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Cardiac Structural and Functional Alterations in Infants and Children with Biliary Atresia, Listed for Liver Transplantation

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Abstract

Background & Aims—Cirrhotic liver diseases are associated with abnormalities in cardiac geometry and function in adults (cirrhotic cardiomyopathy), but rarely explored in cirrhotic infants or children. We proposed that features of cirrhotic cardiomyopathy are present in infants with cirrhosis due to biliary atresia (BA) as early as the time of evaluation for liver transplantation and will correlate with mortality and post-operative morbidity.

Methods—Two-dimensional echocardiography (2DE) of infants with BA (n=40, median age 8 months), listed for transplantation at the Texas Children's Hospital from 2004 to 2010, were reviewed and compared to age- and sex-matched infants without cardiac or liver disease (controls). Length of stay and correlation with 2DE results were assessed.

Results—Compared to controls, children with BA had significant increases in multiple 2DE parameters, notably left ventricle (LV) wall thickness (23% increase), LV mass indexed to body surface area (51% increase) and LV shortening fraction (8% increase). Overall, features of cirrhotic cardiomyopathy were observed in most infants (29/40; 72%); 17 had hyperdynamic contractility and 24 had altered LV geometry. After liver transplantation (33), infants with abnormal 2DE results had longer stays in the intensive care unit (median 6 vs 4 days) and the

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hospital (21 vs 11 days), compared with infants who had normal 2DE reports. On univariate analysis, the length of hospital stay correlated with LV mass index.

Conclusions—Cardiomyopathy is a prevalent condition in infants with end-stage cirrhotic liver disease due to BA (>70%). This under-recognized condition likely contributes to the prolongation of post-transplant hospitalization.

Keywords

pediatric; heart; liver disease; morbidity; cholestasis; remodeling

Cardiac dysfunction in cirrhosis (cirrhotic cardiomyopathy; [CC]) is characterized by multiple alterations in cardiac conduction, physiology, and structure^{1, 2}. In general, there are five key components of CC: left ventricular (LV) and septal hypertrophy, impaired diastolic LV relaxation, hyperdynamic LV contractility, prolonged QTc interval and an attenuated cardiovascular response to stressors (e.g., hypovolemia, septic mediators, and pharmacologic inotropic medications)³. The development of cardiomyopathy in adult cirrhotics increases their risk of development of exercise fatigue, hepato-renal syndrome, post-operative complications, dysrhythmias and death.^{4, 5, 6} In addition, several features of CC subside after transplantation, suggesting that in the setting of cirrhosis, the heart responds to signals from the diseased liver in ways that if prolonged, may prove detrimental to the patient^{7, 8}. The timeline and underlying etiologies of CC are essentially unknown.

There are few informative animal models of CC—some have been explored using bile duct ligation or xenobiotic-induced biliary cirrhosis⁹⁻¹³. In these models, there is a common feature of a rapid development of cardiac hypertrophy and altered function, including an impaired inotropic response. Within 3 weeks of inducing biliary fibrosis in mice, there is a marked hypertrophic and hyperdynamic myocardial response (2-fold increase in cardiac mass, 20-fold increase in β -myosin heavy chain RNA and a ~35% increase in LV ejection fraction) along with altered cardiac metabolic pathways, all suggesting that the mouse heart rapidly and profoundly responds to biliary cirrhosis with features reminiscent of CC in humans^{8, 13}. The underlying mechanisms of altered cardiac structure and function are under investigation, but it appears to relate to the heart's rapid and stereotyped response to circulating factors including cytokines¹⁴ and retained biliary constituents—e.g., bile acids¹⁵⁻¹⁹.

The development of clinically relevant alterations (hypertrophy and hyperdynamic contractility) in mouse heart within a few weeks of damage to the biliary tract suggests that these (mal)-adaptive pathways may be present early in the course of cirrhosis in humans. And if so, then infants with biliary atresia (BA), a disease of biliary cirrhosis that begins soon after birth would be the ideal group to study. However few cardiac evaluations in this susceptible population have been published^{20, 21}, and it is unknown if structural, functional, and electro-physiological abnormalities even exist in infants with BA. The rapid development of cirrhosis in infants with BA, often by 3 months of age, suggests that a detailed cardiac evaluation in this population would shed light on the potential development of CC and perhaps, if any associated cardiac phenotypes correlate with pre- and post-transplant survival, as seen in adults²². Thus, the goal of the current study was to characterize the structural, functional and physiological, characteristics of hearts of infants and children awaiting transplantation due to the principal indication for transplantation in children - BA. Moreover, we sought to determine if there were potential correlates of cardiac findings with outcomes—namely, survival, and post-operative lengths of stay.

Subjects

All children evaluated for liver transplantation at the Texas Children's Hospital (TCH; n=138) between January 2004 and June 2010 were considered potential enrollees for the study. Given the variety of diagnoses, we sought to focus on those with the most prevalent diagnosis, who also have a high rate of mortality on the wait-list—those with BA. Care and evaluation has been relatively uniform during this time period at the institution, including the performance of 2DE in nearly all. During this time period, 48 infants with BA were evaluated and listed for transplantation, of which 42 were < 2 years of age. This young BA cohort (cirrhotic, “failed Kasai”) are at high risk of death awaiting transplantation.^{23, 24} The study plan of enrollees and 2DE evaluations are noted in Figure 1. Of the 42, only 2 listed BA infants did not undergo 2DE prior to transplantation. Thus, a total of 40 BA infants, 33 of which underwent transplantation and 7 who died pre-transplant, form the core group evaluated in this study. This research protocol was approved by Baylor College of Medicine Institutional Review Board.

Echocardiography

2DEs were routinely performed during liver transplant candidacy evaluation at the Cardiology Clinic at TCH. No infants were found with serious structural heart disease. 2DEs of age and gender matched children without cardiac or liver disease (n=30) who presented to Cardiology Clinic were randomly selected as controls. 2DE reports were evaluated for key parameters determining left ventricular (LV) geometry: LV free wall thickness in diastole (LV_d), systole (LV_s), septal thickness in diastole (Sep_d), and systole (Sep_s) and LV end diastolic (LVEDD) and end systolic (LVESD) dimensions. LV mass (LVM) was calculated using the formula by Devereux et al.²⁵ according to American Society of Echocardiography guidelines and indexed to both length^{2,7} (g/m) and body surface area (BSA; g/m²). For characterization of cardiac geometry, LV mass was indexed to BSA to minimize the potential for over-diagnosis of LV hypertrophy in this age group^{26, 27}. Relative wall thickness (RWT), defined as the ratio of LV wall thickness to LV end diastolic dimension, was calculated using the standard formula [RWT= (Sep_d + LV_d) / LVEDD]. LV geometry was then subdivided into four groups based on LVMI (g/m²) and RWT (cm) values²⁸: 1) Normal geometry (normal LVMI and RWT); 2) Concentric remodeling (normal LVMI and increased RWT); 3) Concentric hypertrophy (increased LVMI and RWT); and 4) Eccentric hypertrophy (increased LVMI and normal RWT). LVMI value over 110 g/m² and RWT value over 0.41 cm were considered abnormal as done before²⁸⁻³⁰. LV systolic function was assessed by the shortening fraction (%FS) and LV was considered hyperdynamic if the shortening fraction was > 2 z-scores for age.

Analyses

Subject data regarding age at listing, wait time, age at transplant or death, PELD score at time of listing and transplant/death, systolic and diastolic blood pressure during clinic visit at time of listing, serum biochemical markers for liver injury (ALT, AST, GGT, total bilirubin levels, PT, INR) and platelet count were recorded. Abdominal ultrasounds close to the time of listing were evaluated for spleen span and presence/absence of ascites. Total peri-operative (transplantation) and post-operative hospital length of stay (LOS) as well as post-operative Pediatric Intensive Care Unit (PICU) LOS were recorded from transplanted subjects (n=33).

Statistics

2DE results of normal (n=30) and BA children (n=40) were compared using Student's t test. Non-parametric two tailed t test (with Welch correction) was used to compare variables and

2DE parameters between those transplanted and those that died prior to transplant. Amongst those who were transplanted, median hospital and ICU length of stays (LOS) were compared between those who had a normal ECHO report and those who had either structural and/or functional abnormality using non-parametric Mann-Whitney-Wilcoxon Rank Sum Test. Non-parametric Kruskal-Wallis analysis of variance (ANOVA) with Dunn's post – test was performed to evaluate differences of continuous variables amongst groups stratified according to LV geometry amongst the children with BA. Fisher's exact test was used to compare the prevalence of 2DE abnormalities between patients with BA and controls to calculate Relative Risk (RR) using a contingency table as well as prevalence of non-continuous variables such as gender, presence/absence of ascites, length and weight percentiles. Univariate associations of continuous variables were assessed with Pearson correlation co-efficient. All statistical calculations were done using the PRISM 5.0 software program (Graph-Pad Prism, San Diego, CA, USA). $P < 0.05$ was considered significant. All data are reported as Mean $\pm$ SD unless specified.

RESULTS

Study population and patient demographics

Out of a total of 138 children listed for liver transplant at the Texas Children's Hospital during the period from January 2004 – June 2010, 48 (35%) had BA. Of these, 42 (87%) were under 2 years of age, 40 of which underwent 2DE and are the focus of this study. Seven died awaiting transplantation, while 33 were transplanted. There were no post-operative deaths (Fig.1).

Of the 40 children with BA listed for liver transplant, the majority 65% (26/40) were female, with a mean age at time of listing of 9.2 ± 3.9 months (median, 8 months) and a mean age at transplantation of 11.8 ± 4.9 months (median, 10 months). The average wait time was 68 ± 70 days (median 44 days). Most of the children were growth-impaired, (see Table 1) with 12 (30%) infants below the 3rd percentile for both length and weight, and an additional 5 below the 3rd percentile for length alone. Finally, of these 40, 6 (15%) had abdominal anomalies associated with laterality defects which included polysplenia (100%), situs invertus (75%) and interrupted inferior vena cava (33%).

All children showed evidence of severe liver injury, cholestasis and hepatocellular dysfunction: ALT: 183 ± 97 u/L; AST: 283 ± 117 u/L, GGT: 735 ± 642 u/L, total bilirubin of 9 ± 6.1 mg/dl, INR 1.5 ± 0.5 , albumin 3.2 ± 0.6 mg/dl—all consistent with “failed Kasai” (or non-Kasai, see below) phenotype. The average Pediatric End-stage Liver Disease score (PELD) at the time of listing was 17 ± 8 . Nearly all, (38/40; 95%), had evidence of portal hypertension revealed by: splenomegaly (mean ultrasound-derived spleen span of 8.8 ± 1.8 cm; normal for age is 6.5 ± 0.8 cm³¹; moderate to severe ascites in 11 (28%) thrombocytopenia (platelet count $< 150,000$) in 16 (40%) of the children, and a mean platelet count of $177\pm 92 \times 10^3/\mu\text{l}$. It should be noted that 10/40 (25%) were late referrals (median age 7 months) and did not undergo Kasai portoenterostomy. These subjects' demographic and clinical features did not differ substantially from those who underwent Kasai portoenterostomy.

Echocardiography

None of the infants had congenital cardiac defects known to be associated with BA^{32, 33}. When compared to age and gender-matched controls without cardiac or liver disease, 29 of the 40 (72%) subjects with BA awaiting transplantation showed 2DE abnormalities. These included significant increases in LV and septal thickness, LV mass (both raw un-indexed and when indexed to length or BSA) as well as LV shortening fraction (Table 1). Five (12%)

had hyperdynamic LV alone, 12 (30%) alterations in their LV geometry alone, while 12 (30%) had alteration in both structure and function (Fig.2). Overall, hyperdynamic contractility was present in 17/40 (42%) with BA vs. 5/30 (16%) of controls [RR of 1.44 with 95% CI of 1.06 – 1.98; $p=0.03$]. Structural changes in LV geometry was evident in 24/40 (60%) with BA vs. 3/30 (10%) controls [RR of 2.25 with 95% CI of 1.51 – 3.3; $p<0.0001$]. On further characterization of the 24 children with abnormal LV geometry, 12 (50%) had evidence of concentric remodeling (CR), 9 (36%) with concentric hypertrophy (CH) and 3 (12%) eccentric hypertrophy (EH). Thus, the vast majority (> 70%), of BA infants undergoing evaluation for liver transplantation had identifiable structural and functional cardiac abnormalities detected at a median age of 8 months.

Importantly, we could not detect any association of patient demographic, physiologic and clinical parameters, (gender, age at listing, wait time, height, weight, serum indices of liver function, PELD scores, spleen spans or presence/absence of ascites) with abnormalities in 2DE (Supplemental Table.1s). In addition, typical clinical indices of liver dysfunction and portal hypertension (serum bilirubin levels, spleen span, PELD score) did not correlate with structural and functional modifications by 2DE (Supplemental Table 2s). Taken together, these studies indicate that abnormalities in cardiac structure and function are common in BA infants awaiting liver transplantation.

Clinical and echocardiographic findings of those who died awaiting transplantation

There is a high risk of death in BA infants while waiting for transplantation^{23, 24, 32, 34, 35}. Seven children died awaiting liver transplant at a mean age of 8.7 $\pm$ 2.7 months, while none died post-transplantation. Of the 7, 1 did not undergo Kasai portoenterostomy and 2 had abdominal laterality defects. Comparing the 7 who died awaiting transplantation to the 33 who underwent transplantation, there were no significant differences in any 2DE parameter. Only a slightly lower mean serum albumin level (2.7 vs 3.2 mg/dl) and an increased presence of ascites (85% vs 18%) was present in those who died than those who underwent transplantation (Table 2). Notably, 4/7 infants who died had a normal 2DE report at the time of listing, although the mean age at 2DE was slightly younger in these 7 than those who underwent transplantation (7.3 vs. 9.1 m, $p=0.23$). In this case series, 4/7 (56%) had both length and weight under the 3rd %ile for age, while 6/7 (85%) were female. In general, these infants died of either circulatory insufficiency in the setting of an infection, massive gastrointestinal bleeding, or both. (Supplemental Table.3s). All together, perhaps due to the small number of those who died, we could not detect a clinical or 2DE parameter that correlated with risk of death on the list. Autopsy was performed on 3 of the children, whose cardiac histopathological findings generally support the 2DE results (Supplemental Fig.1s).

Correlation between 2DE findings and Post-operative Length of Stay

The determinants of pre-, peri - and post-operative care in transplant patients that may relate to underlying pre-transplant cardiac function are unknown. As an initial comparison, pre-transplant 2DE findings of those (n=33) who were successfully transplanted were related to hospital and ICU lengths of stay (LOS). When compared to those who did not have any 2DE abnormalities (Normal 2DEs; n=7), children with BA with abnormalities on 2DE (Abnormal 2DEs; n=26) had a significantly longer post-transplant PICU LOS (median 6 vs. 4 days; $p=0.04$) and hospital LOS (median 21 vs. 11 days; $p=0.03$) (FIG 3A). The median total hospital LOS that bridged transplantation (i.e., pre-and post-operative course - “pan-transplant LOS”) was also significantly longer (41 vs. 12 days; $p=0.01$) suggesting that infants with 2DE abnormalities are more likely to need hospitalization prior to transplantation. Of note, all of the 7 children with normal 2DE were admitted directly from home just prior to surgery. Patients with a combination of both structural + functional 2DE abnormalities had increased pan-transplant LOS when compared to either structural or

functional abnormality alone (Fig.3B). When clinically relevant continuous variables such as body weight, height, body surface area (at time of listing), age at transplant, wait time (in days), PELD, ALT, serum bilirubin, spleen size, serum albumin levels, along with 2DE parameters such as LV mass index (LVMI), relative wall thickness (RWT) and shortening fraction (%FS) were correlated with post-op ICU and total and post-op hospital LOS using univariate Pearson correlation model, raw LV mass (LVM) as well as LV mass index (LVMI) correlated with LOS. These data indicate that greater the LVMI, the longer the LOS (Fig.4 and Supplemental Table 4s). Taken together, these are the first findings that suggest a correlation between pre-transplant 2DE structural or functional abnormalities with increased length of peri- and post-hospitalization.

DISCUSSION

This study demonstrates that > 70% of infants with BA and “failed Kasai” phenotype awaiting transplantation exhibit multiple abnormalities in cardiac structure and function. These alterations (increased LV shortening fraction, LV free wall, septal thickness, and LV mass) developed rapidly—often by 8-9 months of age. In addition, thickened and functionally impaired hearts determined on routine 2DE during the pre-transplant evaluation suggested an association with increased post-transplant hospital and ICU lengths of stay. Taken together, this is the first study that has systematically evaluated cardiac manifestations of cirrhosis in infants, and has uncovered a rapid timeline of the development of cardiac manifestations along with associations with post-transplant outcomes. Thus, infants with BA, as opposed to adults with chronic liver disease (who have a lower prevalence and longer period of time before developing cardiac manifestations) may, in fact be the optimal population to explore the clinical attributes and pathophysiological contributors to cardiac (mal)adaptation to cirrhosis. In addition, there may now be a new clinically relevant diagnostic test to systematically explore in these infants that may impact outcomes — echocardiography.

This study was designed to explore the potential for cardiac manifestations by focusing on a relatively homogenous group with a high risk of dying awaiting transplantation — infants with BA²⁴. Since we do not have a known etiology for BA, and some infants with BA have structural cardiac defects^{32, 33} (e.g., ASD, VSD, but none were present in any infant in this study) one may argue that there is perhaps a bias towards cardiac disease in this population. However, this is unlikely given the lack of structural cardiac defects in the population in this study, or the development of cardiac disease either after transplantation or in older BA children. Thus, this population may be considered as pure a group of biliary cirrhotics as possible and thus the ideal group to study for the development of cardiac disease in the setting of cirrhosis. Future work will certainly be needed to explore the possibility of 2DE abnormalities in older BA children as well as other forms of childhood liver disease.

Although the number of subjects was limited, this is the largest group of infants with BA who were systematically reported to have cardiac evaluations. As such, there are a number of items to be highlighted, many of which were unexpected. Among these include the preponderance of females in both the transplanted population (20 of 33) but moreso in those who died awaiting transplant (see below; 6/7). However, there was no difference in the 2DE findings between males and females, nor was there any difference in the lengths, weights, blood pressures, severity of liver injury, cholestasis, PELD scores or ultrasonographic findings between the two sexes (data not shown). Although a gender difference has been seen before in BA in robust studies conducted using BARC^{32, 35} and the SPLIT databases^{24, 36}, any association of gender with outcomes has not been reported, and perhaps may be due some inherent biological gender discrepancy. Finally, this study only reported one time point for 2DE—that when the subject was undergoing evaluation for

transplantation. None of the subjects underwent a 2nd 2DE, and it could be plausible that some of the ¼ who did not have abnormalities at evaluation, eventually developed features later on. A comparison of those who develop abnormalities on 2DE, to those who do not, warrants future consideration.

Another unexpected finding was that patients with abnormal 2DE findings spent ~30% longer in the ICU and stayed twice as long in the hospital post-transplant (Fig. 3). Although a direct relationship between 2DE abnormalities and causation for increased LOS remains to be determined, LOS did not correlate with any routine biochemical, clinical or growth parameter (Table. 3 and Supplemental Table 4s), but in fact, showed a univariate correlation with Left ventricular mass index (Fig.4), suggesting in this study that heavier the LV on 2DE, longer the post-operative course. Thus, an abnormal pre-transplant 2DE may be considered a potential marker of disease severity and clinical status.

Epidemiologic information about the prevalence of cardiac dysfunction in cirrhosis and other forms of liver diseases at baseline is limited in adults and moreso in infants and children. From adult data, the majority of patients are often diagnosed with CC during physiologic (exercise-induced), pharmacologic (inotropic), surgical (transjugular intrahepatic portosystemic shunts [TIPS] or liver transplants), septic and hypovolemic (variceal bleeding) stressors, where the common feature is a lack of appropriate cardiac response. Studies evaluating 2DE results of adult patients with cirrhosis and portal hypertension revealed a prevalence of LV hypertrophy and inappropriately high LV mass in ~ 30% of subjects prior to liver transplantation³⁷. Adult studies have also suggested that cirrhotic cardiomyopathy may be reversible. Pre-transplant LV hypertrophy and hyperdynamic contractility resolve after liver transplantation.³⁸ Pre-transplant prolonged QT interval has also been shown to resolve after liver transplantation in adults⁷ as well as children²⁰. Since >70% of infants with BA had abnormalities of 2DE, it seems that a focus on this population, rather than adults, may reveal new information regarding the underlying causes and exacerbants of cardiac adaptation to cirrhosis.

The consequences of structurally and functionally abnormal hearts in these cholestatic cirrhotic infants remain to be understood. Findings from this study are essentially a beginning, but by connecting what is known in adults with CC, to the findings here, it would be reasonable to consider a BA infant's heart as potentially more likely to poorly respond to a stressor (e.g., sepsis or bleed) than one without such findings. Thus, the issue could be mainly one of inadequate cardiac responsiveness, or maladaptation. And the deaths due to "multi-organ failure" or "sepsis" may be due, in part, to unrecognized contributions from pre-existing cardiac dysfunction. However, perhaps due to the small number of infants who died (n=7) and the fact that nearly ¾ of all BA infants had 2DE abnormalities, we could not correlate 2DE findings with either death or typical clinical indices of liver disease or portal hypertension. Though this study suggests a correlation between abnormal pre-transplant 2DE with increased post-operative LOS, there are still some unresolved potentially confounding issues that currently limit interpretation. Confounders such as location (home or hospital) of the patient pre-transplant or commonly-encountered clinical causes of increased LOS (such as post-operative infections and feeding problems) immediately come to mind. These data can serve as a starting point for the design of multicenter, longitudinal, prospective studies to best evaluate the multiple variables that may be contributing to LOS and other outcomes.

So what can we glean from these findings that can be of important to the care and health of BA infants awaiting transplantation? First, it is likely that systematic and prospective analysis of 2DE findings may uncover the progression and underpinnings of adaptive and maladaptive changes at the level of the myocardium as a consequence of cirrhosis.

Secondly, there needs to be a consideration for analyzing other functioning organ systems such as brain, kidney, muscle, endocrine, bowel and vasculature in a cirrhotic patient that may be linked to cardiac adaptation. And thirdly, the mediators and correlates such as inflammation, nutrition, various metabolites (bile acids) that could lead to cardiac hypertrophy and functional impairments warrant future studies. Some or all of these factors may coordinate or interplay in ways that are yet to be understood, but with current technologies, can begin to be investigated. Future multi-center, controlled, prospective studies should also be directed towards delineating the clinical consequences of cardiomyopathy, especially focusing on hemodynamics under stress of surgery or infection to see if they parallel adult observations. In addition, comparisons to other non-cirrhotic liver diseases that lead to transplantation will need to be made that may indicate a component that relates to cholestasis as a major contributor to altered cardiodynamics, as seen in a mouse model of biliary fibrosis¹³.

In conclusion, this study demonstrates cardiac structural and functional remodeling in infants with BA and end stage liver disease awaiting liver transplantation. This extra-hepatic consequence of cirrhosis though currently under-recognized and under-studied could potentially influence post-operative care in these children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

2DE	(2-Dimensional Echocardiography)
BA	(Biliary Atresia)
BSA	(Body Surface Area)
CC	(Cirrhotic cardiomyopathy)
ESLD	(End Stage Liver Disease)
(ICU)	Intensive Care Unit
LOS	(Length of Stay)
LV	(Left ventricle)
LVMi	(Left Ventricle Mass Index)
PICU	(Pediatric ICU)
RWT	(Relative Wall Thickness)

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Fig.1. Patients with BA selected for study

Flow chart depicting patients listed for liver transplantation during the study period of January 2004 to June 2010. Note: BA (Biliary atresia); LT (Liver Transplantation); TCH (Texas Children's Hospital); 2DE (2-Dimensional Echocardiography).

Fig.2. Prevalence of abnormal 2DE reports in children with BA

Pie chart depicting prevalence of abnormal 2DE findings in children with BA listed for LT (n=40). 11/40 (28%) had normal (N) 2DEs, 5/40 (12%) had functional (hyperdynamic) 2DEs (F), structural (S) abnormality was seen in 12/40 (30%) while both functional as well as structural (F+S) abnormality was seen in 12/40 (30%) of children.

Fig.3. Effect of abnormal pre-operative 2DE reports on post-operative course

(A) Depicts distribution of post-operative Pediatric Intensive care Unit (PICU) , post-operative hospital and total hospital length of stay (LOS) in patients with normal (N) (n=7) and abnormal (ABN) (n=26) pre-operative 2DEs in all those with BA who were successfully transplanted (total n=33). (B) Depicts distribution of PICU, Post-op Hospital and total Hospital LOS in successfully transplanted children with BA (n=33) when children with Normal (N; n=7) 2DE were compared with those with Functional abnormality alone (F; n=3), Structural abnormality alone (S; n=11) or both (F+S;n=12). (* $p < 0.04$; Stats: 2-tailed Mann-Whitney-Wilcoxon-Rank Sum Test; Results: Box (25-75%^{ile}) and Whiskers (10-90%^{ile}) depicts median in days.

Fig.4. Univariate Correlation of LVMI to post-operative PICU, hospital and total hospital LOS
 Among all the clinically relevant continuous variables studied by linear regression analysis, only LVMI revealed a positive correlation with LOS. (Statistics: Univariate Pearson's correlation)

Table.1
Children with BA listed for LT have abnormal 2DE findings

Depicts general demographic and Echocardiographic parameters of patients with BA compared with age and gender matched controls. 2DEs of patients with BA showed a statistically significant increases in LV shortening fraction (%FS), left ventricular wall thickness in diastole (LV_d), septal thickness in diastole, relative wall thickness (RWT) and un- indexed LV mass (g) as well as LV mass indexed to both body surface area (g/m²) and height^{2.7} (g/m). (Results: Mean±SD; Statistics: paired Student t test; gender difference evaluated by Fisher exact test)

PARAMETERS	Controls (n=30)	BA (n=40)	p value
Age (mo)	10±4.3	9.2±3.9	0.16
Gender (%F)	53%	66%	0.12
Weight (kg)	8.6±2	7.39±2.1	0.01
Height (cm)	70.7±7.8	63.56±10.8	0.0043
FS (%)	39.8±3.6	43±5	< 0.0005
LV [d] mm	45±10	55±12	< 0.0005
Septum [d] mm	51±10	62±12	< 0.0002
RWT (mm)	36±10	45±9	< 0.0002
LV Mass (g)	25±4.5	33.64±12.8	< 0.0005
LVMI (g/m ²)	60±11	91.1±29	< 0.00001
LVMI (g/m)	64±21	107±47	< 0.00001

Table.2
Comparison of general demographic, physical, laboratory and 2DE parameters of patients with BA who were successfully transplanted (LT) and those who died prior to transplant

Patients who died prior to transplant had statistically lower serum albumin levels and tended to have ascites when compared to those that were successfully transplanted. No difference was found in the 2DE parameters between the two groups in our series. (Results:Mean±SD; Statistics: Unpaired t test with Welch correction; Gender difference, height and weight percentiles and presence/absence of ascites was evaluated by Fisher's exact test; p<0.05 considered significant)

PARAMETERS	LT (n=33)	DIED (n=7)	p value
gender (%F)	60%	85%	ns
list age (mo)	9.5±4	7.7±2.6	ns
age at ECHO(mo)	9.1±3.8	7.3±2.8	ns
age at LT / Death(mo)	11.8±4.9	8.7±2.7	ns
days on list	75.5±75.2	32.5±17.3	ns
height (cm)	63.5±11.8	62.8±5	ns
weight (kg)	7.4±2.1	6.5±1.4	ns
% below 3 rd percentile (L)	39%	57%	ns
% below 3 rd percentile (W)	33%	57%	ns
% below 3 rd percentile (both)	24%	57%	ns
Heart Rate	131±13	126.4±12	ns
Systolic BP (mm Hg)	110±12.6	102±13.5	ns
Diastolic BP (mm Hg)	63.4±12	52.8±15.1	ns
Mean BP (mm Hg)	78.7±11.2	69.3±13.4	ns
ALT (u/L)	190.2±101.2	143±81.2	ns
AST(u/L)	287±118	266±119	ns
GGT(u/L)	803±692	369±118.7	ns
Total Bilirubin (mg/dl)	8.76±6.1	11.2±6.4	ns
Albumin (mg/dl)	3.2±0.6	2.7±0.6	< 0.05
Prealbumin	12.9±4.7	10.5±2.1	ns
PT	17.6±4	16.9±2	ns
INR	1.5±0.5	1.3±0.3	ns
Platelet count	182.5±91	150±102	ns
Spleen span (cm)	8.9±1.7	8.2±1	ns
Presence of Ascites	18%	85%	< 0.02
PELD score	15.9±8.3	20.5±8.5	ns
FS (%)	43±5	43±6.2	ns
LV [d](mm)	55±10	53±13	ns
Septum [d] mm	62±10	57±12	ns
RWT (mm)	45.2±10	39.7±4	ns
LVM (g)	33.7±12	32.8±11.6	ns
LVMi (g/m ²)	92±29	95.3±27.9	ns
LVMi (g/m)	115.5±63	120.1±38	ns

Table.3
Comparison of demographic, physical and laboratory parameters of patients with BA who were successfully transplanted (total=33) based on 2DE reports at time of listing.

No difference was found between those who had normal reports (n=7) v/s those who had abnormality either structural and/or functional on 2DE (n=26). Results: Mean±SD; Statistics: Unpaired t test with Welch correction; Gender difference evaluated by Fisher's exact test; p<0.05 considered significant)

PARAMETERS	NORMAL 2DE (n=7)	ABNORMAL 2DE (n=26)	p value
gender (%F)	42%	65%	ns
list age (mo)	11±4.7	9±2.9	ns
age at ECHO (mo)	9.8±4.6	8.9±3.8	ns
age at LT (mo)	13±6.2	11.5±4.5	ns
wait on list (days)	62.1±56.7	79.2±80	ns
height (cm)	67.5±4.4	63.1±11.6	ns
weight (kg)	7.8±1.6	7.4±2.2	ns
% below 3 rd percentile (ht)	42%	38%	ns
% below 3 rd percentile (wt)	42%	30%	ns
% below 3 rd percentile (both)	28%	23%	ns
Heart Rate	125±18.8	132.6±11.7	ns
Systolic BP (mm Hg)	108.5±15.2	110.8±12.4	ns
Diastolic BP (mm Hg)	59.6±14.7	64.1±10.9	ns
Mean BP (mm Hg)	75.8±14.2	79.4±10.4	ns
ALT (u/L)	230.4±149.4	175.3±78.9	ns
AST(u/L)	259.7±85.6	287.3±121.7	ns
GGT(u/L)	1029± 909	763.2±607.5	ns
Total Bilirubin (mg/dl)	8.3±6.6	8.9±6.3	ns
Albumin (mg/dl)	3.2± 0.7	3.3±0.6	ns
PT	18.5±3.9	17.5±4.	ns
INR	1.7±0.6	1.5±0.5	ns
Platelet count	192.8±145.7	176.6±73.7	ns
Spleen Span (cm)	8.9±2.5	9.07±1.6	ns
PELD score (at listing)	14.4±8.9	16.3± 8.9	ns
PELD score (at Transplant)	16.5±10.5	21.3±6.2	ns