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## *Cardiac evaluation in pediatric patients waiting for liver transplantation*

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## ORIGINAL ARTICLE

# Cardiac evaluation in pediatric patients waiting for liver transplantation

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## Abstract:

**Background:** Cardiovascular abnormalities are among common complication in patients with cirrhosis waiting for liver transplantation (LT). The aim of the present study was to investigate cardiac abnormalities among pediatric liver transplant candidates.

**Methods:** We prospectively evaluated the pediatric patient aged less than 18 years listed for LT between 2006 and 2008. Besides history taking and physical examination all the patients underwent electrocardiogram, chest radiograph, contrast echocardiography and color Doppler echocardiography, as well as arterial blood gas analyses.

**Results:** Totally 89 patients with mean age of 8.1±4.6 years were included in the study. The most common causes for liver disease were cryptogenic cirrhosis followed by biliary atresia and autoimmune cirrhosis. Clubbing was found in 27 out of 89 patients and was the most common abnormalities in physical examination. In 22 patients (24.7%) heart murmur was heard by a pediatric cardiologist. Sixty nine patients (77.5%) had normal cardiac findings in chest radiograph. Cardiomegaly was found in 17 (19.1%) patients as the most common abnormal finding in chest radiograph. Electrocardiogram showed sinus tachycardia in 16 (18%) patients. Eleven patients (12.4%) had tricuspid regurgitation as the most common abnormal findings in echocardiography. Thirteen (14.6%) patients had positive contrast echocardiography in favor of intrapulmonary shunt.

**Conclusion:** As the leading cause of post transplant death after graft rejection are cardiovascular complications cardiac evaluation should be considered in all pediatric patients before LT to lower morbidity and mortality during and after transplantation.

**Keywords:** Pediatric liver transplantation, Cardiac evaluation, Contrast echocardiography  
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## Introduction

Cirrhotic cardiomyopathy, ischemic heart disease (IHD), portopulmonary hypertension (PPH), alcoholic cardiomyopathy, and hypertrophic cardiomyopathy (HCM) are cardiac abnormalities that may be present in patients with cirrhosis [1-5].

Patients undergoing liver transplantation (LT) are at higher risk for development of cardiac complications, and post transplantation cardiovascular events are the major causes of death after graft rejection among these patients [6]. Recently several published studies especially among adult patients have described high incidence of cardiovascular abnormalities in patients with cirrhosis waiting for LT [3-4]. However, there is still few data among pediatric liver transplant candidates.

Furthermore, cardiac evaluation in pediatric liver transplant candidates before operation can predict and

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decrease the rate of morbidity and mortality after transplantation. This study aimed to evaluate cardiovascular involvement in pediatric patients with end stage liver disease listed for LT.

## Material and Methods

In a prospective manner, we evaluated the pediatric patients aged less than 18 years listed for LT between April 2006 and April 2008 in Organ Transplant Center affiliated to Shiraz University of Medical Sciences. This study was approved by local ethics committee of Shiraz University of Medical Sciences. We used a questionnaire including information about age, sex, underlying liver disease, history of cardiac disease, physical examination including cardiac exam, as well as results of arterial blood gas analysis, chest radiograph, electrocardiogram (ECG),

echocardiography, and contrast enhanced echocardiography (CEE). All the patients were visited by an experienced pediatric cardiologist. ECG had obtained from all the patients and abnormal findings such as evidence of coronary artery disease, sinus tachycardia, axis deviation, Q-T prolongation etc. were recorded. Prolonged corrected Q-T (QTc) interval defined as QTc interval more than 0.46 second. M-mode, two-dimensional, and Doppler echocardiography were performed using GE VIVID 3 echocardiographic machines by probe 3 MHz.

Table 1. The underlying liver disease in children candidate for liver transplantation

Liver disease	Number	Percent (%)
Cryptogenic cirrhosis	21	23.6
Biliary atresia	16	18
Autoimmune cirrhosis	13	14.6
Progressive familial intrahepatic cholestasis	7	7.9
Wilson disease	5	5.6
Crigler-Najjar Syndrome	4	4.5
Glycogen storage diseases type III	4	4.5
Hyperoxaluria	3	3.4
Thyrosinemia	3	3.4
Hypercholesterolemia	3	3.4
Idiopathic neonatal hepatitis	3	3.4
Congenital hepatic fibrosis	2	2.2
Primary biliary cirrhosis	2	2.2
Caroli's disease	1	1.1
Budd chiary syndrome	1	1.1
Primary sclerosing cholangitis	1	1.1
Total	89	100

Transthoracic CEE with two-dimensional apical four-chamber views was performed after the intravenous injection of the agitated normal saline. Positive CEE as evidence for intrapulmonary shunt was defined by the appearance of micro bubbles in the left side of the heart not before 4 heart beats after their appearance in the right side of the heart. Hepatopulmonary syndrome (HPS) is defined as the presence of the combination of advanced liver disease, hypoxemia ( $\text{PaO}_2 < 70$  mmHg) or alveolar-arterial oxygen gradient more than 20 mmHg, and pulmonary vascular dilatation. Definition of pulmonary hypertension was according to peak pulmonary regurgitation gradient more than 25 mmHg or peak tricuspid regurgitation gradient more than 30 mmHg or pulmonary relaxation time more than 100 milliseconds. Also echocardiographic data collected for ejection fraction below 50% and shortening fraction less than 28%, E wave

velocity, A wave velocity and E/A ratio more or less than 5 and 95 percentile for age and body surface area are recorded into the forms. Hypoxemia defined as  $\text{PaO}_2$  less than 70 mmHg or alveolar-arterial gradient more than 20 mmHg.

Results are expressed as mean $\pm$ SD. Data were analyzed using SPSS software (version 12.0 for the PC, SPSS Japan Inc., Tokyo) by independent sample t-test, two-tail Fisher's exact and Chi Square tests when appropriate. A p-value less than 0.05 were considered statistically significant.

## Results:

There were 48 boys (53.9%) and 41 girls (46.1%). The mean age of patients was  $8.1 \pm 4.6$  years. The most common underlying liver diseases were cryptogenic cirrhosis, biliary atresia, autoimmune cirrhosis, progressive familial

**Table 2. Cardiovascular findings of the children on the liver transplantation waiting list.**

Characteristics	Number	Percent (%)
Clubbing	27	30.3
Heart murmur	22	24.7
Cyanosis	9	10.1
Dyspnea	6	6.7
Cough	3	3.4
Chest pain	1	1.1
Rales	1	1.1

intrahepatic cholestasis, and Wilson disease, respectively. Other causes of liver disease were outlined in Table 1. The clinical cardiac characteristics of the patients were provided in Table 2.

Clubbing was the most common abnormal finding in physical examination (n=27, 30.3%). Mean systolic and diastolic blood pressure in our patients were 101.3±12.8 mmHg and 61.9±10.1 mmHg, respectively. The mean partial pressure of arterial oxygen (PaO<sub>2</sub>) was 71.1±27.3 mmHg and the mean arterial oxygen saturation was 88.5±10.9% in our patients. Thirty one (34.8%) patients had severe hypoxemia i.e. PaO<sub>2</sub><60 mmHg and 44 (50.6%) patients had mild hypoxemia i.e. PaO<sub>2</sub><70 mmHg.

Sixty nine patients (77.5%) had normal cardiac findings in chest radiograph.

The most common abnormal finding in chest radiograph was cardiomegaly found in 17 (19.1%) patients. The other abnormal findings in chest radiograph were interstitial infiltration (n=7, 7.9%) followed by diaphragmatic

**Table 3: Frequency of each abnormality in echocardiography**

Echocardiography Finding	Number	Percent (%)
Tricuspid regurgitation	11	12.4
Mitral regurgitation	6	6.6
Atrial septal defect	3	3.3
Pulmonary hypertension	2	2.2
Patent foramen ovale	2	2.2
Pulmonary insufficiency	1	1.1
Mitral valve prolapse	1	1.1
Aortic insufficiency	1	1.1
Septal hypertrophy	1	1.1
Bicuspid aortic valve	1	1.1
Situs inversus	1	1.1
Total	30	33.7

elevation and perihilar infiltration; each of them accounts for 5.6% (n=5) of the patients.

The most common abnormality in ECG was sinus tachycardia observed in 16 (18%) patients. Sixty eight (76.4%) patients had normal ECG. The other abnormal findings in ECG were T-wave inversion (n=1), ST depression (n=2), Q-T prolongation (n=1) and low voltage ECG (n=1). Fifty nine (66.3%) patients had normal echocardiography. The frequencies of abnormal findings were outlined in Table 3.

Eleven patients (12.4%) had tricuspid regurgitation as the most common abnormal findings in echocardiography. Thirteen (14.6%) patients had positive CEE in favor of intrapulmonary shunt, of these 9 patients met the criteria for HPS and 4 other patients did not have hypoxemia.

## Discussion

Pediatric patients with end stage liver disease may suffer from several cardiovascular complications in the course of underlying liver disease such as Wilson disease or glycogen storage diseases or may result from hemodynamic functional and anatomical abnormalities [7,8]. Cirrhotic cardiomyopathy with unknown cause was described as decreased cardiac contractility under exercise or pharmacological stress in patients with cirrhosis [9]. Ischemic heart disease (IHD) is another cardiovascular problem that may involve patients with cirrhosis especially among older individuals with different risk factors such as diabetes and hypertension. In a study conducted by Carey et al. the incidence of IHD among liver transplant candidates over 50 years of age was 27% [10]. Only two patients in our study had abnormal ECG changes in favor of IHD. It was absolutely predictable due to the age of our patients since our patients were all under 18 years of age. Alcoholic related cardiomyopathy is another cause of cardiovascular disorders among alcohol abuser cirrhotic patients [5]. Since the present study was conducted among pediatric patients, none of our patients had cardiac abnormalities related to alcohol consumption. HCM seems to be as a relative contraindication for LT because the hemodynamic changes associated with LT like decreased vascular resistance and hypervolemia exacerbate the hemodynamic disturbances of the underlying cardiomyopathy [11], however, Harley et al. reported two patients with HCM undergoing LT without any post operation complications [1].

Although there are several studies among adult patients regarding cardiovascular evaluation in liver transplant candidates, there is absence of such reports in pediatric patients.

In this study we evaluated our patients in the waiting list of LT to find the presence and prevalence of cardiovascular complications.

**Table 4: Frequency of liver diseases in patients with positive contrast echocardiography**

Disease	Number	Percent (%)
Cryptogenic cirrhosis	5	38.5
Autoimmune cirrhosis	3	23.1
Biliary atresia	1	7.7
Wilson disease	1	7.7
Caroli's disease	1	7.7
Thyrosinemia	1	7.7
Glycogen storage disease III	1	7.7
Total	13	100

The prevalence of clubbing in our patients was 30.3 % which is compatible with other reported prevalence of clubbing in chronic liver disease ranged from 23 to 29% [12]. It is also nearly similar to the prevalence of clubbing (32%) in Ozçay et al. study [13].

Cyanosis was the other abnormal finding in our patients preceding by clubbing and heart murmur. Despite cyanosis is the clinical sign of hypoxemia, cyanotic appeared pediatric patients may not be hypoxemic due to pathologic or physiologic conditions such as anemia, crying, or jaundice. So it is not surprising if we observed 9 cyanotic patients among them only 3 patients had severe hypoxemia (PaO<sub>2</sub><60 mmHg). However, defining hypoxemia as PaO<sub>2</sub><70 mmHg, from 9 cyanotic appearance patients 6 patients were really found to have hypoxemia. The prevalence of hypoxemia even in mild stages has been reported to be 56% in patients with end stage liver disease which is consistent with our results (50.6%) [14]. Decreased compliance of the lung by massive hepatomegaly, ascites, basal atelectasis, or pleural effusions causing decreased total lung capacity, diminished diffusion capacity due to interstitial pulmonary edema and pulmonary arteriovenous shunt are the possible mechanisms of hypoxemia in patients with end stage liver disease [15]. All of our patients with severe hypoxemia had massive hepatomegaly and tense ascites.

We used CEE with agitated normal saline to identify patients who had pulmonary arteriovenous shunting. Using this method will be helpful to diagnose patients with HPS characterized by chronic liver disease, intrapulmonary shunt and hypoxemia [16]. Although 13 patients in our study had positive CEE; 9 patients met the three criteria for HPS and 4 other patients did not have hypoxemia. In the present study all of the patients had systolic function in the normal range (ejection fraction and shortening fraction more than 50% and 28%, respectively) and systolic function according to measurement of E and A wave velocity was in the normal limit for age and body surface area.

Since there is no guideline for preoperative cardiac evaluations in liver transplant candidates, generally accepted guidelines to rule out IHD and other cardiovascular abnormalities must be considered in patients beyond 45 years old. In pediatric patients, however, the prevalence of IHD is definitely low and cardiac evaluation should be targeted to other cardiac conditions such as valvular heart disease as the higher prevalence of valvular heart disease among our patients.

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