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Features of Cirrhotic Cardiomyopathy Early in the Lives of Infants With Biliary Atresia Correlate With Outcomes Following Kasai Portoenterostomy

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Cirrhotic cardiomyopathy (CCM), detected during two-dimensional echocardiography (2DE), is prevalent in patients with biliary atresia (BA) awaiting transplant. Whether CCM occurs early in the lives of infants with BA is unknown. The aim of this study was to explore the incidence and consequence of CCM in patients with BA, focusing on the earliest ages when 2DE was performed. A cohort of 78 patients with BA at a single center underwent 2DE (median age = 132 days) during the first year of life. Left ventricular mass index (LVMI) to upper limit of normal (ULN) ratio ≥ 1.0 was present in 60% of patients who never underwent Kasai portoenterostomy (KPE; n = 15), 49% with nondraining KPE (n = 41), and 21% with draining KPE (n = 19). Patients with a draining KPE (median age at 2DE = 72 days) had a lower LVMI/ULN ratio (0.75 [interquartile range [IQR] 0.70, 0.91]) compared to those with a nondraining KPE (0.99 [IQR 0.78, 1.17] median age of 141 days; *P* = 0.012). In those whose 2DE was performed within 7 days of KPE (n = 19, median age of 61 days), the LVMI/ULN ratio was lower in those with a future draining KPE (0.73 [IQR 0.66, 0.75]) compared to the group with a future nondraining KPE (1.03 [IQR 0.88, 1.08], *P* = 0.002). Logistic regression modeling revealed LVMI/ULN ratio ≥ 1.0 as a predictor of KPE outcome, with an odds ratio of 16.7 (95% confidence interval 1.36-204; *P* = 0.028) for a future nondraining KPE compared to those with a LVMI/ULN ratio < 1.0. *Conclusion:* 2DE early in the lives of patients with BA revealed features of CCM that correlated with future outcomes. If validated in a multicenter study, this could lead to 2DE as a useful clinical tool in the care of infants with BA. (*Hepatology Communications* 2022;6:1413-1424).

Cardiac dysfunction has been noted for decades in patients with cirrhosis.[1,2] Those exhibiting a group of specific parameters were further defined as having cirrhotic cardiomyopathy (CCM).[3-6] The presence of CCM contributes to increased mortality and morbidity, including the development of multiorgan dysfunction, increased incidence of perioperative complications, acute heart failure, and graft rejection.[7-15] In 2005 a working definition and criteria were proposed for adults characterizing CCM as a combination of systolic dysfunction, impaired diastolic relaxation, and electrophysiological disturbances such as prolonged QTc interval in the absence of known cardiovascular

Abbreviations: 2DE, two-dimensional echocardiography; ALB, albumin; ALT, alanine aminotransferase; ANOVA, analysis of variance; AST, aspartate aminotransferase; BA, biliary atresia; BSA, body surface area; CCM, cirrhotic cardiomyopathy; DB, direct bilirubin; EF, ejection fraction; GGT, gamma glutamyltransferase; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; IVSd, interventricular septum dimension in diastole; KPE, Kasai portoenterostomy; LV, left ventricle; LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; LVMI, left ventricular mass index; LVMI/ULN, left ventricular mass index to upper limit of normal ratio; LVPWd, left ventricular posterior wall dimension in diastole; OR, odds ratio; PELD, Pediatric End-Stage Liver Disease; SF, shortening fraction; SNL, survival with native liver; TB, total bilirubin; ULN, upper limit of normal.

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disease.[6] Features of cirrhosis are also present early in life in infants with BA, the principal indication for solid organ transplantation in children, suggesting that CCM may be an underrecognized and underdiagnosed condition in children with advanced liver disease.[16]

Several recent studies have investigated and established the presence of cardiac dysfunction in children with liver disease.[10,11,17-20] Specifically, reports in infants with BA awaiting transplantation suggest that specific two-dimensional echocardiography (2DE) parameters of pediatric CCM correlate with clinical outcomes. Among the first studies in children, approximately 72% of infants with BA awaiting liver transplantation had identifiable structural and/or functional abnormalities detected on 2DE when compared with age-matched controls.[17] In a follow-up study, a definition for CCM in pediatrics was proposed using 2DE parameters, principally left ventricular mass index (LVMI) and relative wall thickness (RWT).[20] The presence of elevated LVMI or thickened RWT correlated with adverse pretransplant and posttransplant clinical indices (e.g., death, intensive care unit [ICU] stay, need for advance ICU therapies). These findings suggest that infants awaiting liver transplant with BA and features of cardiac dysfunction are at risk of poorer outcomes than those without features of CCM.

It is not known whether aberrant 2DE CCM features are present early in the lives of infants with BA, nor if present, does CCM correlate with future outcome of the Kasai portoenterostomy (KPE). This study aims to describe and characterize 2DE parameters associated with CCM in childhood in patients with BA starting at the age of KPE, which is often during initial interactions of these families with hepatologists and other specialists. We sought to explore whether there were features of CCM in these infants with profoundly cholestatic BA during this first crucial year of life, and whether CCM early in life may be a contributor to future outcomes.

Materials and Methods

STUDY DESIGN

This is a single-center retrospective cohort study of pediatric patients with BA followed principally by hepatologists between January 2010 and December 2018 at Children's Healthcare of Atlanta, the only pediatric transplant program in Georgia and one of the largest pediatric liver-transplant programs in North America. All patients between 1 month and 18 years with a 2DE done were enrolled, whereas those with hemodynamically significant congenital heart disease were excluded. A KPE was termed "draining" as defined by a serum total bilirubin (TB) level ≤ 2.0 mg/dL 3 months following KPE.[21] Three groups were studied: those with a draining KPE, a nondraining KPE, and those who were directly evaluated for liver transplantation without a KPE. This

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study was approved by the Institutional Review Board at Children's Healthcare of Atlanta.

VARIABLES

The primary study clinical outcome of patients with BA was fulfilling the definition of draining with a TB ≤ 2.0 mg/dL at 3 months after KPE. Key 2DE parameters were selected to evaluate structural and systolic function of the left ventricle (LV). For structure, the parameters were interventricular septum dimension in diastole (IVSd), left ventricular internal dimension in diastole (LVIDd), left ventricular internal dimension in systole (LVIDs), and left ventricular posterior wall dimension in diastole (LVPWd). LVMI was derived from a composite score calculated according to the American Society of Echocardiography, indexed to height.[22] The LVMI 95th percentile (upper limit of normal [ULN]) was calculated for each patient given the variability with age and sex for patients <9 years.[22] To standardize this variable, we used a ratio of the LVMI to the LVMI 95th percentile, termed LVMI/ULN. For LV systolic function, shortening fraction (SF) and ejection fraction (EF) were recorded in addition to mitral valve lateral annulus and septal annulus in systole (MV s' and S s'). Diastolic dysfunction in children was evaluated by mitral valve lateral annulus in early diastole (MV e') and late diastole (MV a'), as well as septal annulus in early diastole (S e') and late diastole (S a'). Mitral valve doppler inflow in early and late diastole, as well as the mitral and septal E/e', were also recorded.[23,24]

An LVMI greater than or equal to the LVMI 95th percentile or LVMI/ULN ratio ≥ 1.0 was considered abnormal. SF > 40% and EF > 75% were considered hyperdynamic, and septal E/e' > 11.0 was considered abnormal.

Other parameters collected include age, length, weight, and body surface area (BSA) at time of 2DE, and age at KPE. Secondary outcome data, such as age at transplant listing, survival with native liver (SNL) at age of 2 years, and age at transplant were also collected. Laboratory data were obtained closest to the time of 2DE, not exceeding 30 days, with most values obtained within 1-2 days of 2DE. These biochemical indices included aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), TB, direct bilirubin (DB), platelets (PLT), international normalized ratio (INR), and albumin (ALB).

STATISTICS

Descriptive statistics were reported as medians and interquartile ranges (IQRs; 25th-75th) for continuous variables, counts, and percentages for categorical variables. Overall comparisons among the three groups (draining, nondraining, and no KPE) were conducted using analysis of variance (ANOVA) or Kruskal-Wallis tests. If the equal variance assumption was violated, comparisons were run using linear mixed models adjusting for unequal group variances. Any overall significant difference across the three groups was further assessed using Tukey-adjusted pairwise comparisons. Two-group comparisons were run using Wilcoxon rank-sum tests (if nonnormal) or Student *t* tests. Categorical variables were compared using chi-squared tests or Fisher's exact tests for expected cell counts <5. Pearson correlation coefficients were computed to assess linear associations between LVMI/ULN with markers of disease severity. Statistical significance was assessed at the 0.05 alpha level. Analysis was conducted using SAS 9.4 (Cary, NC).

Results

From January 2010 to December 2018, 106 patients with BA had 2DE performed (Fig. 1). Of these, 78 had their first 2DE < 1 year of age: 63 underwent KPE (19 draining, 44 nondraining), and 15 did not undergo a KPE. The bias toward nondraining KPE reflects those within this cohort specifically referred for 2DE as a component of transplant evaluation.

Females accounted for most within the entire cohort (64%); however, there was no difference in sex, race, or ethnicity among the three groups (Table 1). Within the no-KPE group, Black patients accounted for >50% of cases. For patients who underwent KPE, there was no significant difference at age of KPE between the nondraining and the draining groups (63 vs. 58 days). Of the 78 children, 62 underwent liver transplant and 2 died before transplant. In the nondraining KPE group, 43 were transplanted and 1 died before transplant. Finally, in the no-KPE group, 14 were transplanted and 1 died. Twenty-six percent of the patients with a draining KPE eventually received a liver transplant. Patients who had no KPE or nondraining KPE were transplanted much earlier than those with a

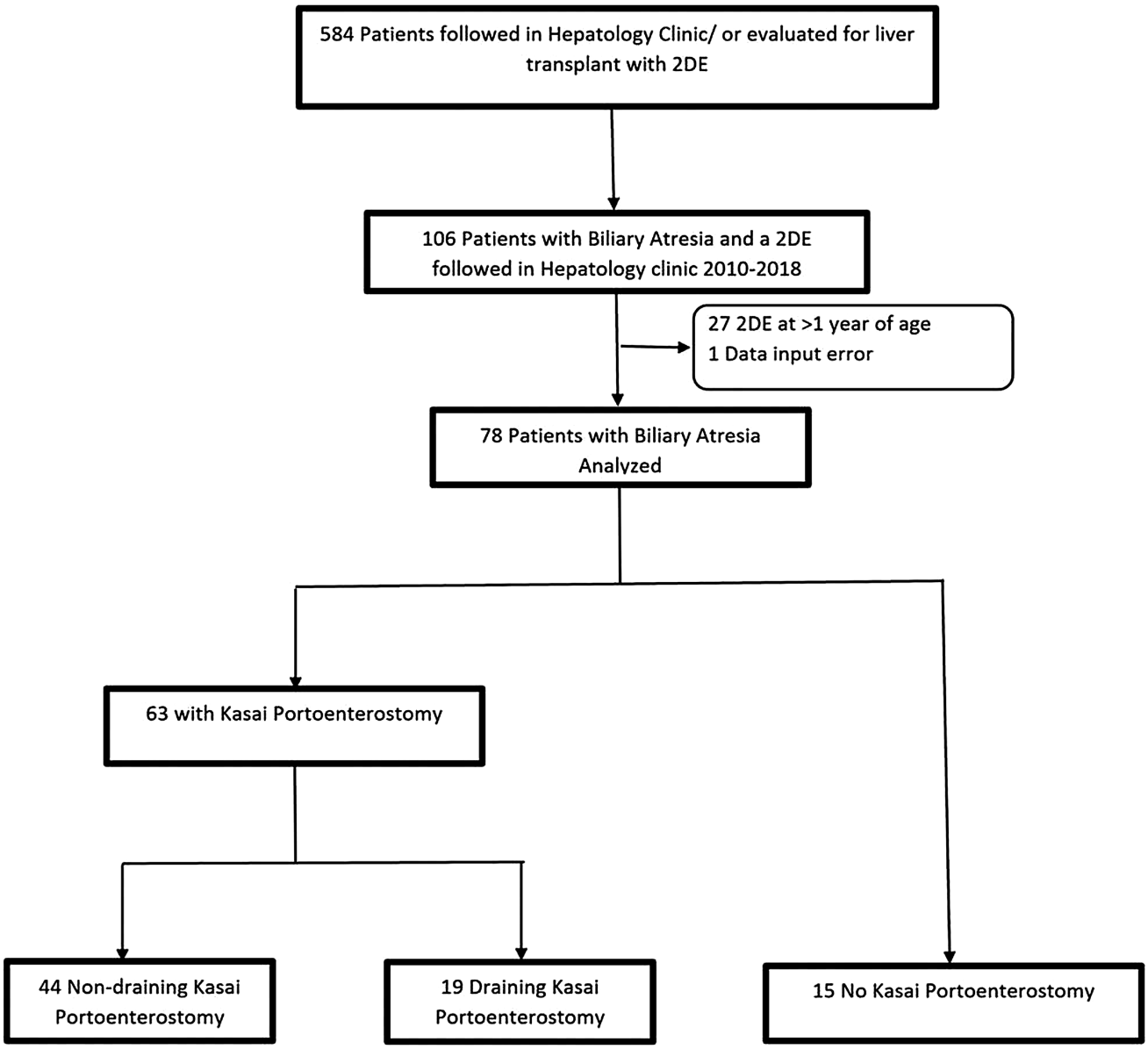

FIG. 1. Patients with BA selected for analysis. Consort diagram illustrating selection of patients with BA and a 2DE done within the first year of life during the study period January 2010 to December 2018.

draining KPE, with a median age at transplant for no KPE at 6.5 months (IQR 6, 9), nondraining KPE at 8.5 months (IQR 7, 13), and draining KPE at 23 months (IQR 21, 32).

Serum AST, ALT, DB, TB, and INR were more elevated in patients with BA with a nondraining KPE or no KPE compared to those with a draining KPE ($P < 0.05$; Table 2). PLT counts were lower in no KPE and nondraining KPE groups than in the draining KPE group ($P = 0.044$; Table 2) but were not clinically abnormal (all >150,000). Calculated Pediatric End-Stage Liver Disease (PELD) score at the time of 2DE was higher in the nondraining (15.5 [IQR 10, 19]) and no KPE (15.0 [IQR 12, 23]) groups than those who were draining (8, [IQR 2, 10]; $P < 0.001$). These results were not unexpected, reflecting the progression to end-stage liver disease in the no KPE and the nondraining KPE groups.

Median age at 2DE was 132 days, significantly different ($P = 0.001$) between the nondraining (141 days

TABLE 1. PATIENT CHARACTERISTICS AND OUTCOME ACCORDING TO SUBSEQUENT KPE STATUS

		Overall	Draining KPE	Nondraining KPE	No KPE	
Variable n (%) or median [IQR]	n	n = 78	n = 19	n = 44	n = 15	*P* Value*
Sex	78					0.128
Female		50 (64)	11(58)	26 (59)	13 (87)	
Male		28 (36)	8 (42)	11 (41)	1 (13)	
Race	78					0.071
White		35 (45)	9 (47)	22 (50)	4 (27)	
Black or African American		33 (42)	7 (37)	18 (41)	8 (53)	
Asian						
Not specified/		6 (8)	2 (11)	4 (9)	0 (0)	
Unknown		4 (5)	1 (5)	0 (0)	3 (20)	
Ethnicity	76					0.115
Hispanic or Latino		14 (18)	1 (6)	8 (19)	5 (33)	
Non-Hispanic or Latino		62 (82)	17 (94)	35 (81)	10 (67)	
Age at KPE	63	62 [46, 76]	58 [38, 74]	62 [49, 80]	—	0.445
Transplanted	78					**<0.001**
No		16 (21)	14 (74)	1 (2)	1 (7)	
Yes		62 (79)	5 (26)	43 (98)	14 (93)	
Age at transplant	62	8.5 [7, 13]	23† [21, 32]	9* [7, 13]	6.5* [6, 9]	**<0.001**
Death						
No	76	76 (97)	19 (100)	43 (98)	14 (93)	0.396
Yes	2	2 (3)	0 (0)	1 (2)	1 (7)	

Note: *P* value: ANOVA for normally distributed data or Kruskal-Wallis for nonnormally distributed data. If overall *P* value < 0.05, pairwise comparisons were computed for continuous data. Categorical data were compared using chi-squared or Fisher's exact tests.
P < 0.05 values are indicated in bold.
* Pairwise comparisons that are significantly different (*P* < 0.05).
† Pairwise comparisons that are significantly different (*P* < 0.05).

[IQR 105, 198]) and the draining (72 [IQR 40, 170]) groups (Table 3). The 15 in the no KPE group had a median age of 2DE of 129 days (IQR 88, 140), reflecting the role of 2DE as part of the evaluation for liver transplantation. On evaluation of parameters of the initial 2DE performed within the first year of life (Table 3), the only 2DE parameters significantly different between groups were LVMI and the LVMI/ULN ratio; the nondraining KPE group had a significantly greater LVMI than the draining KPE group (57.5 vs. 74.5 g/m$^{2.7}$; *P* = 0.013) as well as the LVMI/ULN ratio (0.75 vs. 0.99; *P* = 0.012) (Fig. 2). LVMI/ULN ratio ≥ 1.0 was present in 44% of subjects—more prevalent in the no KPE (60%, median age 134 days) and the nondraining KPE groups (49%, median age 141 days) compared with the draining KPE group (21%, median age 72 days; *P* = 0.05) (Supporting Fig. S1). There were no significant differences in SF and EF in the 2DE < 1 year group, although values were close to the ULN (SF 40%, EF 75%) overall. In addition, there was no detectable difference between the groups when comparing tissue Doppler parameters to assess diastolic dysfunction (Supporting Table S1).

To determine features of CCM in early life, we focused on the subset of 19 patients with BA (subsequently 11 in the draining KPE group, 8 in the nondraining KPE group) who had their 2DE performed within 7 days of KPE. There were no differences in sex, race, and body metrics (height, weight, BSA) between the groups (Supporting Table S2), nor was there a statistical difference in calculated PELD (11 vs. 10; *P* = 0.149) between the groups, suggesting that the groups were phenotypically and clinically similar. Comparison of the laboratory values at this age revealed a potential statistical difference between the nondraining and draining group serum AST levels (252 vs. 137; *P* = 0.047) and PLT counts (348 vs. 456; *P* = 0.050) (Table 4).

Evaluation of 2DE parameters performed within 7 days of KPE revealed that compared with the draining KPE group, the nondraining KPE group had significantly elevated LVMI (76.9 vs. 54.7 g/m$^{2.7}$;

TABLE 2. BIOCHEMICAL AND PELD DATA ACCORDING TO SUBSEQUENT KPE STATUS

		Overall	Draining KPE	Nondraining KPE	No KPE	
Variable, median [IQR]	n	n = 78	n = 19	n = 44	n = 15	*P* Value
AST	78	208 [129, 375]	121† [82, 208]	235* [146, 393]	277* [173, 503]	**0.001**
ALT	78	174 [94, 244]	90† [65, 160]	183* [109, 271]	202* [122, 249]	**0.002**
GGT	75	581 [293, 980]	618 [485, 1042]	518 [188, 851]	867 [501, 1,127]	0.113
DB	66	6.2 [4.1, 8.8]	3.4† [0.8, 6.2]	6.9* [5.0, 9.5]	7.6* [6.1, 11.7]	**<0.001**
TB	78	8.7 [6.1, 11.7]	5.6* [1.1, 8.2]	9.6* [6.4, 12.7]	11.3* [8.5, 15.8]	**<0.001**
Alb	78	2.8 [2.4, 3.4]	2.9 [2.5, 3.6]	2.7 [2.4, 3.4]	2.8 [2.3, 3.1]	0.663
PLT	78	313 [197, 423]	420 [279, 488]	275 [171, 374]	333 [215, 423]	**0.044**
INR	78	1.2 [1.0, 1.4]	1.0† [1.0, 1.1]	1.2* [1.1, 1.6]	1.4* [1.1, 1.9]	**<0.001**
BUN	78	7 [5, 10]	7 [5, 9]	8 [5, 11]	7 [4, 8]	0.421
Creatinine	78	0.2 [0.2, 0.2]	0.2 [0.2, 0.3]	0.2 [0.2, 0.2]	0.2 [0.2, 0.2]	0.332
PELD score	78	12 [9, 18]	8† [2, 10]	16* [10, 19]	15* [12, 23]	**<0.001**

Note: *P* value: ANOVA for normally distributed data or Kruskal-Wallis for nonnormally distributed data. If overall *P* value < 0.05, pairwise comparisons were computed for continuous data. Categorical data were compared using chi-squared or Fisher's exact tests.
P < 0.05 values are indicated in bold.
* Pairwise comparisons that are significantly different (*P* < 0.05).
† Pairwise comparisons that are significantly different (*P* < 0.05).
Abbreviation: BUN, blood urea nitrogen.

P = 0.003) and LVMI/ULN values (1.03 vs. 0.73; *P* = 0.002) (Table 5, Fig. 3). One of 11 (9%) of future draining KPE patients and 5 of 8 (63%) of future nondraining KPE patients had an LVMI/ULN ≥ 1.0 (*P* = 0.041). When stratified for future survival with native liver at 2 years of age, LVMI at the time of KPE was greater in the SNL < 2 years (74.0 [61.8, 80.0]) than in the SNL > 2 years group (54.7 [53.6, 57.5]; *P* = 0.028) (Supporting Table S3). Similar distinctions between groups were seen when measuring LVMI/ULN. EF at the time of KPE was greater in the nondraining KPE group compared with the draining KPE (72.6% vs. 64.5%; *P* = 0.047) (Table 5). Together, these findings indicate that features of CCM seen around the age of KPE correlate with both future nondraining KPE status and SNL < 2 years of age.

Pearson correlation coefficients used to compare LVMI/ULN to standard biochemical markers of liver disease revealed a negative correlation with PLT counts (−0.55 [−0.8, −0.12]; *P* = 0.012) (Supporting Table S4). There were no correlations with other biochemical markers. LVMI/ULN also showed no correlation with PELD score using this analysis (0.17 [−0.32, 0.57]; *P* = 0.50). This observation remained true when applied to the entire cohort. Finally, logistic regression models revealed LVMI as a predictor of subsequent lack of biliary drainage for every 1-unit increase (odds ratio [OR] 1.14; 95% CI 1.02-1.26; *P* = 0.019) as well as LVMI/ULN for every 0.1-unit increase (OR 2.27; 95% CI 1.11-4.63; *P* = 0.025) (Table 6). In this group, there is an OR of 16.7 (95% CI 1.36-204; *P* = 0.028) for a future nondraining KPE for those with a LVMI/ULN ratio ≥ 1.0 compared to those with an LVMI/ULN ratio < 1.0 (Table 6). Taken together, these data indicate that features of CCM are not only present in many patients with BA around the age of KPE, but that the LVMI/ULN ratio at this early age may predict future successful drainage of the KPE and transplant-free survival.

Discussion

This single-center retrospective cohort study describes 2DE features of CCM early in life in patients with BA. LVMI and the LVMI/ULN ratio in patients with a nondraining KPE was significantly greater than in those with a draining KPE in the first year of life. LV hypertrophy, as defined by LVMI > 95th percentile or LVMI/ULN ratio ≥ 1.0, was more prevalent in the no KPE (60%) and the nondraining KPE (49%) groups compared with the draining KPE group (21%). This difference was further evident when applied to early 2DE subgroup, who underwent

TABLE 3. 2DE PARAMETERS AMONG PATIENTS WITH BA ACCORDING TO SUBSEQUENT KPE STATUS

		Overall	Draining KPE	Nondraining KPE	No KPE	
Variable, median [IQR]	n	n = 78	n = 19	n = 44	n = 15	*P* Value
Age at 2DE (days)	78	133 [85, 189]	72† [40, 170]	142* [105, 198]	134* [116, 157]	**0.001**
Length (cm)	78	61 [56, 64]	57 [53, 65]	61 [58, 64]	59 [56, 64]	0.07
Weight (kg)	78	5.7 [4.7, 6.8]	4.7 [3.5, 6.5]	6.0 [4.8, 6.8]	5.8 [5.1, 7.0]	0.253
BSA (m^2)	78	0.31 [0.28, 0.35]	0.30 [0.24, 0.35]	0.33 [0.29, 0.36]	0.31 [0.30, 0.36]	0.068
SF (%)	77	39 [34, 45]	37 [33, 41]	39 [36, 43]	37 [33, 46]	0.565
EF (%)	77	71 [58, 86]	69 [64, 74]	73 [68, 76]	70 [65, 80]	0.585
IVSd	75	0.44 [0.39, 0.50]	0.40 [0.35, 0.45]	0.47 [0.41, 0.52]	0.48 [0.36, 0.52]	**0.010**
IVSd Z-score	73	–0.44 [–1.25, 0.35]	–0.75 [–1.5, –0.08]	–0.17 [–1.15, 0.55]	–0.69 [–1.8, 0.64]	0.131
LVIDd	77	2.43 [2.13, 2.64]	2.29 [1.94, 2.61]	2.49 [2.20, 2.65]	2.38 [2.02, 2.60]	0.121
LVIDd Z-score	75	0.05 [–0.76, 0.96]	–0.06 [–0.49, 0.55]	0.16 [–0.70, 1.28]	–0.35 [–1.22, 1.06]	0.468
LVIDs	76	1.45 [1.28, 1.66]	1.38 [1.23, 1.69]	1.48 [1.28, 1.63]	1.40 [1.07, 1.77]	0.705
LVIDs Z-score	44	0.64 [–0.43, 1.48]	0.46 [–0.07, 1.18]	0.82 [–0.47, 1.65]	0.60 [–1.61, 2.28]	0.863
LVPWd	77	0.41 [0.36, 0.47]	0.37 [0.29, 0.42]	0.42 [0.36, 0.47]	0.43 [0.36, 0.52]	**0.006**
LVPWd Z-score	75	–0.32 [–1.24, 0.43]	–0.70 [–2.15, 0.17]	–0.32 [–0.98, 0.35]	–0.21 [–1.14, 0.86]	0.326
LVMI ($g/m^{2.7}$)	75	71.4 [58.0, 86.1]	57.5† [53.6, 68.9]	74.5* [64.4, 86.1]	77.5* [58.7, 87.2]	**0.013**
LVMI/ULN	75	0.97 [0.78, 1.17]	0.75† [0.70, 0.91]	0.99* [0.90, 1.14]	1.10* [0.80, 1.20]	**0.012**

Note: *P* value: ANOVA for normally distributed data or Kruskal-Wallis for nonnormally distributed data. If overall *P* value < 0.05, pairwise comparisons were computed for continuous data. Categorical data were compared using chi-squared or Fisher's exact tests.
P < 0.05 values are indicated in bold.
* Pairwise comparisons that are significantly different (*P* < 0.05).
† Pairwise comparisons that are significantly different (*P* < 0.05).

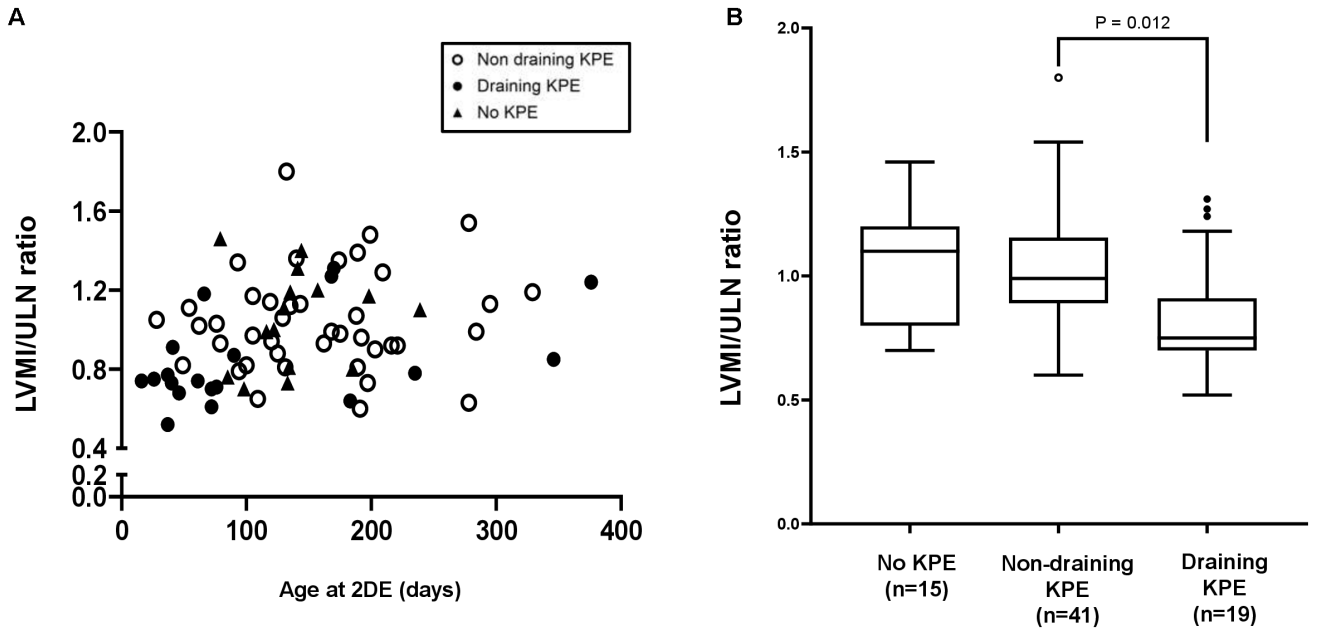

FIG. 2. (A) Age at 2DE performed within the first year of life in patients with BA (*P* = 0.001). (B) LVMI/ULN ratio in patients with BA is significantly higher in patients with a nondraining KPE compared to those with a draining KPE. There is no statistical difference between nondraining KPE and no KPE.

TABLE 4. BIOCHEMICAL AND PELD DATA FOR EARLY 2DE SUBGROUP ACCORDING TO SUBSEQUENT KPE STATUS

		Overall	Draining KPE	Nondraining KPE	
Variable, median [IQR]	n	n = 19	n = 11	n = 8	*P* Value
AST	19	177 [124, 288]	137 [111, 240]	252 [174, 406]	**0.047**
ALT	19	160 [90, 207]	105 [67, 194]	183 [167, 314]	0.177
GGT	18	626 [476, 996]	661 [476, 1,308]	591 [366, 996]	0.558
DB	18	5.3 [3.6, 6.8]	5.5 [3.6, 6.6]	5.3 [4.1, 6.8]	0.933
TB	19	7.6 [6.1, 8.8]	7.6 [5.6, 8.7]	7.5 [6.2, 9.0]	0.461
Alb	19	3.3 [2.8, 3.6]	2.9 [2.8, 3.6]	3.4 [2.8, 3.5]	0.710
PLT	19	444 [346, 516]	456 [441, 593]	348 [304, 443]	**0.050**
INR	19	1.0 [1.0, 1.2]	1.0 [0.9, 1.1]	1.2 [1.0, 1.3]	0.054
BUN	19	6 [5, 9]	5 [4, 9]	7 [5, 11]	0.333
Creatinine	19	0.2 [0.2, 0.3]	0.2 [0.2, 0.3]	0.2 [0.2, 0.3]	1.000
PELD score	19	10 [8, 12]	10 [8, 10]	11 [9, 18]	0.149

Note: *P* value: Student *t* tests for normally distributed data or Wilcoxon rank-sum tests for nonnormally distributed data. Categorical data were compared using chi-squared or Fisher's exact tests.
P < 0.05 values are indicated in bold.
Abbreviation: BUN, blood urea nitrogen.

TABLE 5. 2DE PARAMETERS FOR EARLY 2DE SUBGROUP ACCORDING TO SUBSEQUENT KPE STATUS

		Overall	Draining KPE	Nondraining KPE	
Variable, median [IQR]	n	n = 19	n = 11	n = 8	*P* Value
Age at 2DE (days)	19	61 [37, 76]	46 [37, 72]	69 [52, 90]	0.090
Length (cm)	19	56 [53, 58]	56 [53, 60]	56 [53, 57]	0.505
Weight (kg)	19	4.7 [3.7, 5.4]	4.4 [3.3, 5.4]	4.7 [4.4, 5.1]	0.603
BSA (m^2)	19	0.28 [0.24, 0.30]	0.27 [0.22, 0.30]	0.28 [0.24, 0.29]	0.752
SF (%)	19	37 [33, 39]	34 [32, 37]	39 [38, 40]	0.056
EF (%)	19	69 [64, 73]	65 [63, 70]	73 [70, 73]	**0.047**
IVSd	19	0.39 [0.35, 0.44]	0.35 [0.33, 0.42]	0.41 [0.39, 0.46]	0.194
IVSd Z-score	17	–0.67 [–1.37, 0.12]	–0.75 [–1.50, –0.39]	–0.40 [–1.25, 0.08]	0.407
LVIDd	19	2.16 [1.95, 2.42]	2.05 [1.92, 2.42]	2.18 [2.11, 2.42]	0.659
LVIDd Z-score	17	–0.13 [–0.70, 0.68]	–0.13 [–0.69, 0.05]	0.04 [–0.84, 1.49]	0.321
LVIDs	19	1.31 [1.23, 1.47]	1.31 [1.23, 1.47]	1.32 [1.23, 1.52]	1.000
LVIDs Z-score	12	0.53 [–0.09, 1.40]	0.53 [0, 1.08]	0.80 [–0.43, 1.75]	0.790
LVPWd	19	0.37 [0.31, 0.41]	0.35 [0.28, 0.40]	0.40 [0.34, 0.43]	0.092
LVPWd Z-score	17	–0.60 [–1.63, 0.18]	–0.92 [–2.15, –0.59]	–0.45 [–1.12, 0.25]	0.405
LVMI ($g/m^{2.7}$)	19	58.0 [54.5, 77.2]	54.7 [53.4, 57.5]	76.9 [67.6, 83.4]	**0.003**
LVMI/ULN	19	0.78 [0.71, 1.03]	0.73 [0.68, 0.75]	1.03 [0.88, 1.08]	**0.002**

Note: *P* value: Student *t* tests for normally distributed data or Wilcoxon rank-sum tests for nonnormally distributed data. Categorical data were compared using chi-squared or Fisher's exact tests.
P < 0.05 values are indicated in bold.

2DE within 7 days of KPE. Focusing on this subset of patients with 2DE performed in the peri-KPE period, we demonstrated that elevated LVMI can be seen earlier than expected in patients with BA, and if present, is a predictor of poor outcomes following KPE. Taken together, it appears that in an infant with a profoundly cholestatic and cirrhotic disease like BA, there is not only a great risk of significant alterations in cardiac structure and function early in life, but that these early features of CCM may correlate with future reductions in SNL.

Elevation of LVMI is a predictor of perioperative mortality, postoperative adverse events, and organ dysfunction in children with BA awaiting liver

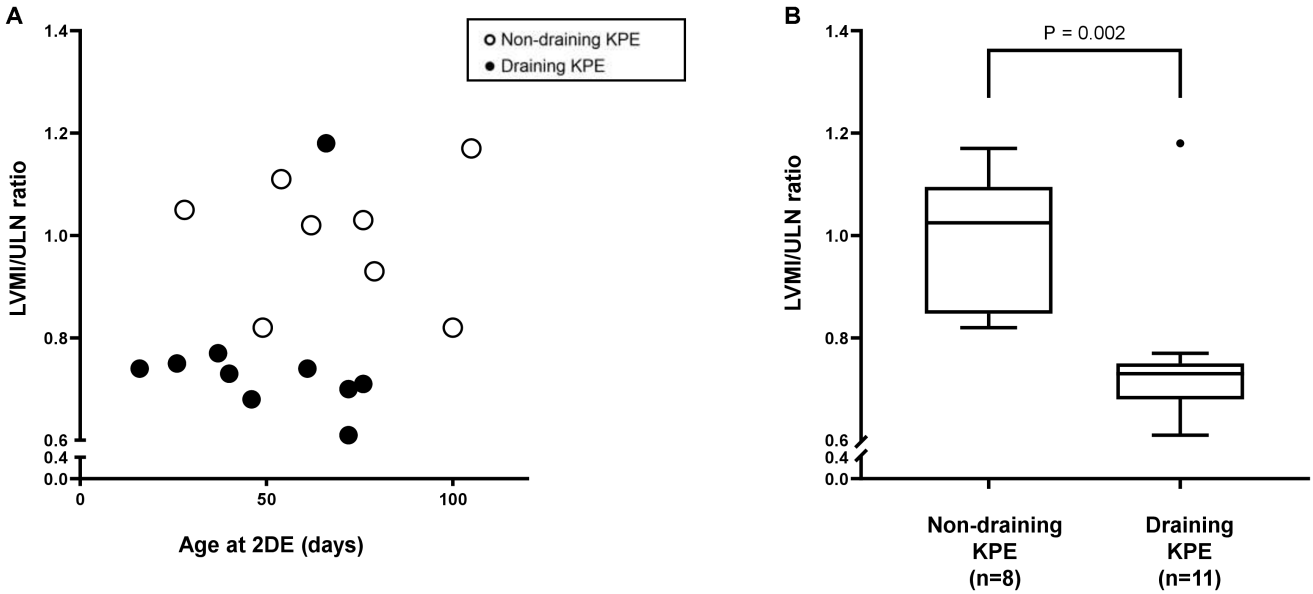

FIG. 3. The difference in LVMI/ULN ratio between draining and nondraining KPE in the early 2DE subgroup remains statistically significant when there is no difference in age at 2DE. (A) Age at 2DE in the early 2DE subgroup ($P = 0.09$). (B) The LVMI/ULN ratio remains significantly different between nondraining and draining KPE in the early 2DE subgroup ($P = 0.002$).

transplantation.[10,11,17,20] These studies have looked at the LVMI in the pretransplant 2DE and identified elevated LVMI as a component of end-stage liver disease in the pediatric population. In an older group of patients, Gorgis et al. defined LVMI ≥ 95 g/m$^{2.7}$ in patients with BA with end-stage liver disease. Similar to these studies, LVMI remained a strong component in the diagnosis of CCM in our study, which focused on the peri-KPE 2DE findings.

Our analyses suggest that CCM is present early in BA, and the factors that initiate and propagate this feature are likely multifactorial, currently not fully understood, and thus ripe for a multidisciplinary approach to discover etiologic contributors. Among the potential considerations include a cardiac response to an in-utero process or an enhanced postnatal myocardial response to mediators of cholestasis and inflammation. The natural history of LVMI is to decrease with increasing age up to 9 years.[22] Therefore, an LVMI increasing with age in patients with cholestatic BA suggests that there is an early cardiac response to liver disease reflected in structural remodeling already present at diagnosis of BA. Elevated circulating bile acids, perhaps by engaging bile acid receptors farnesoid X receptor and TGR5 have been implicated in cardiac dysfunction

TABLE 6. EARLY 2DE SUBGROUP LVMI AND LVMI/ULN AS PREDICTOR OF SUBSEQUENT NONDRAINING KPE

Variable	OR	95% CI	*P* Value
LVMI (g/m$^{2.7}$)*	1.14	1.02-1.26	0.019
LVMI/ULN†	2.27	1.11-4.63	0.025
LVMI/ULN ≥ 1.0	16.7	1.36-204	0.028

* Per 1.0-unt increase.
† Per 0.1-unit increase.

in preclinical models of cirrhosis and CCM.[25-27] Nitric oxide, endogenous opioids, and endocannabinoids are other factors that may play a role in the cardiovascular abnormalities observed in infants with cholestasis. Together these may cause vasodilation and blunt cardiovascular responses to sympathetic stimulation.[28] This combinatorial scenario is further supported by the observation of the concomitant resolution of cardiomyopathy with reductions of liver injury and cholestasis.[25] Although there are associative and preclinical studies that support contributions from circulating bile acids and a host of signaling molecules in the development of CCM, future studies are needed to determine whether elevated circulating bile acid concentrations or specific

cytokines/chemokines or other circulating mediators in life in infants with BA correlate with early features of CCM.

Although there is no consensus on the cardiomyocyte proliferative capability after birth, there is evidence to suggest that children and adolescents have the mechanistic underpinnings for enhanced cardiomyocyte proliferation, and that abnormal cardiomyocyte proliferation may play a role in the myocardial response to diseases in this age group.[29] Factors noted in chronic disease states such as hemodynamic stress and chronic inflammation, which can be seen in infants with BA, contribute to the development of pathological cardiac hypertrophy.[30,31] Cardiomyocytes respond to a variety of pathologic stimuli by releasing inflammatory cytokines, chemokines, and damage-associated molecular patterns, further adding to the inflammatory response.[30-32] This immune response may then incite pro-hypertrophic and profibrotic pathways, which induces cardiac hypertrophy and remodeling.[32] In addition, neurohormonal stimulation from increased circulating catecholamines and angiotensin II leads to modulation of cellular responses including gene expression, protein synthesis, sarcomere assembly, and cell metabolism. Thus, there is a complex response that leads to maladaptive cardiac changes characterized by cardiac hypertrophy.

We believe that the most significant discovery made with this study is the realization that structural cardiac changes are evident in many infants with BA at the time of KPE, namely, elevated LVMI and LVMI/ULN, and this may affect the outcome of KPE and the predicted trajectory of their clinical course. Elevated LVMI and LVMI/ULN were present early in the lives of infants with BA, and with logistical regression analysis we were able to demonstrate that for every 1-unit increase in LVMI and 0.1-unit increase in LVM/ULN, there was an increased OR of a nondraining KPE. This is likely important, as it contributes to the understanding of the evolution of CCM in patients with BA. If validated by a multicenter prospective study, then 2DE at diagnosis of BA should be encouraged, as it may have an onset early in the course of the disease and affect its outcomes. Moreover, such findings would then lead to explorations of revised clinical algorithms as well as a host of translational research of the extrahepatic ramifications of BA earlier in life, including potential molecular, cellular, and vascular understandings of the development of CCM.

This study also explored SF and EF to denote systolic function. There was no statistical difference in SF; however, EF was higher in the nondraining KPE group than in the draining KPE group on 2DE done within 7 days of KPE. Elevated EF is associated with the hyperdynamic state described in CCM. Overall, the median SF and EF were at the upper limits of normal for all groups, although no statistically significant difference was attained. This is in keeping with the LV EF observed at rest in patients with CCM.[33,34] Desai et al. also observed this increase in SF and included it in their proposed diagnostic criteria in patients with BA and CCM. These findings provide insight into the possible development of a structural component in early BA disease followed by a functional component emerging in late BA disease.

In younger infants with BA, there was no demonstrable correlation of LVMI with ALT, GGT, TB, ALB, and INR. There was also no statistically significant difference in these laboratory parameters between the nondraining KPE and draining KPE groups in the cohort of 2DE within 7 days of KPE. PLT count, although not pathologically abnormal, and AST were significantly different between the early 2DE nondraining KPE group compared with the draining KPE group. PLT also had a negative correlation with LVMI/ULN; a lower PLT count was associated with a higher LVMI/ULN ratio. PLT were the only laboratory parameter that correlated with the LVMI/ULN ratio. Taking into consideration the role of PLT in the AST-to-PLT ratio index and the profound liver fibrosis in children with BA, these findings may corroborate LVMI/ULN as a sensitive marker of disease severity at the time of KPE.[35-37]

Before KPE or at the time of KPE, there are few parameters with strong evidence to predict outcome. Age is one such factor, if not the strongest predictor of outcome.[38] Fanna et al. showed an increased survival with native liver when KPE was performed at a younger age. With no difference in age in the early 2DE cohort, LVMI remains a potential predictor of outcome post KPE. Thus, if age at KPE is a primary driver of outcome, but is not a perfect marker, perhaps exploring the consequences of underlying disease severity, such as an elevated LVMI, may be of great help in modeling BA outcomes. These findings are intriguing and clearly indicate that a prospective study

is needed to evaluate 2DE parameters at diagnosis and at discrete intervals throughout the disease process to describe the progression of CCM in patients with BA.

This study is not without limitations, not the least of which is the single-center nature of this study. 2DE is not yet a standard practice to perform at diagnosis of BA, and only 19 of the 78 who underwent 2DE during the first year of life underwent 2DE at the time of KPE. Many of the other patients in the study underwent KPE elsewhere and underwent 2DE as a component of the transplant evaluation process. This study, in addition to limited explorations of systolic and diastolic dysfunction, was also limited to left-sided dysfunction, and could not investigate potential effects of liver disease on right-sided cardiac function. Despite these limitations, the study found a substantial proportion of infants undergoing evaluation for liver transplant, or more importantly at the time of KPE, had features of CCM that correlated with future outcomes.

Moreover, these single-center findings are not intended to inform the decision for KPE based on 2DE parameters—rather that there was an unanticipated elevated LVMI early in the lives of patients with BA, often present at the age when BA was diagnosed. If elevated, the LVMI/ULN ratio at the age of KPE, an extrahepatic feature, correlated with and may contribute to, future outcomes.

This study describes echocardiographic parameters in the first year of life in patients with BA, with a focus on 2DE at the age of KPE. Patients with BA with a nondraining KPE are significantly more likely to have an elevated LVMI and LVMI/ULN ratio, which indicates that the developing heart of patients with cholestatic BA elaborates features of CCM. An elevated LVMI and LVMI/ULN ratio at the time of KPE appears to be a predictor of poor outcome following KPE. These findings strongly suggest a need for confirmation and evaluation with a well-designed multicenter prospective study, to determine whether early incorporation of 2DE may play a role in pathogenesis and clinical decision making for infant patients with BA.

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