Clinical Outcomes and Genetic Analyses of Restrictive Cardiomyopathy in Children

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Running title

Genotype-outcome correlation in pediatric RCM

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ABSTRACT

Background: Restrictive cardiomyopathy (RCM) in children is rare and outcomes are very poor. However, little information is available concerning genotype-outcome correlations.

Methods: We analyzed the clinical characteristics and genetic testing, including whole exome sequencing, of 28 pediatric RCM patients who were diagnosed from 1998 to 2021 at Osaka University Hospital in Japan.

Results: The median age at diagnosis (interquartile range) was 6 (2.25–8.5) years. Eighteen patients received heart transplantations and five patients were on the waiting list. One patient died while waiting for transplantation. Pathologic or likely-pathogenic variants were identified in 14 of the 28 (50%) patients, including heterozygous *TNNI3* missense variants in 8 patients. *TNNT2*, *MYL2*, and *FLNC* missense variants were also identified. No significant differences in clinical manifestations and hemodynamic parameters between positive and negative pathogenic variants were detected. However, 2-year and 5-year survival rates were significantly lower in patients with pathogenic variants (50% and 22%) compared with survival in patients without pathogenic variants (62% and 54%) ($P = 0.0496$, log-rank test). No significant differences were detected in the ratio of patients diagnosed at nationwide school heart disease screening program between positive and negative pathogenic variants. Patients diagnosed by school screening showed better transplant-free survival compared with patients diagnosed by heart failure symptoms ($P = 0.0027$ in log-rank test).

Conclusions: In this study, 50% of pediatric RCM patients had pathogenic or likely-pathogenic gene variants, and *TNNI3* missense variants were the most frequent. Patients with pathogenic variants showed significantly lower transplant-free survival

compared with patients without pathogenic variants. (250 words)

Nonstandard Abbreviations and Acronyms

CI	Cardiac index
LOS	Low output syndrome
VAD	Ventricular assist device
VUS	Variant of unknown significance
WES	Whole exome sequencing

Introduction

Restrictive cardiomyopathy (RCM) is an extremely rare form of cardiac muscle disease characterized by ventricular diastolic dysfunction with preserved systolic function. A cohort study of the North American Pediatric Cardiomyopathy Registry from 1990 to 2008, which included 152 RCM patients, demonstrated that RCM accounted for 4.5% of cardiomyopathy cases and the 5-year transplant-free survival was approximately 30%. [1] This survival rate was much worse than pediatric dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM), which had 5-year transplant-free survival rates of 50% and 90%, respectively. Another study in the Mayo Clinic over 38 years included 20 patients and demonstrated similar outcomes, with a 5-year transplant-free survival rate of 38%. [2] Recently, a Japanese multicenter retrospective cohort study of 54 pediatric RCM patients revealed a 5-year transplant-free survival of approximately 40%. [3] However,

these previous studies did not consider genetic evaluation. Therefore, genetic evaluations are required to improve the assessment of clinical outcomes in pediatric patients with RCM.

Recently, genetic analyses, including whole exome sequencing (WES), have identified various candidate pathogenic gene variants in RCM patients, such as *TNNI3*, *TNNT2*, *MYL2*, *FLNC*, and *MYH7*. [4–6] Approximately 25%–50% of pediatric RCM patients have candidate single nucleotide variants. However, the correlation between genotypes and outcomes in RCM has not been fully elucidated due to the rarity of this disease.

In this study, we analyzed clinical characteristics, hemodynamic parameters, and outcomes of 28 pediatric RCM patients under 15 years old who were diagnosed between 1998 and 2021 at the Osaka University Hospital in Japan. WES was conducted and correlations between clinical parameters and genetic backgrounds were analyzed. In Japan, a nationwide school heart disease screening is conducted for all pupils at 6–7 years old (year 1 at primary school), 12–13 years old (year 1 at junior high school), and 15–16 years old (year 1 at high school). The screening includes electrocardiograms, interview forms, and physical examinations by school doctors. [7] Since this system is unique to Japan, we also analyzed the effects of school heart screening on outcomes of pediatric RCM and the correlation with genetic testing.

Methods

The method of this study is described in the supplemental material.

Transparency and Openness Promotion (TOP) Guidelines statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

IRB approval

The genomic analyses and retrospective study of RCM were approved by the Osaka University Clinical Research Review Committee (no. 442 and no. 19266). The investigation conformed with the principles outlined in the Declaration of Helsinki. Written informed consents were obtained from all patients and/or their parents.

Results

Genetic Analysis of Pediatric RCM Patients

According to the clinical records from our hospital, thirty-seven patients under 15 years old were diagnosed with idiopathic or familial RCM between 1998 and 2021. We analyzed 28 patients who underwent genetic evaluations. The other 9 patients were excluded from the study because we could not obtain informed consent for genetic testing. Genetic analyses revealed pathogenic or likely-pathogenic single nucleotide variants in 14 (50%) of the 28 pediatric RCM patients. Eight patients had *TNNI3* missense variants, including R170W, K178E, R192H, R192L, and R204H, all of which were previously reported as pathogenic variants for RCM or HCM. [5, 8–11] The other missense variants were identified in *MYL2* (G162R), *TNNT2* (R104H), *MYH7* (R369Q), and *FLNC* (G1978R and G2118S). Those variants were also previously reported as causing RCM, HCM, or noncompaction cardiomyopathy. [12–17] A missense variant of I195T was identified in *TNNI3*, which was not previously reported. The clinical data of this patient having the I195T variant are

described in the supplemental material. We considered this a variant of unknown significance (VUS) and excluded the patient from the comparative analyses between pathogenic variant-positive and negative patients to ensure the accuracy of the study. We could not find any significant candidates in the other 13 patients.

Patient Characteristics and Hemodynamic Parameters

The clinical characteristics and hemodynamic data are summarized in Table 1. Fifteen RCM patients were male (54%), and the median age (interquartile range: IQR) at diagnosis was 6 (2.25–8.5) years. The median observational period was 8.75 (4–11) years. A nationwide school heart disease screening program was the most common reason for the final diagnosis of RCM. Sixteen of 28 patients (57%) were referred to hospitals for further examination after electrocardiogram abnormalities were detected at school screenings. Among them, 11 of the 16 patients (69%) were diagnosed at grade 1 of primary school (6–7 years old) and the remaining 5 patients (31%) were diagnosed at grade 1 of junior high school (12–13 years old). Two patients were diagnosed by chest x-ray abnormalities and one patient was diagnosed by heart murmur when the patients went to the hospitals or clinics for noncardiac reasons (e.g., respiratory infection). Thus, 20 of 28 (71%) pediatric RCM patients were diagnosed without any symptoms. Eight patients (29%) experienced cardiac symptoms, including low output syndrome (LOS) like fatigue during exercise and facial or leg edema. Four patients (14%) had family histories of cardiomyopathy, which were all RCM in parents or sisters. Among them, three patients were diagnosed by school heart screening. Another patient was diagnosed using echocardiography after her sibling died. Later, this patient's father was diagnosed with RCM. Six of 28 patients (21%) had

ventricular tachycardia or ventricular fibrillation (VT/Vf) events, and two of these patients received cardioverter-defibrillator implants. One patient died while waiting for transplantation due to VT/Vf. Eighteen patients received heart transplantations. Cardiac deaths (death or heart transplantation) occurred in 19 of 28 (68%) patients by the end of the observation period (October 2022). Four patients required ventricular assist device (VAD) implantation, and all of these patients finally received heart transplantations. Five patients (18%) were still on the waiting list at the end of the observation period. Four patients (14%) continued medical treatment without being on the waiting list. The indications for heart transplant of all patients are summarized in Table 2. There were no significant differences between pathogenic variant positive and negative patients regarding their indications.

The 5-year, 10-year, and 15-year overall survival rates for all RCM patients were 96%, 96%, and 84%, respectively (Figure 1A). In contrast, transplant-free survivals were poor as previously reported; the 2-year, 5-year, and 10-year transplant-free survival rates were 54%, 37%, and 27%, respectively (Figure 1B). Clinical characteristics and hemodynamic status were compared for patients with and without pathogenic gene variants, excluding the one patient with VUS in *TNNI3*. No significant differences between patients with and without pathogenic gene variants were detected in sex, age at diagnosis, school heart disease screening detection, symptoms, family history, the incidence of VT/Vf, cardiac death, and VAD implantation (Table 1). The reasons for hospital referral and overall outcomes were also not significantly different between patients with or without pathogenic variants (Figure 2).

The hemodynamic parameters at diagnosis were analyzed (Table 3). The median (IQR) left

ventricular end systolic pressure and right ventricular end systolic pressure were elevated to 22 mmHg (19.25–24.75) and 13 mmHg (7.25–15.75), respectively. Cardiac index (CI) was slightly decreased in most RCM patients (median: 3.0 L/min/m^2, IQR: 2.4–3.7). Mean pulmonary arterial pressure and pulmonary vascular resistance index (PVRI) were elevated in some patients, suggesting that both postcapillary and precapillary pulmonary arterial remodeling had already started. Left ventricular ejection fraction estimated by echocardiography was preserved in all patients. No significant differences between patients with and without pathological gene variants were detected in any hemodynamic parameters (Table 3).

Overall Survival and Transplant-free Survival With or Without Pathogenic Variants

We compared the probability of overall survival in patients with or without pathogenic gene variants after the diagnosis of RCM using the Kaplan–Meier method with log-rank tests. No significant differences in overall survival were detected between patients with and without pathogenic variants after diagnosis ($P = 0.106$; Figure 3A). Patients positive for the pathogenic variants had significantly worse transplant-free survival compared with patients without the pathogenic variants (Figure 3B); the 2-year and 5-year survival rates were 50% and 22% in patients with pathogenic variants and 62% and 54% in patients without any candidate variants, respectively (log-rank test, $P = 0.0496$). We also analyzed whether the types of pathogenic variants correlated with survival. Since *TNNI3* was the most common pathogenic gene in our study, patients with *TNNI3* pathogenic variants were compared to patients with the other gene variants. No significant differences in overall survival or transplant-free survival were detected between patients with *TNNI3* variants compared with

patients with other gene variants (P = 0.429 and P = 0.391, respectively; Figures 3C and 3D).

Correlation Between School Heart Disease Screening and Genetic Backgrounds and Outcomes

Since the nationwide school health screening program for cardiovascular disease is a unique public health service in Japan, we analyzed whether this screening resulted in better outcomes for pediatric RCM patients. All of the reasons why the patients were referred to the hospital for further examinations were electrocardiogram abnormality, including abnormal P wave in V1 and V2, and ST-T change. We compared clinical characteristics and hemodynamic data in patients diagnosed via school heart screening (n = 16) with patients diagnosed by symptoms, including LOS and edema (n = 8) (Table 4). The age at diagnosis was significantly younger in patients who showed symptoms (median: 7 years for school screening vs. 2 years for symptoms, P = 0.0012). RCM patients diagnosed by the school heart screening showed significantly lower rates of death and heart transplantation at the end of the observation period (44% vs. 100%; P = 0.0095). The correlation between patients with pathogenic gene variants and RCM detected at school screenings was determined. Eight of 16 patients (50%) diagnosed by the school screening had pathogenic gene variants, whereas 2 of 8 patients (25%) diagnosed by symptoms had pathogenic gene variants. However, the ratios were not significantly different (P = 0.38). CI (median: 3.25 L/min/m^2 vs. 2.55 L/min/m^2) and PVRI (median: 1.75 Wood Unit·m^2 vs. 2.65 Wood Unit·m^2) tended to be impaired in patients diagnosed by symptoms; however, no significant differences were detected between patients diagnosed via school screening and patients

diagnosed by symptoms ($P = 0.058$ and $P = 0.076$, respectively). No significant differences in overall survival between patients diagnosed via school screening and patients diagnosed by symptoms were detected. However, patients diagnosed by school screening had a better transplant-free survival rate compared with patients diagnosed by symptoms. The 2-year and 5-year transplant-free survival rates were 75% and 68% in the school screening group and 25% and 0% in the symptomatic group, respectively (log-rank test, $P = 0.0027$) (Figures 4A and 4B).

Discussion

The genetic backgrounds of 28 patients with pediatric RCM were analyzed and correlated with clinical outcomes. To the best of our knowledge, this study is the largest genetic analysis of pediatric RCM patients. We identified pathogenic or likely-pathogenic variants in 14 of 28 (50%) pediatric RCM patients. This rate is consistent with the recent WES study of adult and pediatric RCM patients showing that the genetic test positive ratio was approximately 50%. [6] Eight pediatric patients who were diagnosed with RCM under 15 years of age were included in that study, and 3 of them (38%) had pathogenic or likely-pathogenic variants in *TNNI3* and *MYH7* genes. Despite previous studies of pediatric RCM patients, the correlation between genotype and outcome is unclear, mainly due to the rarity of this disease. The pediatric cardiomyopathy database in North America contains only 152 RCM patients over the 19-year study. [1] The Japanese multicenter retrospective cohort study included only 54 patients over a period of 24 years. [3] Moreover, these studies did not analyze the genetic information. Therefore, further accumulation of genetic information is required to uncover the genotype-phenotype correlation in pediatric RCM.

We demonstrated that the clinical characteristics and hemodynamic parameters at diagnosis were not significantly different between patients with and without pathogenic gene variants. However, the Kaplan–Meier analysis revealed that the transplant-free survival rate was significantly worse in RCM patients with pathogenic variants. Among the various pathogenic genes identified in this study, *TNNI3* was the most frequent. All patients with *TNNI3* mutations were transplanted or dead by the end of the observation period. Thus, we analyzed the differences in transplant-free survival rates between patients with *TNNI3* mutations and patients with other mutations (Figure 3D). However, no significant differences were detected. Recently, extensive investigations into genotype-phenotype correlations in adult DCM have been conducted. [18] Adult DCM patients with *LMNA* variants experienced earlier onsets and worse prognoses compared with other variant types. [19,20] In this study, we demonstrated that pathogenic variants in pediatric RCM patients correlated with worse prognoses. This result suggested that the genetic diagnosis might be useful for the determination of transplant eligibility.

However, we could not clarify precise reasons regarding why the pathogenic variant positive patients showed worse transplant-free survival than variant negative patients. In our previous study, we speculated that cardiac fibroblasts, which were the most abundant cell type in the heart, played important roles in the pathogenesis of RCM. [21, 22] In variant positive patients, the key players in cardiac diastolic dysfunction were speculated to be cardiomyocytes harboring abnormal sarcomere (e.g, troponin I) structures. Conversely, in the variant negative patients, cardiomyocyte may not be a central player. Impaired cardiac fibroblasts themselves or the intercellular communication between cardiomyocytes and cardiac fibroblasts may play more important roles in such variant negative RCM

patients. Although the hemodynamic parameters at diagnosis were not significantly different between the variant positive and negative patients, the main player in the cardiac diastolic dysfunction (cardiomyocytes or cardiac fibroblasts) may be a key regulator of disease progression in RCM. Further investigations are required to uncover why the pathogenic variant positive patients showed poor prognosis and whether a specific gene mutation is associated with worse outcomes. Accurate genotype-outcome correlations for pediatric RCM would facilitate appropriate clinical risk classification.

The correlation between genetic background and detection in school heart disease screenings and the effects of public health screening on the prognosis of pediatric RCM were analyzed. In Japan, the nationwide school cardiovascular disease screening system was established in 1995. All pupils in the first years of elementary school (6–7 years old), junior high school (12–13 years old), and high school (15–16 years old) are provided with physical examinations, interview forms, and electrocardiograms. [7] This system is very unique and facilitates the identification of asymptomatic cardiovascular diseases in children. [23] We compared the clinical characteristics and hemodynamic parameters between patients with RCM detected by school heart disease screening and patients with RCM detected by symptoms. The age at diagnosis was significantly lower in symptomatic patients, suggesting that RCM infants under school age could not be diagnosed in an asymptomatic situation. All patients diagnosed by symptoms were dead or transplanted by the end of the study indicating that the symptomatic patients may have worse prognoses. Importantly, no significant differences were detected in the numbers of patients with pathogenic genes between the patients diagnosed via school screening and the symptomatic patients. We also found no significant differences in hemodynamic parameters, although CI

tended to be lower (3.25 vs. 2.55 L/min/m^2, $P = 0.058$) and PVRI tended to be higher (1.75 vs. 2.65 WU·m^2, $P = 0.076$) in symptomatic patients. The transplant-free survival rate was better in patients diagnosed via school screening. Although it may be possible that younger children with RCM have worse prognoses, this system could facilitate the early detection of pediatric RCM and may improve prognoses, regardless of genetic background.

There are several important limitations to this study. First, the number of patients is small, mainly because pediatric RCM is extremely rare. Second, we could not confirm that pathogenic variant negative patients truly had no mutations in all genes including introns. Third, patient selection bias may have occurred because our hospital is a center for pediatric heart transplantation in Japan.

Conclusion

We identified pathogenic variants in 50% of pediatric RCM patients by intensive gene testing using a next-generation sequencer. Heterozygous *TNNI3* missense variants were the most common variant in our population. Pathogenic gene variant-positive patients had worse transplant-free survival.

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DISCLOSURE

None.

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TABLES

Table 1. Clinical characteristics of the pediatric RCM patients, with or without pathogenic gene variants

	All RCM (n=28)	Pathogenic variant (+) (n=14)	Pathogenic variant (–) (n=13)	*P* value
Male, No. (%)	15 (54%)	9 (64%)	6 (46%)	0.45
Age at diagnosis (yr), median (IQR)	6 (2.25–8.5)	6 (2.75–7.5)	7 (2–11.5)	0.75†
Observation period (yr), median (IQR)	8.75 (4–11)	6.75 (3.75–10.25)	10 (6–14)	0.12†
Detection at school heart screening, No. (%)	16 (57%)	8 (57%)	7 (54%)	1.00
No symptom at diagnosis, No. (%)	20 (71%)	12 (86%)	7 (54%)	0.10
Family history of cardiomyopathy, No. (%)	4 (14%)	2 (14%)	2 (15%)	1.00
VT/Vf, No. (%)	6 (21%)	4 (29%)	2 (15%)	0.65
Dead or heart transplantation, No. (%)	19 (68%)	11 (79%)	7 (54%)	0.24
VAD implantation, No. (%)	4 (14%)	3 (21%)	1 (8%)	0.60

IQR, interquartile range; VT, ventricular tachycardia; Vf, ventricular fibrillation; VAD, ventricular assist device. †Nonparametric Mann–Whitney U test was conducted because normal distribution could not be confirmed by Shapiro–Wilk test.

Table 2. Indications for heart transplant

	All RCM (n=28)	Pathogenic variant (+) (n=14)	Pathogenic variant (–) (n=13)	*P* value
No. of patients listed on for transplant, (%)	23 (82%)	13 (93%)	10 (77%)	0.33
Indications				
VAD implantation, No. (%)	4 (17%)	3 (23%)	1 (10%)	0.59
Low output syndrome, No. (%)	15 (65%)	6 (46%)	9 (90%)	0.25
Uncontrollable ventricular arrhythmia, No. (%)	0 (0%)	0 (0%)	0 (0%)	1.00
High pulmonary vascular resistance, No. (%)	4 (17%)	4 (31%)	0 (0%)	0.25

VAD, ventricular assist device.

Table 3. Hemodynamic status at diagnosis, median (IQR)

	All RCM (n=28)	Pathogenic variant (+) (n=14)	Pathogenic variant (–) (n=13)	*P* value
LVEDP (mmHg)	22 (19.25–24.75)	20.5 (18.25–24.75)	24 (20–25)	0.58
RVEDP (mmHg)	13 (7.25–15.75)	12 (7–14)	13 (8.5–17)	0.57
CI (L/min/m^2)	3.0 (2.4–3.7)	3.05 (2.725–3.675)	2.7 (2.3–3.975)	0.54
mPAP (mmHg)	28 (18–30)	28 (22–31)	19 (17–30)	0.28[†]
PVRI (Wood Unit·m^2)	2.5 (1.7–4.2)	2.7 (1.85–4.575)	2.35 (1.475–3.075)	0.29[†]
LVEF (%)	62.5 (56.25–68.5)	60.5 (54.5–68.5)	67 (58–74)	0.17

IQR, interquartile range; LVEDP, left ventricular end-diastolic pressure; RVEDP, right ventricular end-diastolic pressure; CI, cardiac index; mPAP, mean pulmonary arterial pressure; PVRI, pulmonary vascular resistance index; LVEF, left ventricular ejection fraction.
[†]Nonparametric Mann–Whitney U test was conducted because normal distribution could not be confirmed by Shapiro–Wilk test.

Table 4. Comparison of clinical characteristics and hemodynamic parameters detected by school heart screening

	Detection at school screening (n=16)	Diagnosed by symptoms (n=8)	*P* value
Male, No. (%)	8 (50%)	5 (63%)	0.68
Age at diagnosis (yr), median (IQR)	7 (6–12)	2 (1.25–4.5)	0.0012*
Family history of cardiomyopathy, No. (%)	3 (19%)	0 (0%)	0.53
VT/Vf, No. (%)	4 (25%)	2 (25%)	1.00
Dead or heart transplantation, No. (%)	7 (44%)	8 (100%)	0.0095*
VAD implantation, No. (%)	1 (6%)	1 (13%)	1.00
Pathogenic gene variant positive, No (%)	8 (50%)	2 (25%)	0.38
LVEDP (mmHg), median (IQR)	22 (20–24.25)	24 (16–26)	0.57
RVEDP (mmHg), median (IQR)	11.5 (7.25–14.5)	16 (10.5–18.5)	0.24
CI (L/min/m^2), median (IQR)	3.25 (2.725–3.975)	2.55 (2.25–2.95)	0.058
mPAP (mmHg), median (IQR)	28 (19–30)	19.5 (17.5–29)	0.63†
PVRI (Wood Unit·m^2), median (IQR)	1.75 (1.475–2.875)	2.65 (2.3–6.125)	0.076†
LVEF (%), median (IQR)	63.5 (57.5–70)	64 (50–66)	0.27

IQR, interquartile range; VT, ventricular tachycardia; Vf, ventricular fibrillation; VAD, ventricular assist device; LVEDP, left ventricular end-diastolic pressure; RVEDP, right ventricular end-diastolic pressure; CI, cardiac index; mPAP, mean pulmonary arterial pressure; PVRI, pulmonary vascular resistance index; LVEF, left ventricular ejection fraction.
* $P<0.05$. †Nonparametric Mann–Whitney U test was conducted because normal distribution could not be confirmed by Shapiro–Wilk test.

FIGURE LEGENDS

Figure 1. Overall survival and transplant-free survival in all pediatric RCM patients. (A) Kaplan–Meier curve of overall survival. Freedom from death at 5, 10, and 15 years was 96%, 96%, and 84%, respectively. (B) Kaplan–Meier curve of transplant-free survival. Freedom from death and heart transplantation at 2, 5, and 10 years was 54%, 37%, and 27%, respectively. The shadows delineate the 95% confidence intervals.

Figure 2. Reasons for referral to diagnose RCM and overall outcomes of patients with or without pathogenic gene variants. (A) Reasons why patients were referred to pediatric cardiologists for final diagnosis of RCM. XP, chest x-ray; LOS, low output syndrome. (B) The overall outcomes of patients. HTx, heart transplantation.

Figure 3. The overall survival and transplant-free survival in patients with or without pathogenic variants. (A) Freedom from death at 5, 10, and 15 years were 93%, 93%, and 62% in pathogenic variant-positive patients and 100%, 100%, and 100% in variant negative patients, respectively (log-rank test, $P = 0.106$). (B) Freedom from death and heart transplantation at 2, 5, and 10 years was 50%, 22%, and 0% in pathogenic variant-positive patients and 62%, 54%, and 45% in variant negative patients, respectively (log-rank test, $P = 0.0496$). (C) Kaplan–Meier curve of overall survival in patients with *TNNI3* mutations and other gene mutations, including *MYL2*, *TNNT2*, *MYH7*, and *FLNC*, and without any candidate variants. Freedom from death at 5, 10, and 15 years was 89%, 89%, and 59% with *TNNI3* mutations and 100%, 100%, and 100% with other gene mutations, respectively

(log-rank test, P = 0.429). (D) Kaplan–Meier curve of transplant-free survival with *TNNI3* mutations, other mutations, and no mutations. Freedom from transplant-free death at 2 and 5 years was 38% and 13% with *TNNI3* mutations and 67% and 44% with other gene mutations, respectively (log-rank test, P = 0.391). The shadows delineate the 95% confidence intervals.

Figure 4. The overall survival and transplant-free survival in patients who were referred for diagnosis via the school heart disease screening or due to symptoms. (A) Freedom from death at 5 and 10 years was 93% and 93% in the school screening group and 100% and 100% in the symptomatic group, respectively (log-rank test, P = 0.9064). (B) Freedom from death and heart transplantation at 2 and 5 years was 75% and 68% in the school screening group and 25% and 0% in the symptomatic group, respectively (log-rank test, P = 0.0027). The shadows delineate the 95% confidence intervals.

Figure 1.

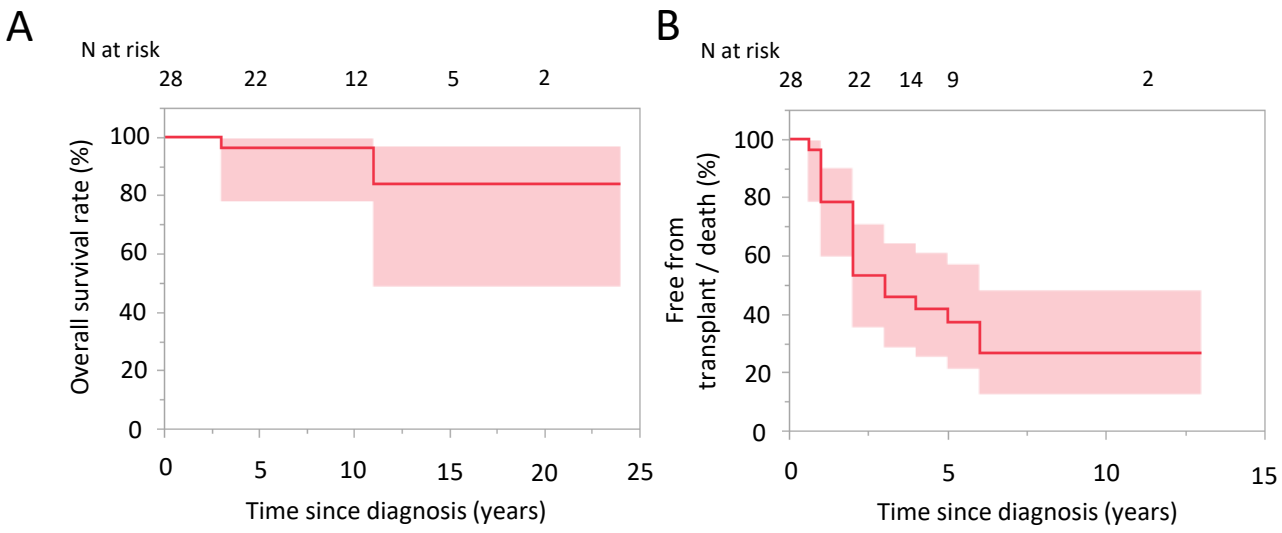

A
N at risk
28 22 12 5 2
Overall survival rate (%)
100
80
60
40
20
0
0 5 10 15 20 25
Time since diagnosis (years)
B
N at risk
28 22 14 9 2
Free from transplant / death (%)
100
80
60
40
20
0
0 5 10 15
Time since diagnosis (years)

Figure 2.

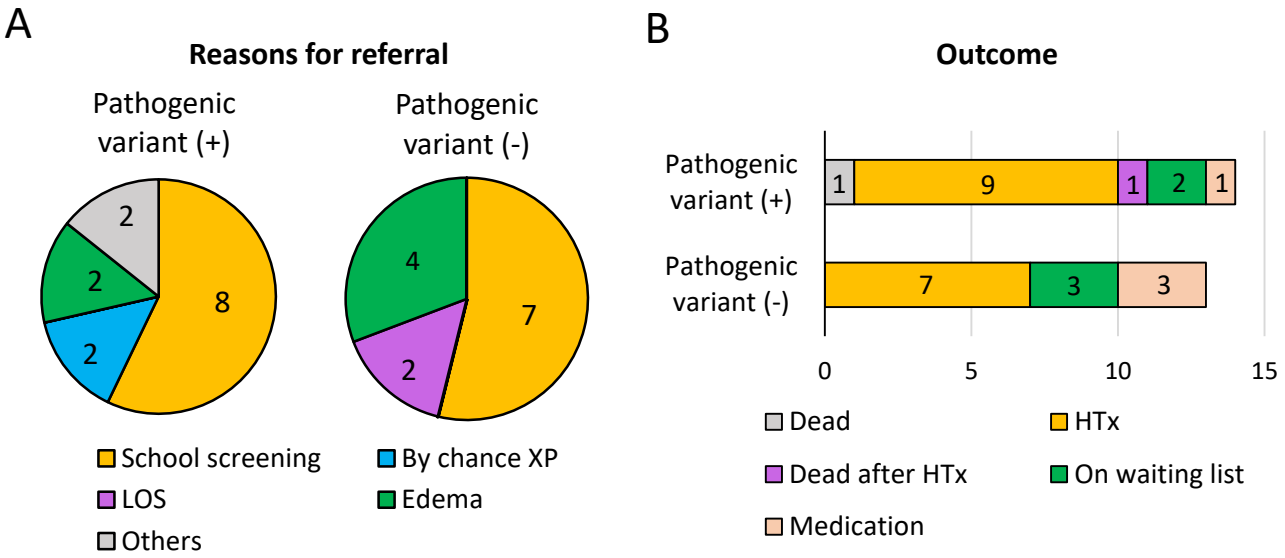

A
Reasons for referral
Pathogenic variant (+)
Pathogenic variant (-)
2
2
2
8
4
2
7
School screening
By chance XP
LOS
Edema
Others
B
Outcome
Pathogenic variant (+)
Pathogenic variant (-)
1
9
1
2
1
7
3
3
0
5
10
15
Dead
HTx
Dead after HTx
On waiting list
Medication

Figure 3.

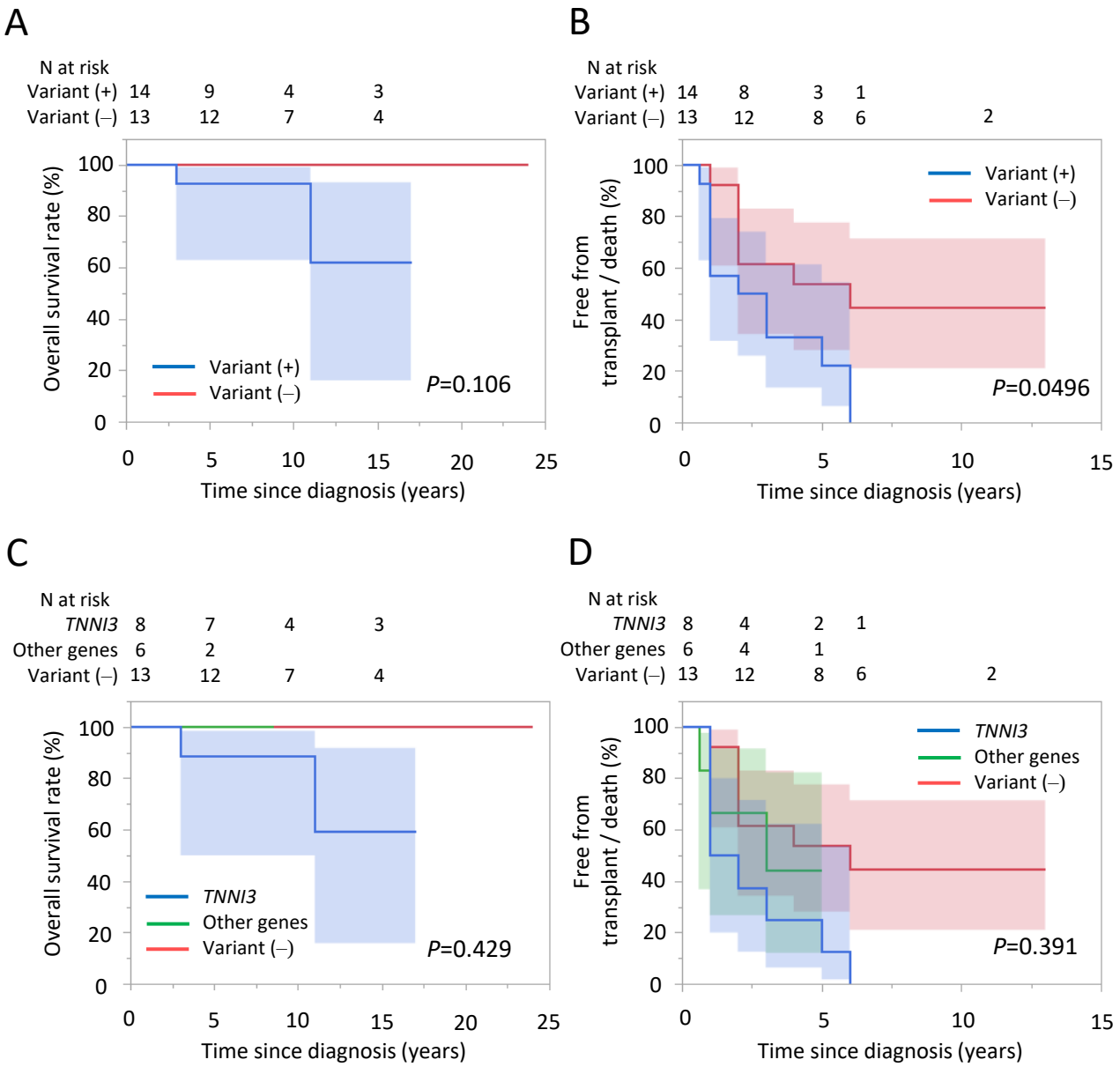
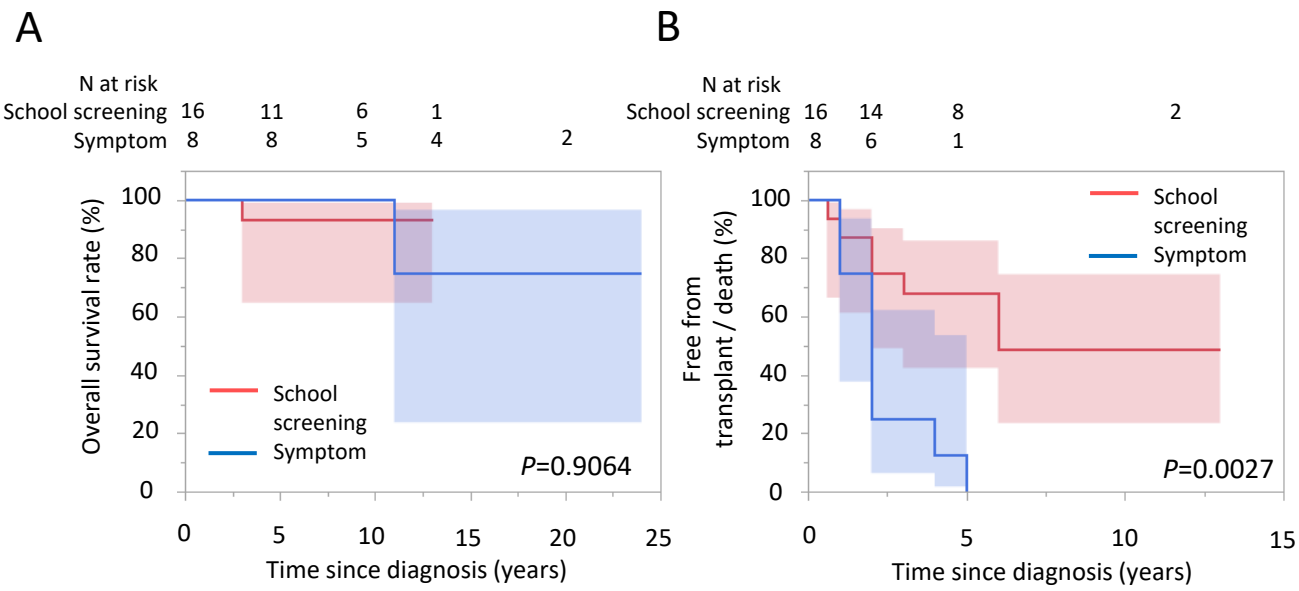

A
N at risk
Variant (+) 14 9 4 3
Variant (–) 13 12 7 4
Overall survival rate (%)
Variant (+)
Variant (–)
P=0.106
Time since diagnosis (years)
B
N at risk
Variant (+) 14 8 3 1
Variant (–) 13 12 8 6 2
Free from transplant / death (%)
Variant (+)
Variant (–)
P=0.0496
Time since diagnosis (years)
C
N at risk
TNNI3 8 7 4 3
Other genes 6 2
Variant (–) 13 12 7 4
Overall survival rate (%)
TNNI3
Other genes
Variant (–)
P=0.429
Time since diagnosis (years)
D
N at risk
TNNI3 8 4 2 1
Other genes 6 4 1
Variant (–) 13 12 8 6 2
Free from transplant / death (%)
TNNI3
Other genes
Variant (–)
P=0.391
Time since diagnosis (years)

Figure 4.


A
N at risk
School screening 16 11 6 1
Symptom 8 8 5 4 2
Overall survival rate (%)
100
80
60
40
20
0
School screening
Symptom
P=0.9064
0 5 10 15 20 25
Time since diagnosis (years)
B
N at risk
School screening 16 14 8 2
Symptom 8 6 1
Free from transplant / death (%)
100
80
60
40
20
0
School screening
Symptom
P=0.0027
0 5 10 15
Time since diagnosis (years)