receptor blockers (ARBs) as part of their medical management (**Table 1**).

TABLE 1 Comparison of Baseline Characteristics of the Study Population by Mutation Status

	Total (N = 94)	P/LP Variant Positive (n = 51, 54%)	P/LP Variant-Negative (n = 43, 46%)	*P* Value
Age of diagnosis, y	47.64 ± 18.90	40.73 ± 19.39	55.84 ± 14.72	***<0.001***
Male	54 (57.4%)	33 (64.7%)	21 (48.8%)	0.121
Dyspnea	68 (72.3%)	39 (76.5%)	29 (67.4%)	0.330
Chest tightness	66 (70.2%)	37 (72.5%)	29 (67.4%)	0.590
Weakness	33 (35.1%)	23 (45.1%)	10 (23.3%)	***0.027***
Bloating	36 (38.3%)	24 (47.1%)	12 (27.9%)	***0.039***
ACEI/ARB	26 (27.8%)	12 (23.5%)	14 (32.6%)	0.314
Beta-blockers	44 (46.8%)	25 (49.0%)	19 (44.2%)	0.640
Diuretic	60 (63.8%)	38 (74.5%)	22 (51.2%)	***0.019***
Familial cardiomyopathy	10 (10.6%)	7 (13.7%)	3 (7.0%)	0.274
LAD, mm	48.5 ± 8.0	50.0 ± 7.6	46.5 ± 8.2	***0.042***
RVD, mm	25.1 ± 5.1	25.3 ± 5.6	24.9 ± 4.4	0.788
LA/AO	1.8 ± 0.5	2.0 ± 0.5	1.6 ± 0.3	***<0.001***
LVEDD, mm	46.1 ± 7.6	46.2 ± 8.7	46.1 ± 6.2	0.950
LVEF, %	52.1 ± 11.6	49.9 ± 11.9	55.0 ± 10.6	***0.042***

Values are mean ± SD or n (%). The bold-italics values in the table represent statistically significant differences between the 2 groups. A *P* value <0.05 is considered statistically significant.

ACEI = angiotensin-converting enzyme inhibitor; ARBs = angiotensin receptor blockers; LA/AO = left atrium/aorta; LAD = left atrial diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; P/LP = pathogenic/likely pathogenic; RVD = right ventricular diameter.

PATIENT OUTCOMES AND FOLLOW-UP. Among the 94 patients diagnosed with RCM, 44 patients (47%) reached the primary endpoint of HTx, and 16 patients (17%) underwent ICD implantation, the secondary endpoint. The median follow-up time was 5 years (Q1-Q3: 2.1-11.0 years) (**Table 2**). The 44 patients who underwent HTx had an average age at transplantation of 37.4 years. The youngest patient to undergo transplantation was 4 years old, while the oldest was 67 years old. In comparison, patients who did not require transplantation (n = 50) had a significantly higher average age at diagnosis of 57.9 years. Among the cohort, 44 patients had pathology data obtained at the time of transplantation. Follow-up was censored at the last recorded clinical visit for patients who did not reach the defined endpoints.

Spectrum of RCM genes. We provide a comprehensive overview of the genomic landscape of the *MYH7* gene, illustrating various mutations that have been identified as significant in the context of RCM (**Figure 1**). A total of 59 disease-related pathogenic or likely pathogenic variants were identified in 51 patients (54%), with higher prevalence in transplant patients (73%) than in outpatient cases (27%). Five patients had 2 pathogenetic/likely pathogenetic variants on different genes (5%) (Supplemental Table 2). Pediatric patients' (age ≤ 18 years) characters are described in Supplemental Tables 4 and 5. There are significant differences in left ventricular end-diastolic diameter and LA/AO compared with adults.

Within this, variants in the *MYH7* gene, which encodes for the MYH7—a motor sarcomeric protein essential for cardiac muscle function—were detected in 15% of all cases, with a higher prevalence in the HTx group (12%) compared to the out-patient group (3%). Four patients with the same missense mutation of an arginine (R) to be replaced by a glutamine (Q) at the 249th position of the protein (**Figure 1B**). Other genes in this category, including *TNNT2*, *TNNI3*, and *TNNC1*, together represent an additional 6% of genetic variations, with these being more commonly identified in the outpatient group. Structural genes—namely *DES* (Desmin), *TTN* (Titin), *VCL* (Vinculin), *LMNA* (Lamin A/C), and *FLNC* (Filamin C)—were responsible for 19% of the genetic variations observed. These genes are crucial in maintaining the integrity and function of the cellular architecture within the cardiac muscle. A majority of the variants within these structural genes were observed in patients who had undergone HTx, indicative of their possible association with the severity of RCM that necessitates such an intervention. Regarding metabolic-related genes, which include *SGSH* (N-sulfoglucosamine sulfohydrolase), *GUSB* (beta-glucuronidase), *GLB1* (beta-galactosidase), *GAA* (acid alpha-glucosidase), *AGXT* (alanine-glyoxylate aminotransferase), and *PCSK9* (proprotein convertase subtilisin/kexin type 9), they collectively accounted for 6% of the genetic variations. They play various roles in metabolic pathways that could

TABLE 2 Clinical Outcomes and Follow-Up Time

		Age of Onset, y	Age at Diagnosis, y	Age at Event, y	Follow-Up Time
Heart transplantation (HTx)	44 (46.8%)	29.2 ± 15.2	36.0 ± 16.7	37.4 ± 15.9	5 (2.1-11.0)
ICD implantation	16 (17.0%)	44.6 ± 19.7	54.7 ± 18.4	51.7 ± 20.9	12.5 (5.6-19.0)
No endpoint (censored)	42 (44.7%)	52.4 ± 14.5	57.6 ± 14.7	/	6.2 (2.3-10.9)

Values are n (%) or mean ± SD.
ICD = implantable cardioverter-defibrillator.

intersect with the pathogenesis of amyloidosis. Additionally, 5 patients had 2 pathogenetic/likely pathogenetic variants, and 2 patients with *PROC* variants were categorized into the other group (Supplemental Table 3, Supplemental Figure 2). All identified variants in Supplemental Table 6 included variant of uncertain significance, likely pathogenic, and pathogenic variants.

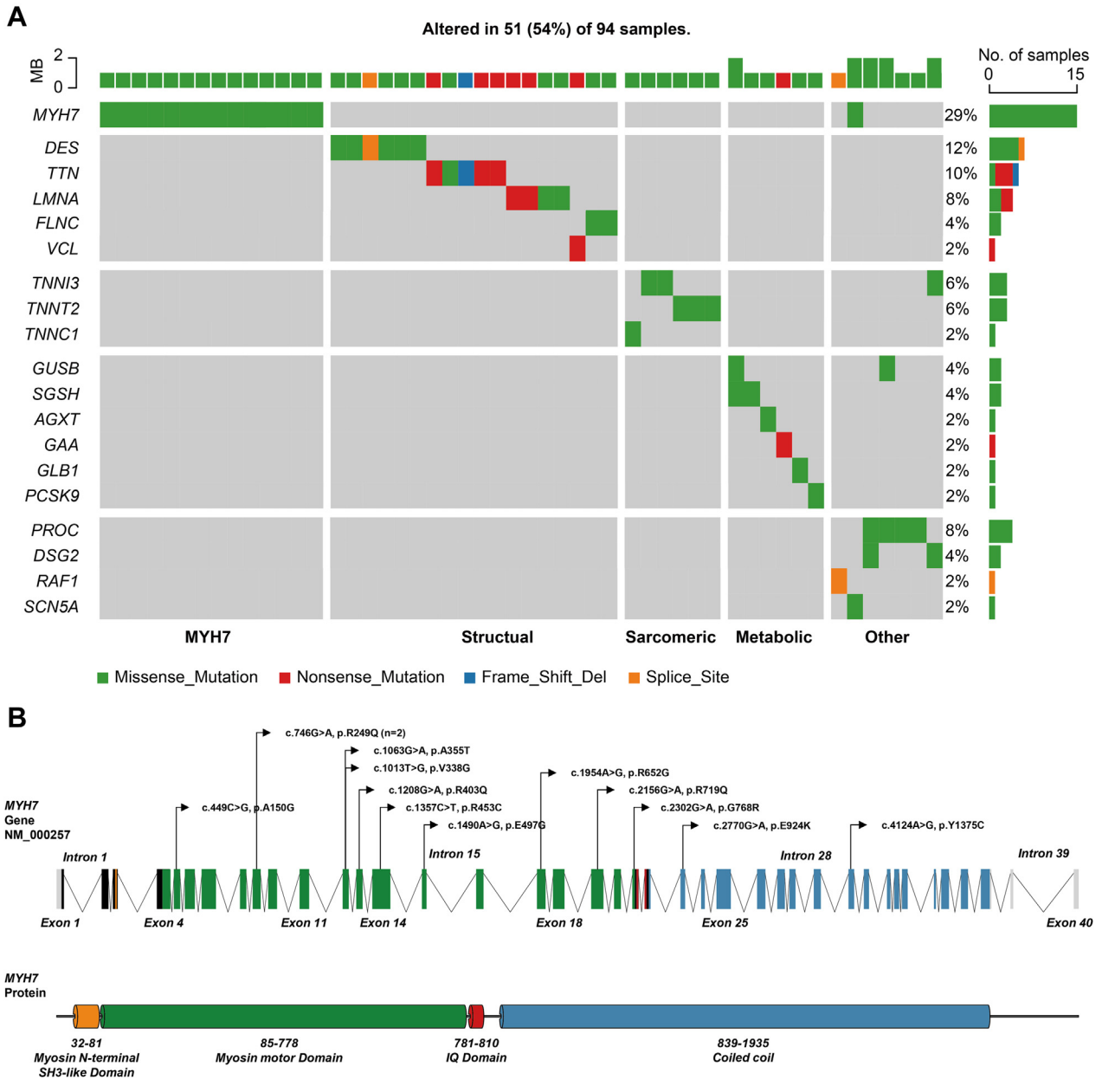
GENE MUTATION AND OUTCOMES. In the RCM cohort study, the comparison of baseline characteristics reveals how the presence of genetic variants correlates with the clinical manifestation of the disease. Notably, the variant-positive group exhibited a higher prevalence of symptoms such as weakness and bloating, which are significant considering that RCM often presents with signs of right heart failure due to diastolic dysfunction (**Table 1**). The statistically significant use of diuretics in the variant-positive group ($P = 0.019$) aligns with the management of fluid overload, a common complication in RCM as the stiffened ventricles lead to fluid retention. The greater left atrial diameter in variant-positive patients ($P = 0.042$) indicates more pronounced atrial enlargement, a reflection of increased left ventricular filling pressures, a hallmark of RCM where the ventricles are unable to relax fully. The marked difference in the LA/AO ratio ($P < 0.001$) further emphasizes the structural cardiac changes associated with RCM and suggests that genetic variants may exacerbate the disease's characteristic ventricular compliance issues. The left ventricular ejection fraction percentages in the variant-positive group are significantly lower, indicating a worse cardiac function.

***MYH7* VARIANTS AND RISK OF HEART TRANSPLANTATION.** After adjusting for sex and the medication of diuretics, Kaplan-Meier curves show that patients with genetic variants (variant-positive, red) have significantly lower survival rates compared to patients without variants (variant-negative, blue) across onset (**Figure 2A**) ($P = 0.002$), diagnosis (**Figure 2B**) ($P = 0.002$), and HTx (**Figure 2C**) ($P = 0.003$). Further analysis indicates worse survival outcomes for variant-positive patients in terms of diagnosis to HTx (**Figure 2E**) ($P = 0.04$), while showing no significant differences in onset to HTx (**Figure 2D**) and onset to diagnosis (**Figure 2F**).

Specifically, patients harboring *MYH7* variants demonstrate a notably increased risk of progression to end-stage heart failure necessitating HTx (**Figure 3A**) ($P = 0.02$), but there is no significant differences in ICD implantation. The survival analyses show a marked reduction in transplant-free survival for those with *MYH7* mutations compared to variant-negative patients. **Figure 3B** shows that patients with sarcomeric variants do not have significantly worse survival rates from diagnosis to HTx. But there is notably increased risk of disease onset to ICD implantation ($P = 0.04$). Then the data comparison with other sarcomeric and nonsarcomeric variants shows that *MYH7* is particularly impactful (Supplemental Table 4, **Figure 3C**), especially with an increased rate of HTx ($P = 0.03$). In addition, we present the HRs for HTx risk associated with various genetic mutation categories in RCM patients, as determined by a Cox regression model. The results indicate that patients with *MYH7* mutations have a 4.5-fold higher risk of HTx compared to those without any mutations ($P < 0.001$) (**Figure 3D**). Our investigation into RCM has also revealed compelling evidence of the heightened risk associated with *MYH7* mutations for developing AF (**Table 3**).

The natural history of individuals reveals distinct patterns in the progression of cardiomyopathy based on genetic variations, particularly highlighting the rapid progression from diagnosis to HTx in patients with *MYH7* mutations (**Figure 4**). Specifically, individuals with *MYH7* mutations showed an average age at diagnosis of 44.1 years and progressed to transplantation by an average age of 45.5 years, indicating a notably swift escalation in disease severity that necessitates earlier intervention. Patients with other genetic variants displayed a slower progression to HTx from diagnosis, with an average of 2.5 years. In addition, the analysis distinctly shows that variant-negative patients experience a later onset of cardiomyopathy, with symptoms typically manifesting at an older age compared to those with

FIGURE 1 Genetic Test Results of the RCM Cohort

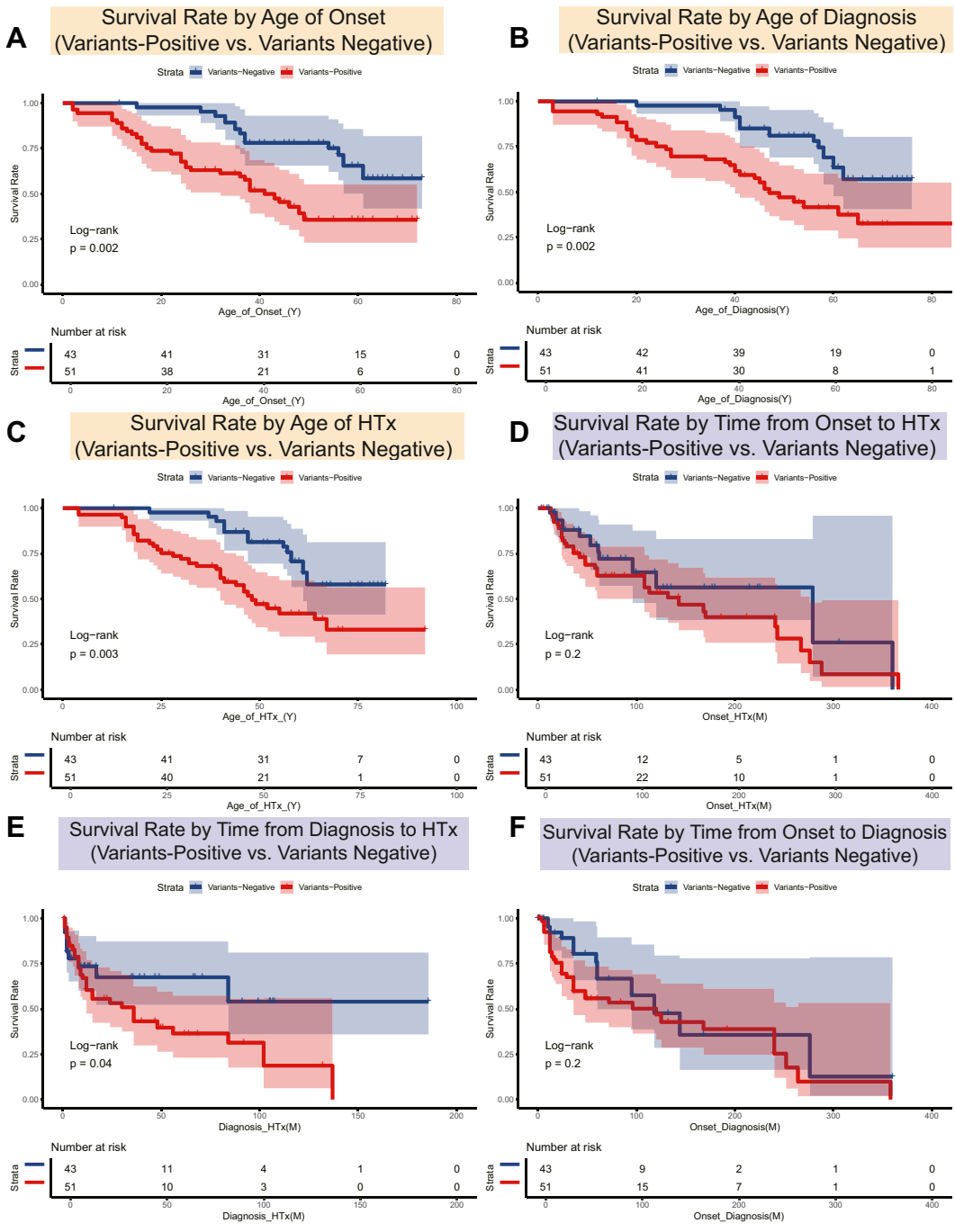


(A) Oncoplot of patients carrying P/LP variants. (B) *MYH7* is the most mutated gene, and its visualization on the transcript. MYH7 = myosin heavy chain 7; P/LP = pathogenic/likely pathogenic; RCM = restrictive cardiomyopathy.

genetic mutations. Specifically, the average age of onset for variant-negative patients is around 40 years, later than those observed in groups with *MYH7* mutations or other genetic variants.

***MYH7* MUTATIONS ARE ASSOCIATED WITH EXTENSIVE IVS FIBROSIS.** Figure 5A shows representative histological sections from the anterior, lateral, and posterior free walls of the LV, IVS, and the anterior and posterior free walls of the RV for *MYH7* mutation, *SGSH* mutation, and variant-negative cases. The *MYH7* mutation cases exhibited significantly more fibrosis (indicated by blue staining) compared to both SGSH mutation and variant-negative cases. Figure 5B, 5C, 5D

FIGURE 2 **Kaplan-Meier Survival Curves Comparing the Clinical Time of RCM Patients in Variant-Positive vs Variant-Negative Groups**



(A to C) Comparing variant-positive (red) and variant-negative (blue) patients by age of onset, diagnosis, and HTx. (D to F) Comparing variant-positive (red) and variant-negative (blue) patients for onset to HTx, diagnosis to HTx, and onset to diagnosis. Shaded areas represent the 95% CIs, and log-rank *P* values show significant differences. HTx = heart transplantation; RCM = restrictive cardiomyopathy.

FIGURE 3 **Kaplan-Meier Survival Curves and Cox Regression Model Comparing the Clinical Time Intervals of RCM Patients Based on Genetic Variant Status**

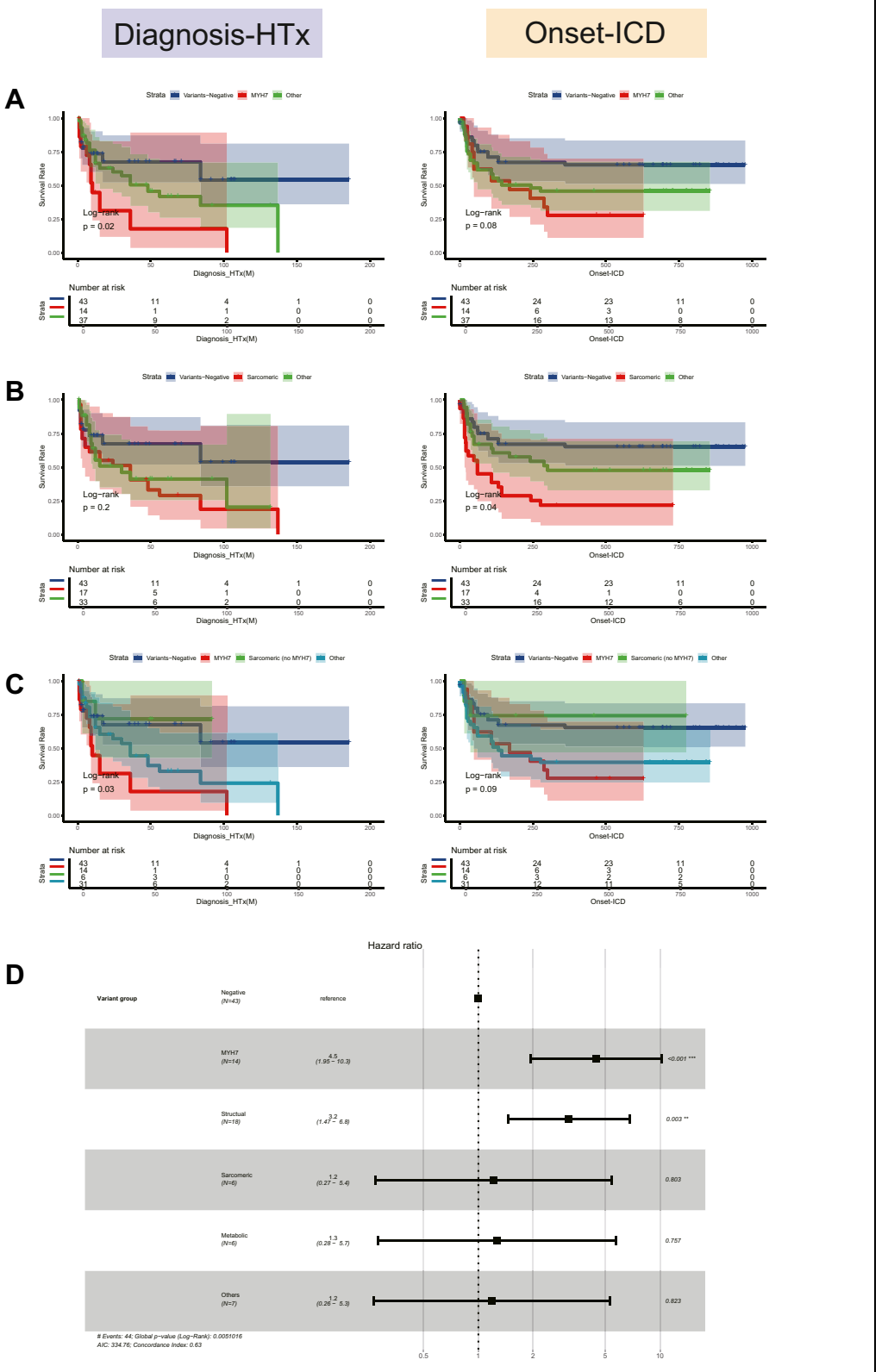


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TABLE 3 Comparison of Baseline Characteristics of the Study Population by Mutation Status, Especially the *MYH7*

	Total Variant Positive (N = 51)	MYH7 (n = 14)	Other Variant (n = 37)	*P* Value
Male	33	8	25	0.487
Dyspnea	39	9	30	0.207
Chest tightness	37	8	29	0.129
Weakness	23	5	18	0.407
Bloating	24	7	17	0.682
Atrial fibrillation	31	12	19	***0.025***
Jugular vein distention	11	2	9	0.437
ACEI/ARB	12	3	9	0.753
Beta-blockers	25	9	16	0.18
Diuretic	38	10	28	0.756
Familial cardiomyopathy	7	4	3	0.058
LAD, mm	50	52.9 ± 4.3	49.0 ± 8.3	0.108
RVD, mm	43	27.3 ± 7.0	24.5 ± 4.9	0.148
LA/AO	36	2.1 ± 0.5	2.0 ± 0.6	0.577
LVEDD, mm	49	45.4 ± 4.3	46.4 ± 9.7	0.728
LVEF, %	48	50.6 ± 10.5	49.6 ± 12.5	0.81

Values are n or mean ± SD. The bold-italics values in the table represent statistically significant differences between the 2 groups. A *P* value <0.05 is considered statistically significant.

MYH7 = myosin heavy chain 7; other abbreviations as in Table 1.

provide a quantitative comparison of myocardial, fibrotic, and adipose tissue proportions in the LV, IVS, and RV, respectively. The LV and RV show no significant differences in fibrosis among the different groups. However, the IVS shows a marked increase in fibrosis in *MYH7* mutation patients compared to other mutations and variant-negative cases, as indicated by the asterisks in Panel C. The statistical significance is denoted by *($P < 0.05$), highlighting the higher fibrotic burden in the IVS of *MYH7* mutation patients.

DISCUSSION

This study investigated the genetic and clinical factors influencing the prognosis of RCM in a cohort of 94 patients (Central Illustration). Among the patients, 51 (54%) were found to carry at least one pathogenic or likely pathogenic genetic mutation, and 14 (15%) had mutations in the *MYH7* gene, which is a key sarcomeric protein implicated in cardiomyopathy. Patients with *MYH7* mutations were significantly more likely to progress to HTx, with 73% of *MYH7* mutation carriers requiring transplantation, compared to 27% in the mutation-negative group. *MYH7* mutations were also associated with an increased risk of AF and greater fibrosis burden. Additionally, genes such as cardiac *TNNT2*[6] and *TNNI3*,[7] myosin-binding protein C3 (*MYBPC3*, OMIM: 600958),[8] myosin light chain-2 and 3 (*MYL2*, OMIM: 160781, *MYL3*, OMIM: 160790),[9] *DES*,[5] myopalladin (*MYPN*, OMIM: 608517),[10] *TTN*,[11] Bcl2-associated athanogene 3 (*BAG3*, OMIM: 603883),[12] discoidin, *CUB* and *LCCL* domain containing 2 (*DCBLD2*, OMIM: 607709),[13] *LMNA*,[14] *FLNC*,[15] and αB-crystallin (CRYAB, OMIM: 123590)[16] have been implicated in the pathogenesis of RCM. These genetic insights not only aid in understanding the pathological mechanisms of RCM but also offer new molecular criteria for diagnosis and lay the groundwork for personalized treatment approaches for patients.[13] The study cohort indicates a clear trend: individuals with pathogenic or likely pathogenic mutations have a greater prevalence of transplantation than those without such variants, emphasizing the genetic risk associated with transplantation.

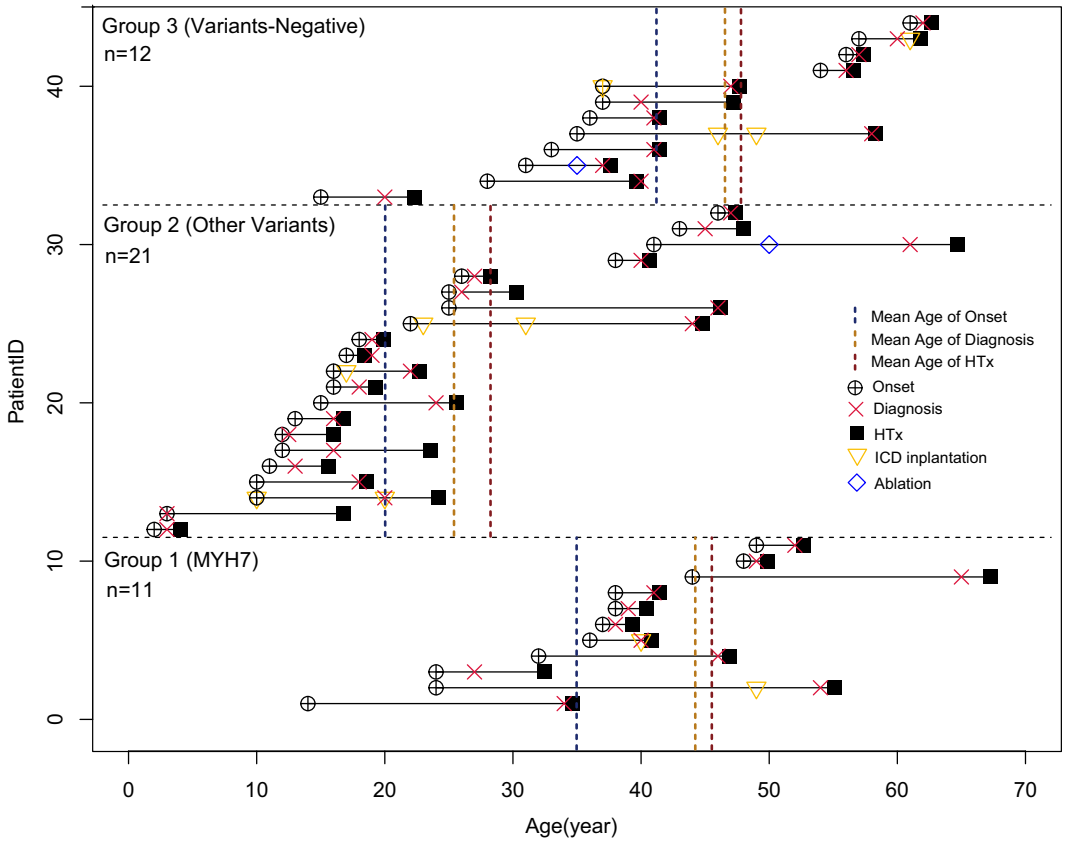
We further evaluated the epicardial-to-endocardial distribution of fibrotic tissue. The distribution of myocardium (red), fibrosis (yellow), and adipose (green) are correspondingly shown. The MYH7 mutation cases show a full layer of fibrosis, while the SGSH cases show a significant fibrosis area in the middle layer. These results show that RCM patients carrying *MYH7* gene mutations exhibit more severe intraventricular septum fibrosis, which is directly related to a higher need for HTx.

Our investigation into RCM, focusing on genetic predispositions and their clinical manifestations, has also revealed compelling evidence of the heightened risk associated with *MYH7* mutations for developing AF.[17] In hypertrophy cardiomyopathy, it had been reported that compared with other sarcomeric genes, patients with likely pathogenic or pathogenic variation in *MYH7* had a higher rate of incident AF

FIGURE 3 Continued

Kaplan-Meier survival curves comparing patients (A) with no variants (blue), MYH7 variants (red), and other variants (green) for survival from diagnosis to heart transplantation (HTx, left) and from disease onset to ICD implantation (right). (B) Patients with no variants (blue), sarcomeric variants (red), and other variants (green) for survival from diagnosis to HTx (left) and from disease onset to ICD implantation (right). (C) Patients with no variants (dark blue), MYH7 variants (red), sarcomeric variants excluding MYH7 (green), and other variants (light blue) for survival from diagnosis to HTx (left) and from disease onset to ICD implantation (right). The number of patients at risk at various time points is noted below. Shaded areas represent the 95% CIs, and log-rank P values show significant differences. (D) HRs for heart transplantation risk associated with different mutations in RCM patients, as determined by a Cox regression model. ICD = implantable cardioverter-defibrillator; other abbreviations as in Figures 1 and 2.

FIGURE 4 The Natural History of 44 RCM Patients From Initial Symptoms to Heart Transplantation in Each Group

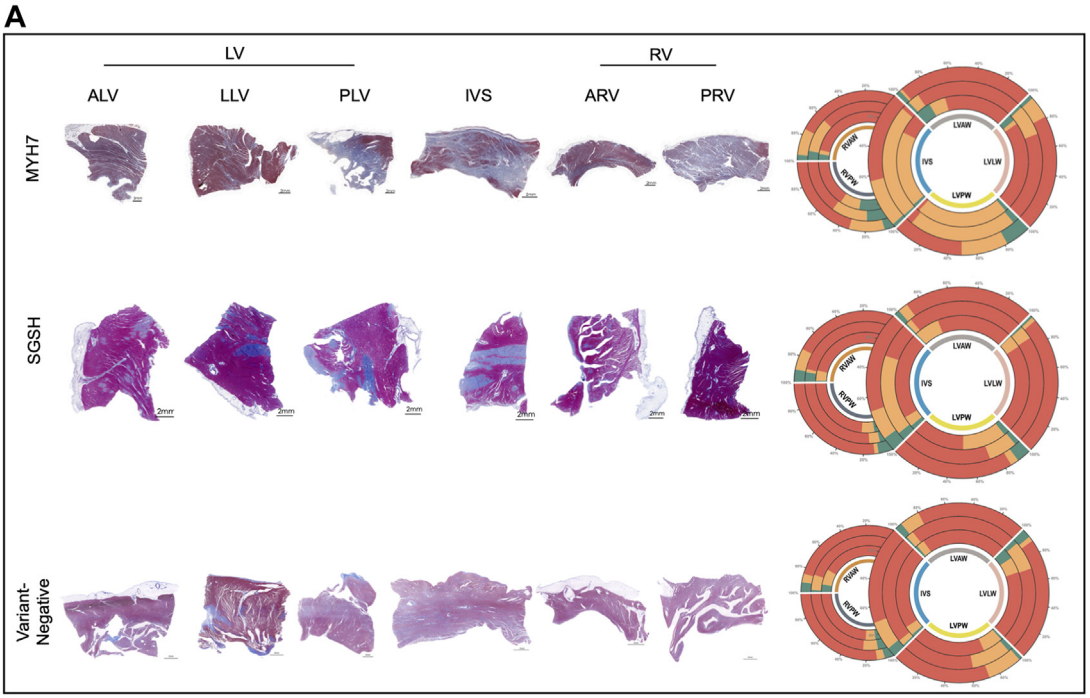


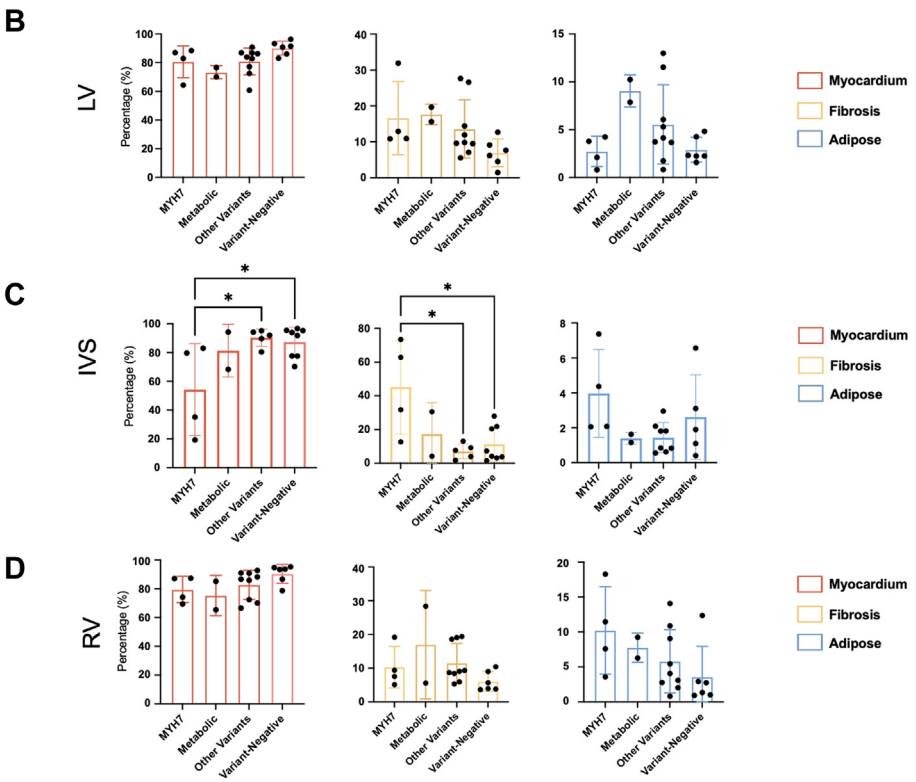
HTx = Heart Transplantation; RCM = restrictive cardiomyopathy.

independent of clinical and echocardiographic factors.[18] AF is likely to be associated with intracardiac thrombosis, and the presence of AF increases the risk of heart failure.[17] The observed correlation between *MYH7* mutations and an increased incidence of AF in RCM patients highlights the critical need for a tailored approach in the management of this patient subgroup. Given the elevated risk of thromboembolic events associated with AF, our findings advocate for a proactive stance on anticoagulation therapy in RCM patients harboring *MYH7* mutations. This approach not only aligns with the intention to minimize stroke risk but also emphasizes the importance of genetic screening in identifying patients at heightened risk for AF, thus enabling the early initiation of appropriate therapeutic interventions.

MYH7 mutations may trigger earlier extracellular matrix remodeling and more extensive remodeling. This distinct pathological feature can be linked to the critical role of the β-myosin heavy chain, encoded by the *MYH7* gene, in cardiac muscle mechanics and structural integrity. The septal predominance of fibrosis in *MYH7*-related RCM may result from the unique biomechanical stress endured by this region, which is exacerbated by the altered functionality of the myosin protein due to the mutation. The impact of *MYH7* mutations extends beyond typical myocardial dysfunction; it specifically enhances structural disorganization within the septum. This disorganization likely leads to localized cellular responses that culminate in increased fibrotic activity. The genetic specificity of the *MYH7* mutation contributes to this localized septal pathology, differentiating it from the effects observed with other mutations, which may not localize or manifest similarly. Comparative studies highlight that this severe septal fibrosis is significantly more prevalent in cases with *MYH7* mutations as opposed to those involving other genetic variants or no detectable mutations, emphasizing the potent pathogenic influence of *MYH7* on cardiac architecture, particularly in the septal region.

FIGURE 5 Comparative Histopathology of RCM Affected by *MYH7* Mutation vs Other Mutations and Nonmutation Cases





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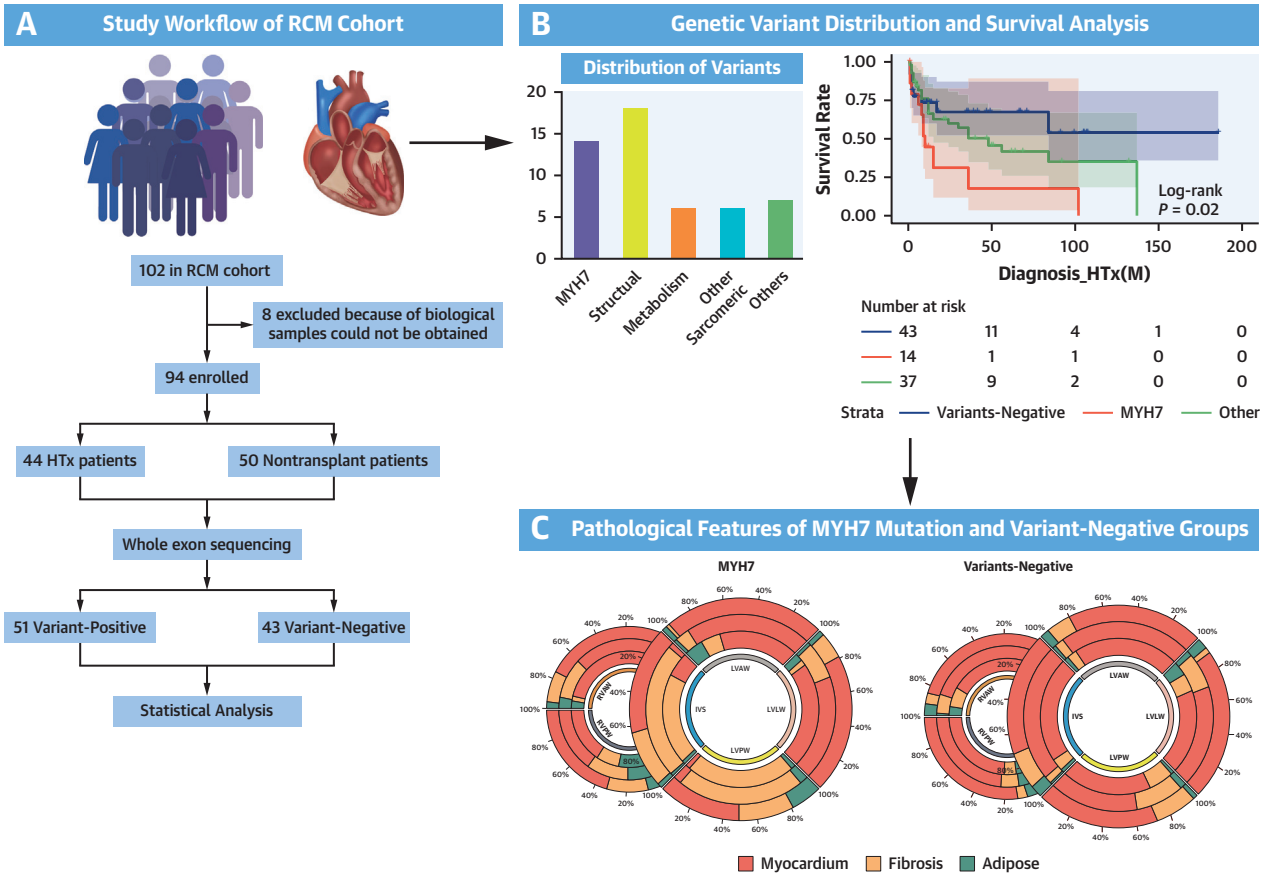
CENTRAL ILLUSTRATION **MYH7 Mutations in Restrictive Cardiomyopathy**



Zhao Y, et al. JACC Adv. 2025;4(5):101693.

(A) Study workflow for the RCM cohort. (B) Genetic variant distribution and heart transplantation outcomes, with the distribution of genetic variants identified in the RCM cohort, including MYH7 mutations, structural variants, metabolism-related variants, other sarcomeric variants, and variants in other categories (left), and the Kaplan-Meier survival analysis compares heart transplantation-free survival among patients with MYH7 mutations, other variants, and variant-negative cases (right). (C) Pathological features of MYH7-positive and variant-negative patients. Abbreviations as in Figure 1.

In the hypertrophy cardiomyopathy cohort, *MYH7* mutation carriers without left ventricular hypertrophy had both higher procollagen type I carboxy-terminal propeptide levels (indicating increased collagen synthesis) and lower early diastolic levels (indicating more impaired relaxation) than *MYBPC3* mutation carriers.[19] In addition, the study found that cardiac fibroblasts derived from RCM patients have unique gene expression signatures compared with healthy individuals and exacerbate cardiomyocyte relaxation dysfunction by secreting paracrine factors.[20] These findings further highlight the critical

FIGURE 5 Continued

(A) Masson's trichrome staining map of 6 site pathology of transplant patients. RCM myocardium with *MYH7* mutation, highlighting extensive blue-stained collagen indicating significant fibrotic tissue and accumulation of lipofuscin. The distribution of myocardium (red), fibrosis (yellow), and adipose (green) are correspondingly shown. (B-D) Qualitative pathological analysis was used to quantify the degree of myocardium proportions, fibrosis, and adipose invasion at different sites (LV, IVS, and RV) in *MYH7* mutation, metabolic-related mutations, other mutations, and nonmutation transplant patients. *$P < 0.05$; **$P < 0.01$. IVS = interventricular septum; LV = left ventricle; RV = right ventricle; other abbreviations as in Figure 1.

role played by interactions between cardiomyocytes and cardiac fibroblasts in addition to tissue fibrosis in the pathophysiology of RCM. Genetic variation in *MYH7* is associated with higher levels of propeptide of type I procollagen, a marker of collagen synthesis, suggesting that fibrosis could mediate a link between *MYH7* and AF.[18,19] Therefore, there may be a direct link between *MYH7* and the incidence of AF that is independent of the hemodynamic effects, mediated by processes such as atrial fibrosis or extracellular matrix remodeling that should be investigated further.

Mutations in genes encoding sarcomeric proteins can lead to different types of cardiomyopathies but have been relatively rarely reported in RCM.[21,22] Sarcomere function is very sensitive to any type of disturbance. Even a dysfunctional sarcomeric protein, alterations in protein-protein interactions, changes in sarcomeric structure and dynamics, altered expression, proteolytic degradation, etc, can progress to contractile dysfunction and ultimately myocardial infarction disease and heart failure. Sometimes, compensatory mechanisms are triggered to overcome the deficit, but over time, this mechanism can also become pathological.[23-25] Human cardiac myosin is a hexameric protein complex consisting of β myosin heavy chains (encoded by *MYH7*), 2 essential light chains (encoded by *MYL3*), and 2 regular myosin light chains (encoded by *MYL2*).[26,27] While genetic sequencing was conducted post-transplantation, the mutations identified are inherent germline variants. These mutations, including MYH7 and other sarcomeric genes, have been extensively validated as primary contributors to the pathogenesis of restrictive cardiomyopathy (RCM). Their role as precursors to the disease is independent of the timing of sequencing, as they reflect lifelong genetic predispositions rather than acquired alterations due to medical treatment or transplant procedures.

The survival curves depicted illustrate not only just the heightened risk of progression to HTx in the presence of *MYH7* mutations but also the relative impact of these mutations when contrasted with other sarcomeric and nonsarcomeric gene variations. While all variants seem to influence the disease trajectory, *MYH7* mutations stand out, suggesting that they may lead to more rapid progression to severe heart failure. This observation could be due to the integral role of the *MYH7*-encoded beta-myosin heavy chain in cardiac muscle contraction; mutations here might lead to a more significant compromise of myocardial function. Among these mutations, R249Q mutations account for the largest number of patients. R249Q mutation in *MYH7* gene has been previously associated with hypertrophic cardiomyopathy, suggesting that hypertrophy is a compensation for decreased contractility.[25,28] But for the first time, we describe it in the RCM cohort. It demonstrates the remarkable phenotypic variability in cardiomyopathy.

The analysis further suggests that *MYH7* mutations could serve as a potent predictor of a more severe RCM phenotype that may necessitate earlier and more aggressive clinical interventions, including HTx. This association warrants a strategic approach in the clinical management of RCM, wherein genetic testing for *MYH7* variants might become a routine part of patient assessment, guiding decisions regarding surveillance intensity, timing of intervention, and potentially, eligibility and prioritization for HTx.

STUDY LIMITATIONS. Currently, it is unclear why mutations in the same gene cause different cardiomyopathies. Given the rarity of RCM, some subcategories in this study had small sample sizes. This reflects the inherent challenges of studying rare diseases and underscores the importance of collaborative research to gather larger datasets. For subcategories with very few cases, we chose to focus on descriptive analyses to illustrate the clinical and genetic spectrum of RCM without performing underpowered statistical analyses. Additionally, no adjustments for multiple comparisons were made in the statistical analyses, and results were interpreted with caution due to the exploratory nature of the study. This approach was taken to identify potential associations that warrant further investigation in larger cohorts. Genetic overlap also exists between RCM and myofibrillar myopathies. Gene overlap between the 2 diseases may indicate the deleterious involvement of pathological cardiac protein aggregates.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Genetic testing, particularly for MYH7 mutations, is crucial in identifying high-risk RCM patients, enabling early interventions and prioritization for HTx. MYH7 mutations are strongly associated with AF and interventricular septal fibrosis, necessitating proactive arrhythmia management. The findings emphasize the rapid disease progression in MYH7 mutation carriers, underscoring the need for timely, personalized treatment strategies to improve outcomes.

TRANSLATIONAL OUTLOOK: Further research is required to understand how MYH7 mutations drive fibrosis and cardiac dysfunction, providing a basis for targeted therapies. Developing interventions to address MYH7-related complications can help slow disease progression and improve patient outcomes. Integrating genetic insights into clinical guidelines will enhance the adoption of precision medicine in managing RCM.

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KEY WORDS heart transplantation, MYH7, restrictive cardiomyopathy

APPENDIX For a supplemental Methods section as well as supplemental tables and figures, please see the online version of this paper.