



Original Article

# Pulmonary hypertension and cardiac hypertrophy in children recipients of orthotopic living related liver transplantation ☆☆☆



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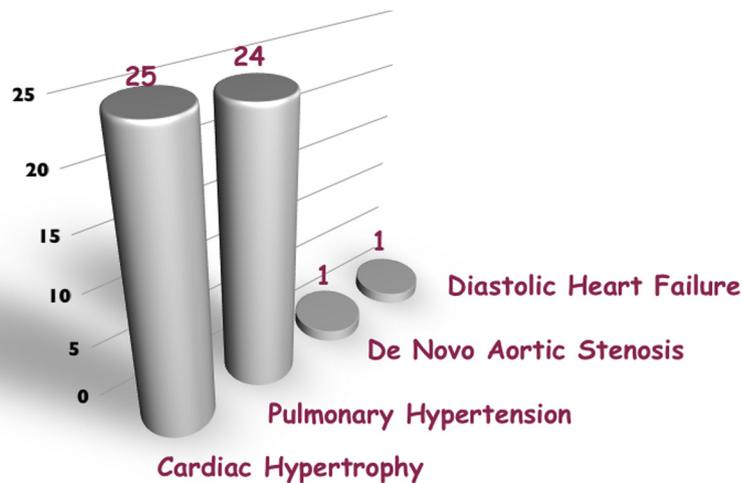
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## GRAPHICAL ABSTRACT



**Echocardiographic findings in  
25 Recipients of Orthotopic Living Related Liver Transplantation  
Mean duration ± SD of follow up= 7.02 ± 3.02 years**

*Abbreviations:* OLRLT, orthotopic living related liver transplantation; ECG, electrocardiogram.

☆ It is an observational study that does not require registration.

☆☆ Part of this work was accepted as an oral presentation in Saudi heart Association Conference, 2015 and poster presentation in Royal Collage for Pediatrics and Child Health, UK 2016 annual conference.

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## ABSTRACT

Surgical stress, liberation of cytokines associated with re-perfusion injury, and long standing use of immune suppressive medications in children recipients of orthotopic living related liver transplantation (OLRLT) pose cardiovascular risk. Reported cardiovascular adverse effects vary from left ventricular wall thickening, hypertrophic cardiomyopathy to resting ECG abnormalities, asymptomatic ST depression following increased heart rate and ventricular arrhythmias. Twenty-five consecutive children recipients of OLRLT were assessed by conventional 2-D, M-mode echocardiography and Doppler. The mean age  $\pm$  SD at transplantation and at enrollment in study was  $6.3 \pm 4.5$  and  $13.5 \pm 5.6$  years respectively. All children were on immunosuppressive medications, with tacrolimus being constant among all. Long-term post-transplant echocardiography revealed statistically significant interventricular septal hypertrophy among all (mean thickness  $0.89 \pm 0.16$  cm), ( $P = 0.0001$ ) in comparison to reference range for age, 24 had pulmonary hypertension (mean mPAP  $36.43 \pm 5.60$  mm Hg,  $P = 0.0001$ ), and early diastolic dysfunction with a mean Tei index of  $0.40 \pm 0.10$ . However cardiac function was generally preserved. Children recipients of OLRLT have cardiac structural and functional abnormalities that can be asymptomatic. Pulmonary hypertension, increased cardiac mass, de novo aortic stenosis and diastolic heart failure were among abnormalities encountered in the studied population. Echocardiography is indispensable in follow-up of children recipients of OLRLT.

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## Introduction

Pediatric liver transplantation for end-stage liver disease is one of the most successful solid organ transplantations [1]. Long-term survival after pediatric liver transplantation is now the rule rather than the exception [2]. While postmortem studies had proved uniform cardiomegaly in children recipients of orthotopic living related liver transplantation (OLRLT) on tacrolimus [3,4], not all children manifest clinically significant hypertrophic cardiomyopathy. Others suggested that this effect was transient [5]. Cardiovascular complications following orthotopic liver transplantation are not uncommon in adults (25–70%) and result in 7% of mortality [6]. They are related to coronary artery disease, acute coronary syndrome, stable angina, congestive heart failure, stroke, arrhythmia, and peripheral artery disease [7]. The goal of this study was to evaluate cardiac function and structure in children recipients of OLRLT by conventional echocardiography.

## Subject and methods

## Subjects

This study was a single center cross sectional pilot study that included 25 consecutive children recipients of OLRLT. The echocardiography and cardiac assessment was conducted in Echocardiography Clinic, Pediatric Cardiology Unit, Children's Hospital, Faculty of Medicine, Cairo University. All children underwent OLRLT in Wadi El Nil Hospital, Cairo, Egypt. The study spanned February 2012 to June 2013.

All patients underwent OLRLT in Wadi Al Nil Hospital and were placed on protocol immunosuppressive medications. First line comprised tacrolimus, mycophenolate mofetil and steroids, while second line comprised tacrolimus, azathioprine and steroids. The study was approved by Pediatric Department Committee for Post-Graduate Studies and Research, and by Post-Graduate Studies and Research Administration, Faculty of Medicine, Cairo University, Egypt. Strobe statement is presented as supplementary material.

## Methods

All data of children were analyzed. Analyzed data included etiology of disease prior to transplantation, complications and/or

associations of liver disease, age of the patient at the time of the study, age at the time of operation, weight and height percentiles at the time of operation, type of immunosuppressive medications, dose and compliance to the medications and preoperative cardiac and echocardiographic assessment.

All children underwent cardiac examination. Anthropometric measures were plotted against Egyptian Percentiles for weight and height (Diabetic Endocrine and Metabolic Pediatric Unit, 2002) [8] and recorded as percentiles for age.

ECG and echocardiographic examination were performed to examine cardiac structure, dimensions and systolic ventricular function using 2-D, M- mode and Doppler study.

The transthoracic two dimensional (2D) guided (M mode) and Doppler echocardiography was performed using SIEMENS Ocuson CV 70 ultrasonic machine phased array sector scanner with the 4 or 8 MHz probes according to age. Cardiac dimensions were measured according to the recommendations of the American Society of Echocardiography (ASE) by M-mode. Linear measurements of left ventricle (LV) cavity was obtained: Left ventricle end diastolic diameter (LVEDD), left ventricle end systolic diameter (LVESD), walls (interventricular septum [IVS] and posterior wall [PW]) and calculation of fractional shortening (FS%) as an indicator of LV systolic function was done according to the recommendations of the American Society of Echocardiography (ASE). FS value  $< 28\%$  was considered lower than normal with impaired LV systolic function [9,10].

LV Mass was calculated automatically using the validated formula (the ASE cube corrected by Devereux et al.). [11]  $LVM = 0.80 \times [(septal\ thickness + LV\ internal\ diameter + Posterior\ wall\ thickness)^3 - (LV\ internal\ diameter)^3] + 0.6\ g$  [12].

LV Mass Index was also calculated by dividing LV Mass by body surface area (BSA) [13]. Diastolic LV function was evaluated by Doppler (E passive phase of LV inflow/atrial contraction phase of LV inflow (E/A) [14].

Myocardial performance index (MPI) was defined as the ratio of the sum of iso- volumetric contraction and relaxation times over the ejection time [15].

The myocardial performance index (MPI) was calculated for the left ventricles by obtaining the "a" value, i.e., the time from closure to opening of the corresponding, AV valves and the "b" value which is the ejection time of ventricle as obtained by placing the pulsed Doppler just below the aortic valve. An average of three recorded

cycles for the “a” and “b” was obtained and MPI was calculated according to the formula  $MPI = a - b/b$  [16].

In addition, apical 4-chamber, parasternal short-axis, and parasternal long-axis views were used and 3 cardiac cycles were averaged preferably while the subject suspended breathing at the end of a normal expiration if subject is cooperative. Pulmonary artery acceleration time (PAAT) was measured by Doppler continuous wave placed at the pulmonary valve in the short axis arterial view.

## Statistical analysis

All the statistical analyses in this study were conducted using Statistical Package for Social Sciences version 15 (SPSS, Chicago, Ill). Simple frequency, cross-tabulation, descriptive analysis, and tests of significance (*t* test for parametric data) were used. Studied echocardiography parameters were compared to age appropriate reference ranges [17]. Values of echocardiography parameters derived pre-operatively and those derived after long-term post-transplantation were not computed owing to the difference in age-related reference ranges of the studied population pre-operatively and after long-term post-transplant. All echocardiographic used indices have different age related reference norms. Data are presented as mean  $\pm$  standard deviation (SD).

## Results

### Demography and outcome

The enrolled children comprised 13 (52%) males and 12 (48%) females. Their age range at transplantation was 9 months up to 17 years, and at enrollment in the current study was 7–26 years. Mean duration  $\pm$  SD of follow up was  $7.02 \pm 3.02$  years. Among the 25 studied children, the preoperative diagnosis was extra hepatic biliary atresia in 11 (44%), other diagnoses are shown in Table 1. Two children with primary hyperoxaluria underwent combined liver and kidney transplantation. Live donors of orthotopic liver were unrelated in 36% of cases, while 64% of donors were family members; mothers being 32%, fathers 16%, sisters 12% and uncles 4%.

Only one child suffered from transient immediate postoperative hypertension that was controlled on angiotensin converting enzyme inhibitor for 3 months. At enrollment systolic and diastolic blood pressure percentile for age was of group was  $57 \pm 18$  and  $56 \pm 16$  respectively. Yet, 16% of transplanted children were at 75th percentile for age, which is considered pre-hypertension that demanded regular follow up without medications. The children weight and height percentiles are shown in Table 2. All were on tacrolimus, as a single immunosuppressive medicine in only three patients, and in association with steroids or azathioprine or

**Table 1**  
Pre-transplantation diagnoses of the studied children recipient of OLRLT.

Diagnosis	Children (n = 25)	Percentage
Extra hepatic biliary atresia	11	44
Congenital hepatic fibrosis	2	8
Wilson disease	2	8
Primary hyperoxaluria	2	8
Glycogen storage disease 1 4%	1	4
Progressive familial intrahepatic cholestasis	1	4
Budd chiari syndrome	1	4
Autoimmune hepatitis	1	4
Alagille syndrome	1	4
Primary sclerosing cholangitis	1	4
Familial hypercholesterolemia	2	8

**Table 2**  
Weight and height percentiles of the 25 studied children recipient of OLRLT.

Percentile for age	Mean $\pm$ SD	Range	P value
Preoperative weight percentile	$27.6 \pm 23.11$	0.00–75.00	0.0001 <sup>*</sup>
Long term post-transplant weight percentile	$48.8 \pm 22.88$	10.00–95.00	
Preoperative height percentile	$13.72 \pm 15.84$	0.00–50.00	0.0001 <sup>*</sup>
Long term post-transplant height percentile	$34.48 \pm 19.01$	10–75	

<sup>\*</sup>  $P < 0.05$  is of significance.

**Table 3**  
Liver function tests of the 25 studied children recipient of OLRLT.

	Mean $\pm$ SD	Reference range	P value
Total bilirubin	$0.72 \pm 1.21$	0.1–1.1 mg/dL	0.132
Direct bilirubin	$0.40 \pm 1.22$	Up to 0.25 mg/dL	0.201
Alanine aminotransferase	$40.52 \pm 28.44$	Up to 40 U/L	0.373
Aspartate aminotransferase	$46.48 \pm 30.36$	Up to 42 U/L	0.143
Alkaline phosphatase	$0.78 \pm 4.1$	Up to 1	0.113
GGT	$144.28 \pm 148.48$	11–50 U/L	0.388

Alkaline phosphatase is represented in table in folds of upper limit of normal. GGT: gamma glutamyl transferase. Mean duration  $\pm$  SD of follow up was  $7.02 \pm 3.02$  years.

mycophenolate mofetil as double therapy (12 children) or triple therapy (10 children). Their liver functions were within normal range. Table 3 shows final visit liver function tests.

### Echocardiographic findings

Preoperative and long-term post-transplant cardiac indices of studied children are presented in Table 4. It is to be noted that the LVEDD and LVESD increased with statistical significance ( $P = 0.005$  and  $P = 0.032$ , respectively), and that the IVS and PW thickness change was not statistically significant ( $P = 0.733$  and  $P = 0.341$ ) from pre to post-transplantation. The results of the pre-post operative comparison should be regarded with caution as it is acknowledged that the obtained values should be compared to their age matched norms, taking in consideration that the children have grown during the follow up study.

In comparison to reference range for age, all showed significant increase in interventricular septum thickness ( $P = 0.0001$ ), significant increase in ejection fraction ( $P = 0.0001$ ), and fraction shortening ( $P = 0.000$ ), also significant increase in mitral valve velocity time ( $P = 0.001$ ), pulmonary valve acceleration time ( $P = 0.003$ ) and mean pulmonary artery pressure ( $P = 0.0001$ ) and finally significantly high Tei index ( $P = 0.011$ ) Table 5.

**Table 4**  
Preoperative and long-term post-transplant echocardiography indices.

	Preoperative Mean $\pm$ SD	Postoperative Mean $\pm$ SD	P value
LVEDD	$3.53 \pm 0.60$	$4.09 \pm 0.58$	0.005 <sup>*</sup>
LVESD	$2.32 \pm 0.31$	$2.73 \pm 0.68$	0.032 <sup>*</sup>
IVS	$0.94 \pm 0.20$	$0.89 \pm 0.16$	0.733
PW	$0.8 \pm 0.21$	$0.66 \pm 9.33$	0.341
EF	$66.6 \pm 8.70$	$72.42 \pm 6.26$	0.080
FS	$35.68 \pm 3.85$	$37.28 \pm 5.53$	0.026 <sup>*</sup>

The comparison of studied parameters does not consider weight and age related increments, during the duration of follow up, yet there is a decline of pre-operative IVS and PW thickness of the studied cohort. Preoperative mPAP data are lacking. LVEDD: left ventricle end diastolic diameter in cm, LVESD: left ventricle end systolic diameter in cm, IVS: inter ventricular septum in cm, PW: posterior wall in cm, EF: ejection fraction, FS: fraction shortening, mPAP: mean pulmonary artery pressure.

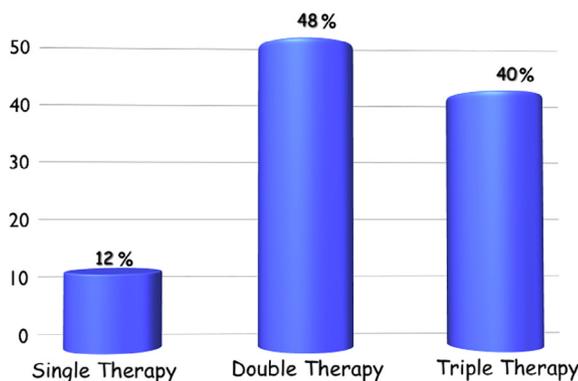
**Table 5**  
Long term post-transplant echocardiography parameters.

	Mean $\pm$ SD	Normal range	P value
LVEDD	4.09 $\pm$ 0.58	3.6–4.9	0.190
LVESD	2.73 $\pm$ 0.68	1.4–3.6	0.162
IVS	0.89 $\pm$ 0.16	0.5–0.8	0.0001*
PW	0.66 $\pm$ 9.33	0.6–0.8	0.76
EF	73.42 $\pm$ 6.26	>60	0.0001*
FS	37.28 $\pm$ 5.53	>28	0.0001*
SV	52.69 $\pm$ 23.1	>40	0.009*
E/A ratio	1.66 $\pm$ 0.44	1–1.7	0.087
LV mass	111.31 $\pm$ 27.77	55–244	0.454
LV mass c	85.17 $\pm$ 20.73	50–100	0.025
MV VTI	22.63 $\pm$ 5.41	13–19	0.001*
AV VTI	21.29 $\pm$ 9.07	18–26	0.465
TRV (m/s)	2.13 $\pm$ 0.29	<2.5	0.161
TRPG (mm Hg)	19.74 $\pm$ 5.21	<25	0.172
PRPG (m/s)	8.15 $\pm$ 2.98	<10	0.077
PVAT (m/s)	93.4 $\pm$ 12.32	<90	0.003*
mPAP (mm Hg)	36.43 $\pm$ 5.60	<25	0.0001*
Tei index	0.40 $\pm$ 0.10	0.24–0.64	0.011*

$P < 0.05$  is of significance (\*). LVEDD: left ventricle end diastolic diameter in cm, LVESD: left ventricle end systolic diameter in cm, IVS: inter ventricular septum in cm, PW: posterior wall in cm, EF: ejection fraction, FS: fraction shortening, LV mass: left ventricle mass, LV mass c: left ventricle mass corrected, SV: stroke volume, E/A: E/A ratio: the ratio of the early (E) to late (A) ventricular filling velocities, MV VTI: mitral valve velocity time integral AV VTI: aortic valve velocity time integral TRV: Tricuspid regurge velocity, TRPG: tricuspid regurge pressure gradient, PRPG: pulmonary regurge pressure gradient, PV AT: pulmonary valve acceleration time, mPAP: mean pulmonary artery pressure and Tei index: myocardial performance index. Normal range refers to indices that vary according to age where reference range value varies according to age of children.

### Medications

Only 12% of studied population was on single therapy, while 88% were on combined therapy whether double or triple therapy guided by their clinical condition and/or post-operative development of complications i.e. biliary complications or rejection of the graft (Fig. 1). Relation of cardiac structural and functional abnormalities to type of immune-suppression was mandatory. Yet, developing a relationship between cardiac findings and immune-suppression is not possible owing to small size of analyzed cohort. All of studied children were on tacrolimus (dose was guided by blood levels [18–20]) and some of them were on mycophenolate mofetil as well, however some of them were shifted to azathioprine because of complications or rejection. Steroids were added to patients with complications or rejection or those weaned with improvement of their clinical condition. Thus, these regimens were not constant as their medications were subject to change on their regular follow up because of complications or rejection upon clinical judgment. Echocardiographic changes did not correlate with immune suppressive medication (Table 6).



**Fig. 1.** Immunosuppressive regimen in studied children.

One child developed de novo aortic valve stenosis. He was transplanted for hypercholesterolemia. His immune suppressive regimen comprised tacrolimus, steroids and mycophenolate mofetil. He underwent change of immunosuppression medications and replaced tacrolimus by azathioprine. The child cardiac condition was stationary with residual aortic stenosis that necessitated cardiac catheterization and dilatation of aortic valve on two separate occasions one year apart.

In another child preoperative diastolic dysfunction progressed to diastolic heart failure during immediate postoperative period. He was maintained on angiotensin converting enzyme inhibitor ACE I for 2 years, attempt to discontinue tacrolimus was not successful, but 4 years later the cardiac function returned to normal while maintained on tacrolimus.

### Discussion

The current study revealed that the studied cohort of children recipients of OLRLT had significant increase in interventricular septum thickness compared to age appropriate norms ( $P = 0.0001$ ), cardiac hypertrophy, and pulmonary hypertension.

Ventricular and interventricular septum hypertrophy can develop due to intrinsic cardiac causes (cardiomyopathy), or secondary to extrinsic causes, such as pressure or volume overload - accompanying systemic or pulmonary hypertension- and valvular disease. Myocardial hypertrophy is also a part of the remodeling process following acute myocardial infarction, and is common in congestive heart failure caused by systolic and/or diastolic dysfunction [21].

The studied cohort had significant increase in interventricular septum thickness ( $P = 0.0001$ ), significant increase in ejection fraction ( $P = 0.0001$ ), and fraction shortening ( $P = 0.000$ ), also significant increase in mitral valve velocity time ( $P = 0.001$ ), pulmonary valve acceleration time ( $P = 0.003$ ) and mean pulmonary artery pressure ( $P = 0.0001$ ) and finally significantly high Tei index ( $P = 0.011$ ). The etiology of the hypertrophy in the studied cohort is not clear, and cannot be attributed to the intrinsic cardiac cause alone, as demonstrated by the significant increase in ejection fraction, and fraction shortening.

The increased cardiac mass in the studied cohort cannot be attributed to valvular disease as only one child developed aortic valvular disease, and not all. The entire cohort had significant increase in mitral valve velocity time ( $P = 0.001$ ), that was not associated with valvular structural or functional lesions [22–25]. It is justified, however to attribute this increase in mass to volume overload, namely pulmonary hypertension but not likely systemic hypertension, as the cohort had within normal blood pressure, where the mean ( $\pm$  standard deviation) systolic and diastolic blood pressure percentile for age was of the group was  $57 \pm 18$  and  $56 \pm 16$ , respectively.

The cohort did not suffer from myocardial stiffness or failure reported by others [26–28], as demonstrated by the significant increase in ejection fraction ( $P = 0.0001$ ), and fraction shortening ( $P = 0.000$ ). The conflicting increase in Tei index ( $P = 0.011$ ), despite the significant increase in ejection fraction, and fraction shortening need more follow up to reveal the underlying conflict. The increase in Tei index is influenced by preload, hemodynamic indices, cardiac perfusion not only myocardial function [29]. All these functions are venues for future research in children recipients of OLRLT.

The statistically significant pulmonary valve acceleration time ( $P = 0.003$ ) and mean pulmonary artery pressure ( $P = 0.0001$ ) in the studied population provide evidence that the cardiomegaly could be attributed to pulmonary hypertension in the studied cohort, that cannot be attributed to post-operative conditions solely.

**Table 6**  
Echocardiography finding with different drugs compared to normal range.

	Normal range	MMF (n = 11)		Azathioprine (n = 11)		Steroids (n = 10)	
		Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value
LVEDD	3.6–4.9	4.18 ± 0.67	0.494	4.05 ± 0.56	0.770	4.07 ± 0.44	0.890
LVESD	1.4–3.6	2.63 ± 0.39	0.529	2.9 ± 0.92	0.294	2.9 ± 0.91	0.325
IVS	0.5–0.8	0.88 ± 0.14	0.866	0.86 ± 0.17	0.487	0.94 ± 0.12	0.240
PW	0.6–0.8	0.69 ± 0.122	0.148	0.64	0.395	0.65	0.641
EF	>60	73.3 ± 6.38	0.940	74.4 ± 6.89	0.503	75.8 ± 6.83	0.165
FS	>28	37.3 ± 5.9	0.978	37.7 ± 5.5	0.716	38.8 ± 5.3	0.264
LV mass	>40	112.1 ± 27.7	0.897	110.8 ± 30.1	0.939	119.6 ± 30.9	0.228
LV mass c	1–1.7	89.6 ± 22.2	0.350	80.2 ± 19.1	0.298	86.3 ± 22.8	0.821
SV	55–244	55.5 ± 28.3	0.539	74.8 ± 71.2	0.307	53.3 ± 18.4	0.456
E/A	50–100	1.7 ± 0.62	0.657	1.68 ± 0.24	0.920	1.7 ± 0.0.32	0.397
MV VTI	13–19	24.12 ± 5.7	0.230	21.1 ± 5.3	0.221	23 ± 6.9	0.790
AV VTI	18–26	20.4 ± 7.5	0.678	22.14 ± 11.5	0.687	23.9 ± 12.06	0.241
TRV m/s	<2.5	2.2 ± 0.23	0.288	2.07 ± 0.36	0.375	2.09 ± 0.40	0.615
TRPG mm Hg	<25	20.65 ± 4.7	0.449	19.0 ± 5.49	0.546	19.7 ± 5.9	0.994
PRPG m/s	<10	8.6 ± 2.9	0.430	7.432.17	0.326	7.07 ± 2.24	0.177
PVAT m/s	<90	95.27 ± 9.5	0.512	89.36 ± 11.2	0.150	90.3 ± 11.3	0.315
M PAP mm Hg	<25	36.16 ± 4.29	0.837	37.5 ± 5.5	0.398	36.9 ± 5.5	0.699
Tei index	0.24–0.64	0.37 ± 0.10	0.174	0.44 ± 0.10	0.085	0.41	0.859

MMF: mycophenolate mofetil and azathioprine. None of the differences in echocardiographic findings with different immunosuppressive medications was statistically significant.

LVEDD: left ventricle end diastolic diameter in cm, LVESD: left ventricle end systolic diameter in cm, IVS: inter ventricular septum in cm, PW: posterior wall in cm, EF: ejection fraction, FS: fraction shortening, LV mass: left ventricle mass, LV mass c: left ventricle mass corrected, SV: stroke volume, E/A: E/A ratio: the ratio of the early (E) to late (A) ventricular filling velocities, MV VTI: mitral valve velocity time integral AV VTI: aortic valve velocity time integral TRV: Tricuspid regurge velocity, TRPG: tricuspid regurge pressure gradient, PRPG: pulmonary regurge pressure gradient, PV AT: pulmonary valve acceleration time, MPAP: mean pulmonary artery pressure and Tei index: myocardial performance index. Normal range refers to indices that vary according to age where reference range value varies according to age of children.

Adult and pediatric patients with liver cirrhosis have been reported to suffer from cirrhotic cardiomyopathy; myocardial remodeling and LV hypertrophy (LVH), repolarization abnormalities associated with systolic and diastolic functional abnormalities and cardiomyopathy. These effects are believed to result from enhanced activity of the sympathetic nervous system and hyperdynamic circulation with subsequent elevation in cardiac output and reduced systemic vascular resistance [30–33]. Cirrhotic cardiomyopathy also complicates cirrhosis in children, and was reported to affect 70% of children with biliary atresia [34,35]. The studied population had heterogenous pre-transplant diseases. Their pre-transplant echocardiography supports a continuation of hypertrophy that started pre-operatively. More studies are needed to define role of initial liver disease on cardiac function and structure post-transplantation.

The preoperative cardiac condition is challenging [34,35], yet recognition of post-transplantation cardiovascular morbidities is an emerging challenge with increased life expectancy after liver transplantation [34], and with the compelling need for immunosuppressive agents that affect cardiac function and structure adversely [1].

The almost unanimous cardiac hypertrophy and pulmonary hypertension encountered in the studied group on tacrolimus suggests a role of tacrolimus in maintaining and/or initiating cardiotoxicity [5,36]. While tacrolimus is believed to cause cardiac hypertrophy, a recent report describes tacrolimus induced interstitial lung disease in patients with rheumatoid arthritis as well [37], suggesting a potential role in pulmonary hypertension.

The cause of pulmonary hypertension in terms of interstitial lung disease in the studied cohort was not studied, yet it seems plausible to investigate immunosuppression effect on lung injury and/or pulmonary hypertension.

Calcineurin inhibitor-based immunosuppression remains the current backbone of immune suppression regimens in children. Currently is the era of evolving new immunosuppressive agents that promise less nephrotoxicity and less cardiotoxicity. They promise more efficient preservation of short and long term graft function, with less opportunistic infections and malignancy [38].

More insight is needed to define underlying pathogenesis, but in any case the cardiac hypertrophy might present clinically as aor-

tic valvular stenosis, contrary to what is believed, i.e., tacrolimus induced cardiac hypertrophy is asymptomatic [39,5]. Tacrolimus associated symptomatic cardiac hypertrophy and pulmonary hypertension is potentially reversible or seen as amenable to improvement in children recipients of orthotopic living related liver transplantation with or without discontinuation of tacrolimus. It is not clear what are the factors that act in concert with tacrolimus in inducing this cardiac hypertrophy or pulmonary hypertension.

Again, the boy with hypercholesterolemia who developed aortic stenosis might be recognized as evidence that tacrolimus induced cardiac hypertrophy might not be reversible, yet this conclusion is not consistent with the case of the other boy who had diastolic dysfunction prior to transplantation that mounted to diastolic heart failure in the immediate postoperative period. The boy completely resolved within 4 years from surgery despite being maintained on tacrolimus. Combining the observations it seems that post-operative cardiotoxicity is related to more than a mechanism that includes direct cardiotoxicity and synergism as well.

The limitation of this study was the lack of delineation of specific factors associated with preoperative cirrhotic cardiomyopathy in this studied group as we appreciated this to be beyond the scope of this study. Also the two children with primary hyperoxaluria who underwent combined liver and kidney transplantation are not solely OLRLT patients due to the combined transplantation where the added kidney transplantation effects on cardiac function may confound the results. Another limitation is that invasive assessment by capillary pulmonary wedge pressure to confirm pulmonary pressure was not employed.

While IVS hypertrophy in adults predicts all cause death in coronary artery disease [40], the predictive role of IVS hypertrophy for all deaths in children recipients of LROLT still awaits further research.

## Conclusions

OLRLT is associated with increased interventricular septum thickness, pulmonary hypertension, diastolic heart failure and de

novo development of aortic valve stenosis. The pre-transplant echocardiographic parameters do not support that the children had pre-transplant cirrhotic cardiomyopathy. More studies are needed to verify the contribution of original hepatic disease, surgical technique and graft perfusion to the cardiac findings. Tacrolimus contribution to post-liver transplantation cardiac adverse effects need to be further evaluated.

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### Conflict of Interest

The authors have declared no conflict of interest.

### Compliance with Ethics Requirements

Informed consent was obtained from all patients for being included in the study.

### Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jare.2017.07.004>.

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