OPEN

Left Ventricular Hypertrophy and Hypertrophic Cardiomyopathy in Adult Solid Organ Transplant Recipients

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Background. Hypertrophic cardiomyopathy (HCM) in pediatric solid organ transplant recipients has been reported in association with use of calcineurin inhibitors. However, data on the incidence and prevalence of HCM in adult posttransplant patients are limited. We sought to describe the clinical characteristics of solid organ transplant recipients who were diagnosed with HCM from 2011 to 2021 at a single center. **Methods.** Patients who had undergone solid organ transplant and exhibited left ventricular hypertrophy with left ventricular wall thickness ≥13 mm on transthoracic echocardiography were included. Clinical history, pedigree analysis, clinical genetic testing, transthoracic echocardiography, cardiac magnetic resonance imaging, treatment, and follow-up testing results were collected. Categorical variables were described as n (%). Continuous variables were described with medians and interquartile ranges and compared using the Wilcoxon rank-sum and Kruskal-Wallis tests. A 2-sided $P < 0.05$ was considered statistically significant. **Results.** Three lung, 5 kidney, and 4 liver transplant recipients from 12 different families were included. Seven patients (58%) did not carry a preexisting diagnosis of hypertension, and none had a history of aortic or subaortic stenosis. A majority of patients exhibited asymmetric septal hypertrophy (67%; medial septal thickness versus left ventricular posterior wall thickness 17 versus 13 mm; $P < 0.001$) and dynamic left ventricular outflow tract (LVOT) obstruction (58%). All patients were managed long term with calcineurin inhibitors. Clinical genetic testing in 6 patients identified 2 with disease-causing variants in 2 sarcomere genes, myosin binding protein-C and myosin heavy chain 7. Four patients (33%) underwent successful septal reduction therapy for treatment of symptomatic LVOT obstruction. **Conclusions.** Symptomatic HCM with dynamic LVOT obstruction can develop in solid organ transplant recipients, and genetic testing can identify individuals with sarcomeric HCM. Medical management and septal reduction therapies are treatment options for severe symptomatic disease.

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INTRODUCTION

Left ventricular hypertrophy (LVH) is a known risk factor for adverse cardiovascular and noncardiovascular outcomes after kidney and liver transplantation.[1-3] Reported causes of posttransplant LVH include hypertension, immune-mediated injury, and immunosuppressant medications. Hypertension, lower glomerular filtration rate, and male sex have been associated with higher left ventricular

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(LV) mass index in liver transplant recipients.[1,2] Significant regression of LV wall thickness and LV mass index has been reported at 6 mo postkidney transplantation and beyond. This is thought to be because of the resolution of hypertension, anemia, and other triggers of adverse LV remodeling.[4,5]

Hypertrophic cardiomyopathy (HCM) is characterized by a LV maximal end-diastolic wall thickness of ≥13–15 mm, depending on the presence of family history or causal genetics and the absence of secondary causes that induce a pressure or volume load on the LV.[6,7] The prevalence of HCM in the United States is estimated to be 1:250–500 adults.[8] Approximately 40% of HCM cases can be attributed to disease-causing genetic variants in sarcomere genes, with variation in myosin binding protein-C (*MYBPC3*) and myosin heavy chain 7 (*MYH7*) accounting for about 70% of genotype-positive cases.[9]

In 1995, Atkison et al[10] reported a series of 5 consecutive pediatric solid organ transplant recipients who developed HCM while on tacrolimus, 2 of which had resultant LV outflow tract obstruction. Over the next decade, additional reports of obstructive HCM in pediatric solid organ transplant recipients were published, including in kidney,[11] liver,[12-15] and small bowel.[16] The etiology of LVH was thought to be because of tacrolimus, since the recognition of this clinical entity was coincident with the rise in its use after its approval by the US Food and Drug Administration. Around the same time, case-level associations between regression of LV hypertrophy after decreasing or discontinuing the tacrolimus dose started to be reported. Since then, very few reports of HCM in adult solid organ transplant recipients on calcineurin inhibitors (CNIs) have been published.[17-20] Attributing causality to the CNI has been controversial since older single-center retrospective analyses have found that the prevalence of HCM in a tacrolimus-treated adult transplant population to be similar to the general population prevalence.[21] In this study, we sought to characterize LVH and HCM diagnosed in adult solid organ transplant recipients at a large organ transplant referral center.

MATERIALS AND METHODS

Subjects and Study Design

Individuals evaluated from 2011 to 2021 at the University of Pennsylvania Center for Inherited Cardiovascular Disease, a referral center for patients with suspected hereditary cardiomyopathies, were reviewed for inclusion in this series. Individuals who are genotype-positive/phenotype-positive, genotype-positive/phenotype-negative, and genotype-negative/phenotype-positive are referred to this Center. Patients who had undergone solid organ transplant and exhibited LVH with LV wall thickness ≥13 mm on transthoracic echocardiography (TTE) were included in this retrospective analysis. Entry into the cohort was assigned by date of initial evaluation in the University of Pennsylvania Health System. The Institutional Review Board of the University of Pennsylvania approved this study (protocol number 843087). Because of the retrospective nature of the study and waiver granted by the Institutional Review Board, no informed consent from the subjects was required.

Data Collection

Clinical history, pedigree analysis, clinical genetic testing, TTE, cardiac magnetic resonance imaging (CMR), treatment, and clinically indicated follow-up testing results were abstracted from the medical record. Baseline demographic data included age at HCM diagnosis, sex, first-degree familial history of HCM or sudden cardiac death, and symptoms at initial visit. Testing was performed according to standard clinical protocols. Echocardiographic chamber quantification was performed in alignment with the 2015 American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations on cardiac chamber quantification for adults.[22] Variants identified as "pathogenic" or "likely pathogenic" in genes known to be causal for HCM identified by Clinical Laboratory Improvement Amendments-certified genetic testing and consistent with published standards from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology were included.[23] Clinical genetic testing results were interpreted and confirmed by licensed genetic counselors (J.L.C. and L.H.-A.). Clinical outcomes were adjudicated by medical record review.

Statistical Analysis

Categorical variables were described as n (%). Continuous variables were described with medians and interquartile ranges (IQRs) and compared using the Wilcoxon rank-sum and Kruskal-Wallis tests, where appropriate. A 2-sided $P < 0.05$ was considered statistically significant. Analyses were performed with Stata 15.1/IC (College Station, TX).

RESULTS

Baseline Characteristics

Between 2011 and 2021, a total of 12 unrelated organ transplant recipients were identified. Basic demographic data are shown in Table 1. Three patients (25%) underwent lung transplant, 5 patients (42%) underwent kidney transplant, and 4 patients (33%) underwent liver transplant. One liver transplant recipient underwent a second liver transplant approximately 4 y after the first for recurrence of disease. Half (50%) of the patients were women, and 42% identified as non-White. Nearly all patients (92%) were the probands in their families. Six patients underwent clinical genetic testing, and of these 3 were heterozygous for genetic variants in sarcomere genes. One lung transplant recipient had a variant of uncertain significance in the gene (*MYBPC3* c.422C>G), 1 kidney transplant recipient had a pathogenic variant in the gene (*MYBPC3* c.3190+1G>A), and 1 kidney transplant recipient had a likely pathogenic variant in the gene (*MYH7* c. 5561C>T).

Most patients (75%) were notably symptomatic with New York Heart Association class II–III symptoms, including dyspnea (67%), chest pain (33%), palpitations (42%), edema (33%), and syncope (17%) at initial cardiac evaluation. Five patients (42%) had a history of hypertension, and none had a history of aortic or subaortic stenosis. The kidney transplant recipient with a likely pathogenic *MYH7* variant had preexisting hypertension.

Arrhythmias were present in the cohort with 2 patients with nonsustained ventricular tachycardia (NSVT), 1 with ventricular tachycardia, 1 with atrial fibrillation (AF), and 2 with supraventricular tachycardia. No patient had a history of sudden cardiac arrest. Two patients (17%) had primary prevention implantable cardioverter defibrillators (ICDs) implanted before the initial cardiology visit; 1 was implanted in the setting of a maximal wall thickness of >30 mm, and the other indication was unknown. One additional patient had an ICD implanted at an outside center during the follow-up period; indication

TABLE 1.

Demographics and clinical characteristics of 12 individuals with hypertrophic cardiomyopathy diagnosed after solid organ transplant

Characteristic	Lung	Kidney	Liver	*P*
N	**3**	**5**	**4**	
Age at cardiac diagnosis, median (IQR), y	56 (37.0–60.0)	61 (51.0–63.0)	35.5 (27.5–47)	
Number of y posttransplant at initial cardiac evaluation, median (IQR)	10.0 (9.2–12.7)	5.8 (0.4–29.7)	14.8 (2.2–21.6)	0.99
Sex, n (%)				1.00
Female	1 (33)	3 (60)	2 (50)	
Male	2 (67)	2 (40)	2 (50)	
Race, n (%)				1.00
White	2 (67)	2 (40)	3 (75)	
Black	1 (33)	0 (0)	1 (25)	
Asian	0 (0)	1 (20)	0 (0)	
Unknown	0 (0)	1 (20)	0 (0)	
Other	0 (0)	1 (20)	0 (0)	
Genetic testing, n (%)	1 (33)	5 (100)	0 (0)	0.006
Proband, n (%)	2 (67)	5 (100)	4 (100)	0.25
Symptoms at initial assessment, n (%)				
NYHA class				0.43
I	0 (0)	2 (40)	1 (25)	
II	2 (67)	0 (0)	2 (50)	
III	1 (33)	3 (60)	1 (25)	
Dyspnea	3 (100)	3 (60)	2 (50)	0.58
Chest pain	1 (33)	2 (40)	1 (25)	1.00
Palpitations	1 (33)	3 (60)	1 (25)	0.77
Presyncope	0 (0)	0 (0)	1 (25)	0.58
Syncope	0 (0)	1 (20)	1 (25)	1.00
Edema	1 (33)	1 (20)	2 (50)	0.76
Hypertension at initial assessment, n (%)	1 (33)	4 (80)	0 (0)	0.07
Systolic blood pressure at initial assessment, median (IQR), mm Hg	121 (118–123)	133 (124–135)	112.5 (90.5–133.5)	0.42
History of NSVT at initial assessment, n (%)	0 (0)	0 (0)	2 (50)	0.14
History of VT at initial assessment, n (%)	0 (0)	0 (0)	1 (25)	0.58
History of AF at initial assessment, n (%)	1 (33)	0 (0)	0 (0)	0.25
History of SVT at initial assessment, n (%)	1 (33)	0 (0)	1 (25)	0.47
ICD present at initial assessment, n (%)	0 (0)	0 (0)	2 (50)	0.14
Family history of SCD, n (%)	0 (0)	1 (20)	0 (0)	1.00
Family history of HCM, n (%)	1 (33)	0 (0)	0 (0)	0.25
CNI, n (%)				0.29
Tacrolimus	3 (100)	3 (60)	4 (100)	
Cyclosporine	0 (0)	2 (40)	0 (0)	
Tacrolimus trough, mean (± SD), µg/L				
Within 30 d posttransplant	12.8 (± 0.6)	8.8 (± 6.0)	15.2 (± 8.5)	
Within 30 d of HCM diagnosis	6.1 (± 3.2)	4.3 (–)	2.9 (± 2.0)	
Within 30 d of most recent follow-up	4.9 (± 2.8)	5.0 (–)	5.0 (± 3.3)	
Duration of CNI therapy starting at time of transplant, median (IQR), y	12.0 (11.0–13.0)	6.0 (4.0–30.0)	11.5 (6.0–17.5)	0.93
Antimetabolite/mTORi, n (%)				
Azathioprine + rapamycin	0 (0)	0 (0)	1 (33)	
Mycophenolate mofetil	3 (100)	3 (100)	1 (33)	
Rapamycin	0 (0)	0 (0)	1 (33)	
Duration of antimetabolite/mTORi therapy starting at time of transplant, median (IQR), y	12.0 (11.0–13.0)	4.0 (0.0–4.0)	6.0 (1.0–15.5)	0.10
Duration of steroid therapy starting at the time of transplant, median (IQR), y	12.0 (11.0–13.0)	30.0 (4.0–33.0)	22.0 (13.0–22.0)	0.36

Percentages are column percentages. Percentages may not add up to 100% for each factor because not all patient data were complete.
The – signifies that there were not enough data to calculate an interquartile range.
AF, atrial fibrillation; CNI, calcineurin inhibitor; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; IQR, interquartile range; mTORi, mechanistic target of rapamycin inhibitor; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

included multiple episodes of syncope. No patient received an appropriate ICD shock during the examined period. One kidney transplant patient underwent catheter ablation for AF.

Regarding immunosuppression regimens, 10 of 12 patients (83%) were treated with tacrolimus, and 2 patients (17%) were treated with cyclosporine. Duration and composition of immunosuppression regimens were variable by type of organ transplant. At the time of most recent follow-up, all patients were on some degree of immunosuppression. When examined in aggregate by drug class, the median duration of CNI therapy starting from time of transplant to most recent follow-up was 11.5 y (IQR, 5.0–17.5 y). Seven of 12 patients (58%)

were on sustained antimetabolite therapy with mycophenolate mofetil; median duration of therapy was 5 y (IQR, 1.0–11.5 y). The median duration of steroid treatment was 13 y (IQR, 12.0–22.0 y).

Cardiac Imaging at First Health System Cardiology Visit and at Time of HCM Diagnosis

All patients had normal to hyperdynamic LV ejection fraction (LVEF) on TTE assessment in the system, with median LVEF 72.5% (IQR, 60%–75%). Median interventricular septal (IVS) thickness on HCM diagnosis TTE was significantly greater than LV posterior wall (LVPW) thickness (17 versus 13 mm; $P < 0.001$). At the time of HCM diagnosis, 8 patients (67%) had asymmetric upper septal hypertrophy, 2 (17%) had concentric hypertrophy, 1 (8%) had apical hypertrophy, and 1 (8%) had neutral septal morphology. Ten patients had echocardiographic LV outflow tract (LVOT) gradients measured; 7 of these patients had resting LVOT gradients in excess of 50 mm Hg. All measured gradients augmented with the Valsalva maneuver (median, 106 mm Hg; IQR, 59–149 mm Hg) (Figure 1). Eight patients (67%) had moderate to severe systolic anterior motion of the mitral valve, and 6 patients (50%) had moderate or severe mitral regurgitation (Table 2). Seven patients (58%) underwent CMR. Those with myocardial tissue characterization (n = 5) all had late gadolinium enhancement (LGE) in the mid-myocardial layer; LGE occurred in the septum (n = 4) and anterior wall (n = 1).

The 2 patients with disease-causing sarcomeric genetic variants had asymmetric septal hypertrophy (IVS 16 and 20 mm; LVPW 13 and 13 mm) at HCM diagnosis.

Treatment and Outcomes

Median cardiology follow-up duration for the cohort was 8.83 y (IQR, 1.9–16.6 y). One patient (renal transplant recipient) developed hypertension posttransplant that was well-controlled on 1 antihypertensive. One patient developed coronary artery disease, and 1 patient developed hyperlipidemia. Nine patients (75%) were on therapy with beta-blocker, 3 (25%) were concomitantly on calcium channel blocker, and 1 (8%) was on beta-blocker and disopyramide. Two patients were on a class III antiarrhythmic drug at the time of most recent cardiac follow-up. Two kidney transplant patients underwent septal

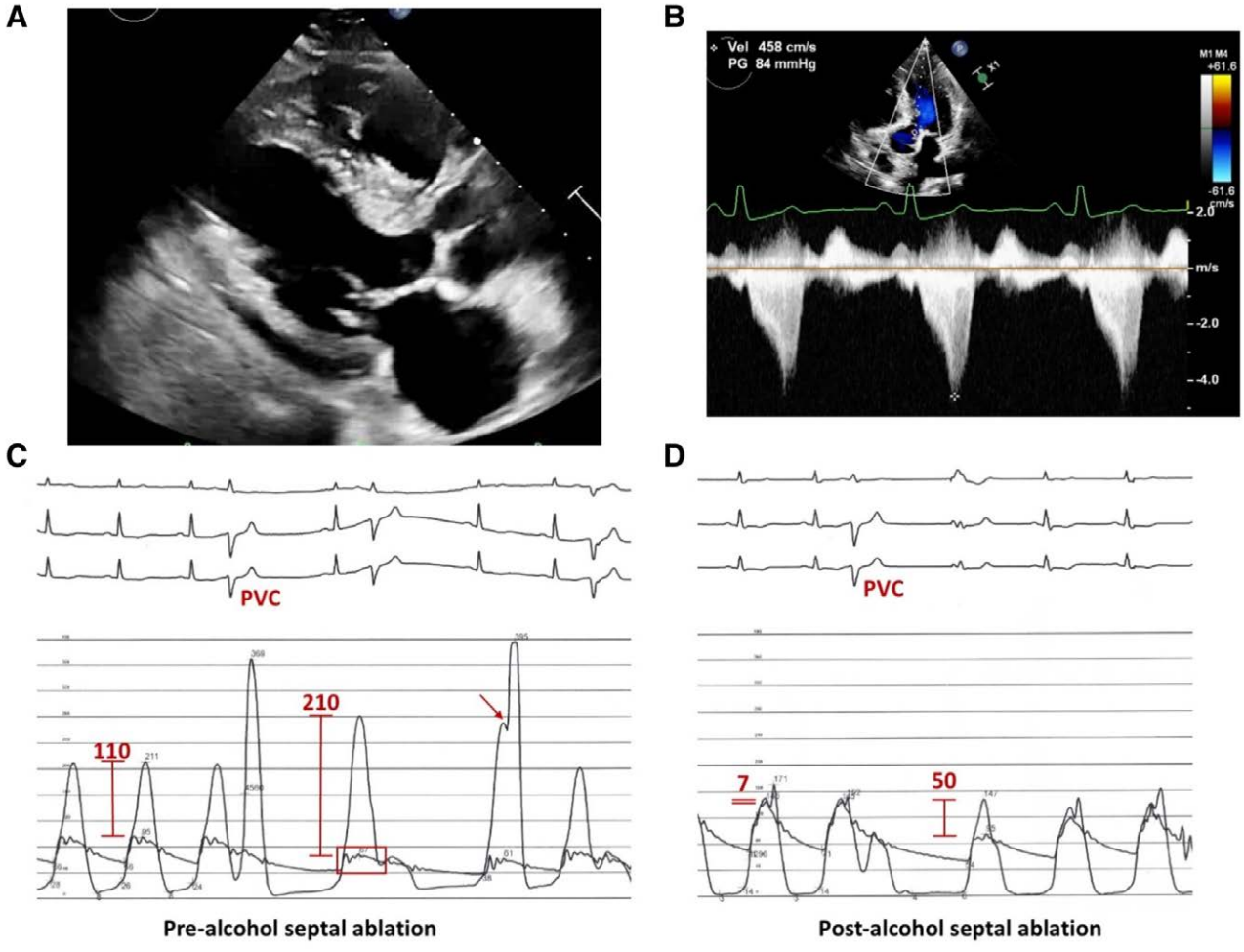

FIGURE 1. Patient with bilateral lung transplant (2009) and subsequent hypertrophic cardiomyopathy with obstruction. A, Transthoracic echocardiogram showed asymmetric basal septal hypertrophy with interventricular septum measuring 1.7 cm and left ventricular posterior wall measuring 1.3 cm. B, Severe left ventricular outflow tract obstruction was present at rest with a peak gradient of 84 mm Hg. C, Invasive hemodynamics demonstrated left ventricular to aortic peak-to-peak gradient of 110 mm Hg and post-PVC gradient of 210 mm Hg. The aortic pressure on the post-PVC beat demonstrated a reduced pulse pressure due to reduced stroke volume from increased obstruction, characteristic of the Brockenbrough-Braunwald-Morrow sign (red box). Anacrotic notch (red arrow) in the second post-PVC beat is indicative of early obstruction. D, Alcohol septal ablation was performed with significant improvement (gradient of 7 mm Hg and post-PVC gradient of 50 mm Hg). PVC, premature ventricular contraction.

TABLE 2.

Baseline and follow-up cardiac imaging characteristics of 12 individuals with hypertrophic cardiomyopathy diagnosed after solid organ transplant

Characteristic	Lung	Kidney	Liver	*P*
N	**3**	**5**	**4**	
HCM diagnosis TTE, median (IQR)				
LVEF, %	70 (57–80)	75 (65–75)	65 (55–70)	0.37
LVEDD, mm	35 (31–46)	37 (37–43)	41.5 (36.5–45)	0.72
IVS thickness, mm	15 (14–16)	19 (16–20)	19 (15.5–21)	0.43
LVPW thickness, mm	12 (11–12)	13 (13–13)	13 (11–14)	0.28
LVOT gradient at rest, mm Hg	54 (26–82)	87 (45.5–145.5)	69.5 (22–121)	0.85
LVOT gradient with Valsalva, mm Hg	103 (103–103)	106 (59–265)	130 (23–149)	0.87
Left atrial diameter, mm	44.5 (43–46)	40 (34–44)	45 (39–51)	0.46
Systolic anterior motion of the mitral valve, n (%)				0.83
None	1 (33)	1 (20)	0 (0)	
Mild	1 (33)	0 (0)	1 (25)	
Moderate	0 (0)	2 (40)	2 (50)	
Severe	1 (33)	2 (40)	1 (25)	
Mitral regurgitation, n (%)				1.00
None	0 (0)	1 (20)	0 (0)	
Mild	1 (50)	1 (20)	2 (50)	
Moderate	1 (50)	2 (40)	2 (50)	
Severe	0 (0)	1 (20)	0 (0)	
Estimated pulmonary artery systolic pressure, mm Hg	33 (33–33)	28 (18–39)	27 (20–37)	0.87
Left ventricular peak systolic pressure, mm Hg	192.5 (155–230)	215 (205–378)	248 (126–256)	0.79
N	**2**	**2**	**4**	
Follow-up TTE in non-SRT patients, median (IQR)				
LVEF, %	72.5 (65–80)	64 (63–65)	72.5 (70–75)	0.17
LVEDD, mm	35 (34–36)	34 (32–36)	41.5 (38–44.5)	0.07
IVS thickness, mm	18 (16–20)	15 (14–16)	17.5 (13.5–23.5)	0.55
LVPW thickness, mm	14 (13–15)	12.5 (12–13)	14 (12–15)	0.49
LVOT gradient at rest, mm Hg	51 (51–51)	55.5 (5–106)	20.5 (10–31)	0.74
LVOT gradient with Valsalva, mm Hg	100 (100–100)	106 (106–106)	70 (12–100)	0.26
Left atrial diameter, mm	–	36.5 (29–44)	44 (37.5–51)	0.35
Systolic anterior motion of the mitral valve, n (%)				1.00
None	1 (33)	1 (50)	1 (25)	
Mild	1 (33)	0 (0)	1 (25)	
Moderate	0 (0)	1 (50)	1 (25)	
Severe	0 (0)	0 (0)	1 (25)	
Mitral regurgitation, n (%)				0.89
Trace	0 (0)	1 (50)	1 (25)	
Mild	2 (100)	0 (0)	1 (25)	
Moderate	0 (0)	1 (50)	1 (25)	
Severe	0 (0)	0 (0)	1 (25)	
N	**1**	**3**	**0**	
Follow-up TTE in SRT patients, median (IQR)				
LVEF, %	68	65 (65–65)		0.16
LVEDD, mm	32	45.5 (45–46)		0.22
IVS thickness, mm	14	15 (10–20)		1.00
LVPW thickness, mm	14	9.5 (9–10)		0.22
LVOT gradient at rest, mm Hg	7	32.5 (10–55)		0.22
Systolic anterior motion of the mitral valve, n (%)				1.00
None	0 (0)	1 (50)		
Mild	1 (100)	1 (50)		
Moderate	0 (0)	0 (0)		
Severe	0 (0)	0 (0)		
Mitral regurgitation, n (%)				
Trace	1 (100)	2 (100)		
Mild	0 (0)	0 (0)		
Moderate	0 (0)	0 (0)		
Severe	0 (0)	0 (0)		

Percentages are column percentages. Percentages may not add up to 100% for each factor because not all patient data were complete.
The – signifies that there were not enough data to calculate an interquartile range.
HCM, hypertrophic cardiomyopathy; IQR, interquartile range; IVS, interventricular septal; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVPW, left ventricular posterior wall; SRT, septal reduction therapy; TTE, transthoracic echocardiography.

myectomy, and alcohol septal ablation was performed in 1 lung transplant recipient and 1 kidney transplant recipient (follow-up imaging data for 1 kidney transplant recipient who underwent myectomy was not available). Three of the 4 individuals who underwent septal reduction therapy had completed genetic testing and all were genotype-negative. Median time from organ transplant to septal myectomy was 15.8 y (IQR, 1.9–29.8 y) and to alcohol septal ablation was 6.7 y (IQR, 2.1–11.2 y).

At the time of most recent follow-up, LVEF for the entire cohort remained normal to hyperdynamic (median, 68%; IQR, 65%–75%) and was not significantly different compared with median LVEF at HCM diagnosis (68 versus 72.5; $P = 0.8$).

For those who did not undergo septal reduction (n = 8), wall thickness remained significantly greater at the IVS compared with the LVPW (median thickness 16 versus 13.5 mm; $P = 0.02$). There were no significant increases in wall thickness between initial and final assessments ($P > 0.1$ for both IVS and LVPW) or in left atrial diameter (median 37 versus 41.5 mm; $P = 0.5$). Five of these 8 patients had LVOT gradients assessed at most recent follow-up; LVOT obstruction remained dynamic with median LVOT gradient at rest 31 mm Hg (IQR, 10–51 mm Hg) and with Valsalva maneuver 100 mm Hg (IQR, 70–100 mm Hg).

Two patients (1 lung and 1 liver) died during the follow-up period, both of noncardiovascular causes (Table 2).

DISCUSSION

Herein, we report the largest series of adult noncardiac solid organ transplant recipients with posttransplant HCM. We found asymmetric LV hypertrophy and LVOT obstruction in a total of 12 lung, kidney, and liver transplant recipients. Upper septal hypertrophy was the most common phenotype; however, other hypertrophy phenotypes occurred. The development of LVH in adult solid organ transplant recipients remains incompletely understood. Although disease states that result in excess pressure load on the LV are known to be causal for LVH, a minority of patients in our cohort had preexisting hypertension, and no patient had aortic or subaortic stenosis. CNI use, of both tacrolimus and cyclosporine, has been causally implicated in the development of LVH in adult solid organ transplant recipients.[17-20,24] In the largest single-center series of cardiac hypertrophy assessed at autopsy in pediatric and adult liver transplant recipients, Roberts et al[24] reported cardiomegaly and asymmetric septal hypertrophy with gross mean IVS thickness of 14–16 mm in 56 adults without pretransplant hypertension who were treated with CNI. However, echocardiographic data including serial wall thickness measurements and LVOT gradients were not reported in their study. In contrast, Coley et al[21] found an overall prevalence of HCM, independent of hypertensive or valvular heart disease, to be similar to that of the general population in their single-center series of 3609 adult solid organ transplant recipients treated with tacrolimus. In their series, the 5 patients with HCM and echocardiographic LVOT obstruction were all renal transplant recipients, and 4 of 5 had a history of hypertension. The pathogenesis of tacrolimus-associated HCM has been attributed to increases in calcium release, which subsequently activate signaling pathways that prompt cardiac hypertrophy[25]; however, the totality of mechanisms involved in hypertrophic myocardial growth remain under active investigation[26] (Figure 2). Prospective characterization of LV size, wall thickness, and mass in adult solid organ transplant recipients as part of routine posttransplant care may be a high-yield strategy for future discovery and mitigation of symptoms and cardiopulmonary limitation.

Observational studies of patients with HCM have demonstrated an approximate 20% prevalence of AF and 15%–30% prevalence of NSVT.[27-31] In our cohort, atrial and ventricular arrhythmias were uncommon, and our patients did not suffer major arrhythmic complications over the follow-up period. These arrhythmias may have gone undetected because routine ambulatory screening for AF and NSVT, as recommended in HCM guidelines, may not have occurred as rigorously in our cohort given their atypical presentation.[6] Alternatively, the incidence of AF might actually be lower in this solid organ recipient cohort because the mechanism of AF may be distinct from the left atrial structural, electrical, and functional

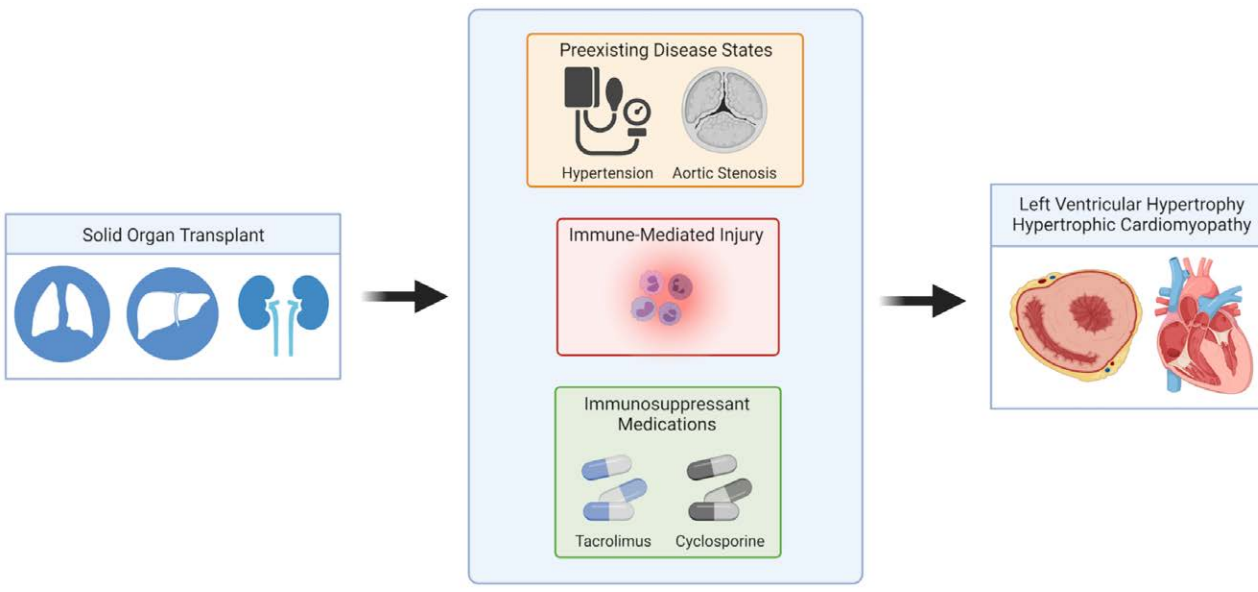

FIGURE 2. Proposed mechanisms of left ventricular hypertrophy and hypertrophic cardiomyopathy in solid organ transplant recipients, created with BioRender.com.

remodelings that are recognized risk factors for atrial arrhythmogenesis in sarcomeric HCM.[32]

A significant proportion of patients in our cohort developed symptomatic and provocable LVOT obstruction and were treated with guideline recommended pharmacologic therapies.[6] Nondihydropyridine calcium channel blockers, often used for the medical management of symptomatic obstructive HCM, increase blood concentrations of CNI through Cytochrome P450, family 3, subfamily A and P-glycoprotein inhibition.[33] Diltiazem is commonly used as a tacrolimus-sparing agent in transplant recipients. Because of this drug interaction, caution is recommended with their concomitant use. Three patients in our cohort were successfully treated for symptomatic LVOT obstruction with nondihydropyridine calcium channel blockers despite the potential drug interaction with CNI.

Four patients underwent successful septal reduction therapy with septal myectomy and alcohol septal ablation, demonstrating that the option of invasive management of severe symptomatic obstructive HCM should be offered to these patients if clinically indicated. Alcohol septal ablation is generally recommended when surgical risk is unacceptably high because of serious comorbidities or advanced age but, compared with myectomy, carries a higher risk of repeat septal reduction procedure.[6] Solid organ transplant recipients are multimorbid, immunosuppressed and may be at elevated risk for periprocedural surgical complications, poor wound healing, and infection. As in other HCM patients, patient selection is critical for success of septal reduction therapy. A few solid organ transplant recipients were successfully enrolled in Clinical Study (MYK -461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy-HCM, the pivotal phase 3, randomized, double-blind placebo-controlled trial of mavacamten, a first-in-class cardiac myosin inhibitor, in obstructive HCM.[34] Myosin inhibitors may emerge an additional therapeutic strategy for patients who develop HCM after solid organ transplant.

Recent observational data from the international Sarcomeric Human Cardiomyopathy Registry registry demonstrated that the incidence of new LV systolic dysfunction in HCM was approximately 7.5% over 15 y.[35] During the median of nearly 9 y of follow-up in our study, no patient developed LV systolic dysfunction. CMR demonstrated evidence of myocardial fibrosis generally localized to the hypertrophic segments; however, quantification of LGE was not uniformly performed.

Nearly all of our patients were their family probands, and only 2 individuals had a family history of HCM or sudden cardiac death. Disease-causing sarcomeric genetic variants were found in 2 of 6 individuals who underwent panel-based genetic testing in our cohort. Identification of causal sarcomeric variants in these patients triggered cascade genetic testing and clinical screening for their relatives. Cascade genetic testing is a critical component of comprehensive care of patients with HCM and enables identification of at-risk family members who require lifelong clinical surveillance and those family members who can be released from screening. Cascade screening and genetic testing offer an additional avenue of investigation into the etiology of LVH and nonfamilial or de novo HCM in solid organ transplant recipients.

Limitations of our analysis include its retrospective nature, small size, and possibility of referral bias. Some clinical data were not available for all individuals because some patients continued clinical follow-up at local centers. Five patients did not have pretransplant echocardiography or electrocardiogram available for review; therefore, it is possible that these individuals may have had LVH before organ transplant.

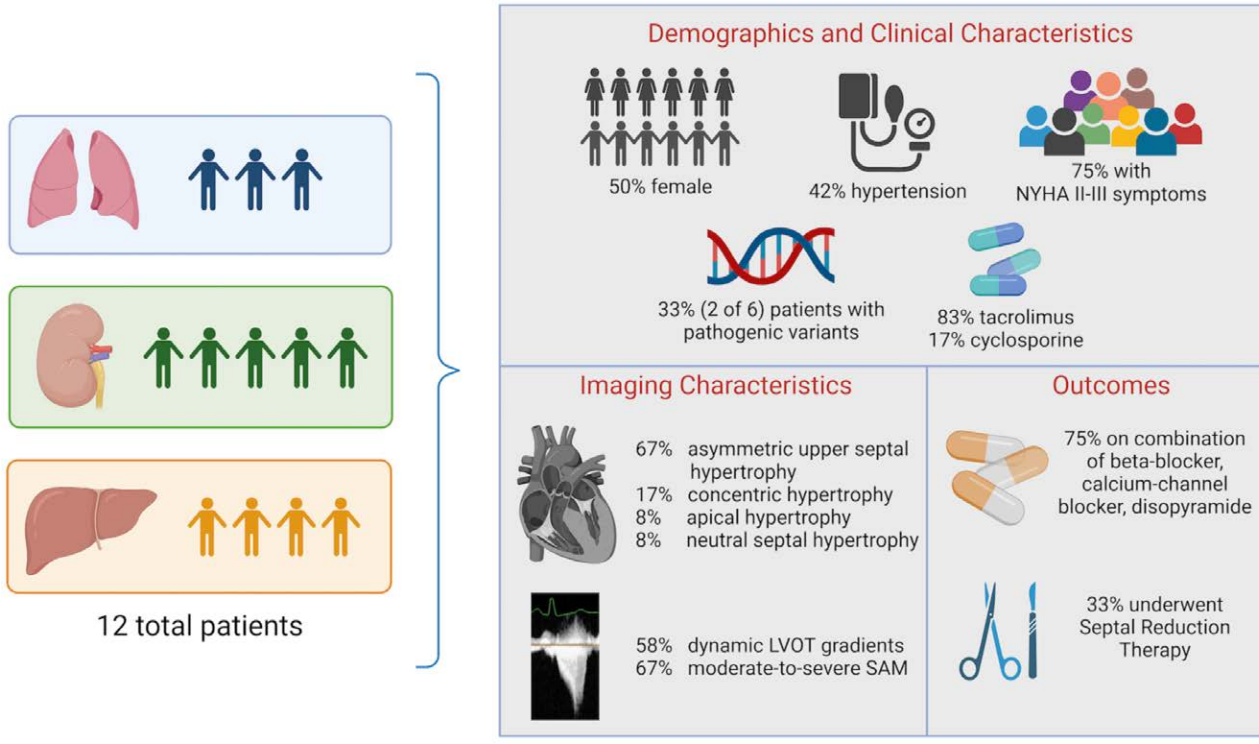

FIGURE 3. Characteristics of 12 noncardiac solid organ transplant recipients with hypertrophic cardiomyopathy, created with BioRender.com. LVOT, left ventricular outflow tract; NYHA, New York Heart Association; SAM, systolic anterior motion of the mitral valve.

CONCLUSIONS

In this study, we describe the largest single-center case series of LVH and HCM in adult solid organ transplant recipients (Figure 3). Although the mechanisms are yet to be elucidated, our data highlight that LVH and HCM with symptomatic obstruction can develop in lung, kidney, and liver transplant recipients. Solid organ recipients may be at risk for cardiovascular morbidity and mortality, and clinicians should be aware of these potential outcomes. Symptomatic LVOT obstruction in these patients can be managed according to current guideline recommendations without significant therapy-related morbidity. Genetic testing and familial screening should be offered to individuals who meet criteria for HCM diagnosis. Further study is needed to identify mechanisms of LVH in solid organ transplant recipients and to characterize their clinical phenotypes over time.

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