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Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis

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Abstract

To evaluate the efficacy of non-transplant surgery for pediatric cholestasis, 58 clinically diagnosed children, including 20 Alagille syndrome (ALGS), 16 Familial Intrahepatic Cholestasis-1 (FIC1), 18 Bile Salt Export Pump (BSEP) disease, & 4 others with low γ -glutamyl transpeptidase disease (levels <100 U/L), were identified across 14 Childhood Liver Disease Research Network (ChiLDReN) centers. Data were collected retrospectively from individuals who collectively had 39 partial external biliary diversions (PEBD), 11 ileal exclusions (IE) and 7 gallbladder-to-colon

diversion (GBC). Serum total bilirubin decreased after PEBD in FIC1 (8.1 ± 4.0 vs. 2.9 ± 4.1 mg/dL, preop vs. 12–24 months postop respectively, $p=0.02$) but not in ALGS or BSEP. Total serum cholesterol decreased after PEBD in ALGS patients (695 ± 465 vs. 457 ± 319 mg/dL; preop vs. 12–24 months postop respectively; $p=0.0001$). Alanine aminotransferase levels increased in ALGS after PEBD (182 ± 70 vs. 260 ± 73 IU/L, preop vs. 24 mos. $p=0.03$) but not in FIC1 or BSEP. ALGS, FIC1, and BSEP patients experienced less severely scored pruritus after PEBD (ALGS: 100% vs. 9% severe, FIC1: 64% vs. 10%; BSEP: 50% vs. 20%, preop vs. >24 mos. postop respectively, $p<0.001$). ALGS patients experienced a trend toward greater freedom from xanthomata after PEBD. There was a trend toward decreased pruritus in FIC1 after IE and GBC. Vitamin K supplementation increased in ALGS after PEBD (33% vs. 77%, $p=0.03$). Overall, there were 15 major complications after surgery. 12 patients (3 ALGS, 3 FIC1, 6 BSEP) subsequently underwent liver transplantation.

Conclusion—This is the first multi-center analysis of non-transplant surgical approaches to intrahepatic cholestasis. Approaches vary, are well tolerated, and generally although not uniformly result in improvement of pruritus and cholestasis.

Keywords

Alagille; familial intrahepatic cholestasis; bile salt export pump; biliary diversion; enterohepatic circulation

Introduction

Surgical interruption of the enterohepatic circulation using partial external biliary diversion (PEBD) has been a mainstay of treatment for cholestatic syndromes, including Alagille Syndrome (ALGS) and Progressive Familial Intrahepatic Cholestasis (PFIC) disease for more than two decades. ALGS is an autosomal dominant disorder characterized by multi-organ involvement including significant cholestasis. Histologically, a paucity of bile ducts and diminutive portal tracts are seen in the liver. Even though bile synthesis by individual hepatocytes is not impaired, diminished access to draining bile ducts may cause reflux of bile into plasma (1). The physiologic consequence is canalicular and intracellular cholestasis with slow progression to irreversible liver damage in up to 20% of ALGS patients (2). The PFIC syndromes are a group of autosomal recessive inherited disorders of impaired biliary transport and excretion. In most affected patients, symptoms of cholestasis begin in infancy and can eventually progress to cirrhosis and hepatic failure during the first decade of life (3–5). A subset of PFIC patients have characteristically low serum GGTP levels (<100 U/L), as a result of defects in either the gene *ATP8B1*, known previously as PFIC1 but now as Familial Intrahepatic Cholestasis-1 (FIC1), the gene *ABCB11*, known previously as PFIC2 but now more descriptively as Bile Salt Export Pump (BSEP) disease, or other as yet unidentified genes (6, 7).

While biliary diversion was described as a treatment for nonobstructive cholestatic liver disease as early as the 1930's, Whittington *et al.* was the first to describe its use in the treatment of children with intractable pruritus from cholestasis by utilizing a jejunal conduit to externally drain the gallbladder (Figure 1 A) (8–11). Since then, numerous studies have demonstrated the short-term efficacy of PEBD at improving pruritus and laboratory

parameters in patients with PFIC (12, 13). PEBD has been demonstrated to improve histology and fibrosis in PFIC (13, 14). Patients with ALGS have been noted to have improvement in pruritus, xanthomata, serum bile acids, and serum cholesterol with PEBD (2, 15).

Numerous other non-transplant surgical procedures have since been described, all aimed at interrupting the enterohepatic circulation with the potential for alteration in the bile acid pool. Chief among these alternative procedures are an ileal exclusion (IE) (Figure 1B), which internally bypasses ~ 15% of the terminal ileum (16, 17), and an internal biliary diversion, which entails connecting the gallbladder either directly to the colon or utilizing a segment of jejunum as a conduit (GBC) (Figure 1C) (18–20). Each operation provides a variable degree of symptom relief. Side effects of internal diversion include choleretic diarrhea, caused by a large amount of bile salt entering the colon directly, and malabsorption. Given the systemic manifestations that occur in FIC1 disease and persist after transplantation, PEBD is a preferred treatment in this condition (17, 21, 22). Unfortunately, particularly in BSEP disease, this surgery does not completely reverse the course of the disease, and many children still progress to liver transplantation (23). Additionally, PEBD, performed for BSEP disease, has not been protective against development of hepatocellular carcinoma, cholangiocarcinoma, or pancreatic adenocarcinoma (24–26).

Although numerous, most studies reporting outcomes of PEBD, internal biliary diversion, and ileal exclusion involve a single center with some reporting the outcomes of only a single surgeon. Furthermore, the ability to analyze outcomes as a function of specific genetic diagnosis has only recently become available. A cross-sectional analysis of the different procedures across a wide range of centers is lacking. No trials to date have performed a head-to-head comparison to evaluate the outcomes of the various surgical techniques (27). Herein, we report a multi-center retrospective analysis of outcomes of non-transplant surgery in PFIC and ALGS.

Methods

The Childhood Liver Disease Research Network (ChiLDReN) is a National Institute of Diabetes, Digestive, and Kidney Diseases/National Institute of Health-funded research consortium of 15 North American pediatric centers with the goal of understanding the etiology, pathogenesis, course, and outcomes of several pediatric cholestatic conditions. Amongst 14 ChiLDReN centers, 58 children were identified with the clinicopathologic diagnoses of ALGS, FIC1, BSEP disease or indeterminate low GGTP intrahepatic cholestasis (GGTP < 100), who underwent non-transplant surgical intervention for cholestasis between 2005 and 2013. Institutional Review Board approval was obtained at each participating hospital. Diagnostic criteria were according to local standards at the ChiLDReN clinical center and may not have included genotyping, which was not readily available for most patients. Data were retrospectively collected at these centers into a central database, using REDCap administered at the University of Southern California (PI: KSW). Demographic and clinical data were collected including medications, laboratories, and symptoms during four time periods (–6 to 0 months preoperatively, 6 to 12 months

postoperatively, 12 to 24 months postoperatively, and greater than 24 months postoperatively). Given the retrospective nature of the data collection, pruritus grading was simplified from a scoring system described by Emerick and Whittington (2), where reported and recorded, as either as absent, mild to moderate (not impairing sleep and school work), or severe (mutilating, impairing sleep and school work). Xanthomata were graded as present or absent. Longitudinal laboratory data were log-transformed as needed to normalize distributions and analyzed with repeated measures mixed models. Categorical longitudinal data were analyzed using Generalized Estimating Equations or Wilcoxon signed rank test for comparing pre- to mean of post-operative values. Statistical tests were performed using SAS/STAT® software version 9.2, at a 2-sided 0.05 significance level.

Results

58 patients who underwent surgical intervention for cholestasis were identified. This included 20 patients clinically diagnosed with ALGS, 16 with FIC1, 18 with BSEP, and 4 others with GGTP levels <100 U/L.

Preoperative demographics and clinical manifestations

Of the 20 ALGS patients, 11 (55%) were male (Supplemental Table 1). The majority of ALGS patients were white (60%) and non-Hispanic (85%). ALGS patients underwent surgery at a median age of 30 months (Q1/Q3 = 26/86 months, range = 2 to 218 months, mean = 65 months). In terms of clinical features of ALGS, histologic bile duct paucity was noted in 16 (80%), clinical evidence of cholestasis in 19 (95%), cardiac defects in 16 (80%), skeletal abnormalities in 6 (30%), and characteristic facial features in 18 (90%). Preoperative complications of ALGS included patients with rickets (3 patients, one of whom had a fracture), ascites (1 patient), and failure to thrive requiring either enteral or parenteral nutritional supplementation (4 patients) (Supplemental Table 2). Indications for surgical diversion included severe pruritus (100%), xanthomata (50%) and progression of liver disease (25%). Information regarding mutations in *JAGGED1* was available in the charts of 7 patients (35%). In addition to bile duct paucity, preoperative histologic findings included giant cell transformation in 6 (30%). Ishak fibrosis scores were available in 15 patients (75%) with a mean of 1.9 ± 1.7 .

Of the 38 PFIC patients (16 FIC1, 18 BSEP, 4 other with GGTP < 100), 14 (38%) were male (Table 1). 75% of PFIC patients were white and 85% were non-Hispanic. PFIC patients underwent surgery at a median age of 18 months (Q1/Q3 = 11/28 months, range = 6 to 228 months, mean = 28 months). Preoperative complications of the 16 FIC1, 18 BSEP, and 4 patients with GGTP < 100 are listed in Supplemental Table 1. Amongst the 38 PFIC patients, indications for surgical diversion included pruritus (92%) and progression of liver disease (59%). Information regarding ATP8B1 mutations was noted in the charts of 8 FIC1 patients (50%) and ABCB11 mutations were noted in the charts of 11 BSEP patients (61%) (Supplemental Table 3). No data regarding mutations were available in the 4 other patients with GGTP < 100 who were not classified as ALGS, FIC1 or BSEP.

Surgical intervention and complications

Of the 58 patients, 40 (15 ALGS, 13 FIC1, 11 BSEP, 1 GGTP < 100) underwent partial external biliary diversion (PEBD), 11 (5 ALGS, 1 FIC1, 2 BSEP, 3 GGTP < 100) underwent an internal ileal exclusion (IE) and 7 (1 ALGS, 3 FIC1, 3 BSEP, 0 GGTP < 100) underwent internal biliary diversion from gallbladder to colon (GBC).

Of the 20 ALGS patients in the study, 15 underwent PEBD. Fourteen patients underwent continuous gallbladder drainage to an external stoma via a conduit of jejunum outside of gastrointestinal continuity. In one patient, the appendix was used as conduit for external drainage. Five ALGS patients underwent internal bypass. Specifically, four underwent IE, with bypass 15% of the jejunal/ileal length from the ileocecal valve with anastomosis of proximal ileum to the right colon. One patient underwent partial internal biliary diversion via GBC.

Of the 37 PFIC patients, 25 underwent PEBD. Two of these patients underwent creation of cholecystocutaneous fistulae, which were intubated with Mic-Key® gastrostomy devices (Halyard Health, Alpharetta, GA) for intermittent drainage; all others had continuous drainage via jejunal conduits. Five patients underwent 15% IE. One underwent 40% IE. Six patients underwent GBC.

Amongst the 40 PEBD, complications included 1 patient with intestinal ischemia, 3 with stoma prolapses, and 1 with bowel obstruction and 4 episodes of dehydration/electrolyte derangements (Supplemental Table 4). Amongst the 11 IE, there were 2 patients with dehydration/electrolyte derangements. Amongst the 7 GBC, there was 1 patient with intestinal ischemia, 1 with anastomotic intussusception, and 2 patients had dehydration/electrolyte derangements.

Postoperative outcomes

Serum laboratory data were analyzed across the various cholestatic diseases in this study after PEBD and IE (Table 1). Following PEBD, neither ALGS nor BSEP patients experienced a significant decrease in serum total bilirubin (ALGS: 0 = 5.3 ± 5.4 , 24 mos. = 4.9 ± 4.1 mg/dL, Figure 1; BSEP: 0 = 2.7 ± 2.9 , 24 mos. = 2.1 ± 2.5 mg/dL). In contrast, FIC1 patients undergoing PEBD experienced a significant decrease in serum total bilirubin (0 = 8.1 ± 4.0 , 24 mos. = 2.9 ± 4.1 mg/dL, $p=0.0004$, Figure 1). Total serum cholesterol decreased in ALGS patients undergoing PEBD (0 = 695 ± 465 , 12m = 365 ± 152 , 24 mos. = 457 ± 319 mg/dL, $p=0.02$). Alanine aminotransferase levels increased in ALGS patients after PEBD (0 = 182 ± 70 , 24 mos. = 260 ± 73 IU/L, $p=0.03$) but not significantly different in FIC1 (0 = 113 ± 134 , 24m = 56 ± 32) or BSEP patients (0 = 123 ± 112 , 24 mos. = 99 ± 83). In our cohort of patients, total serum bile acid measurements were not commonly performed. There were, however, non-significant trends toward a reduction in total serum bile acid levels in both FIC1 and BSEP patients following PEBD (FIC1: 163 $\pm$ 68, 12 mos. = 21 $\pm$ 12, >24 mos. = 46 $\pm$ 76 micromole/dL and BSEP: 0 = 355 $\pm$ 158, 12 mos. = 191 $\pm$ 154, 24 mos. = 203 $\pm$ 75, >24 mos. = 182 $\pm$ 62 micromole/dL). Notably in three FIC1 patients for whom serum total bile acids were measured pre- and postoperatively, there were dramatic reductions in serum total bile acids in FIC1 patients following PEBD (0 = 196 $\pm$ 59, 12 mos.

= 19 ± 11 , 24 mos. = 7 ± 2 micromole/dL). All three reported complete resolution of severe pruritus. In two ALGS patients with measurements before and after PEBD, there were dramatic reductions in serum total bile acids (Patient A: 0 = 277, 12 mos. = 108 micromole/dL; Patient B: 0 = 254, 12 mos. = 60 micromole/dL); both likewise had complete resolution of severe pruritus. In contrast, the two BSEP patients with decreased postoperative serum total bile acid measurements compared to preoperative levels did not experience any improvement in pruritus. No differences in total bilirubin, alanine aminotransferase levels were detected over 24 months postoperatively in FIC1, BSEP, ALGS, and GGTP < 100 patients undergoing IE (Table 2).

The degree of postoperative pruritus was collected where available. When analyzed in aggregate, the fraction of ALGS, FIC1 and BSEP patients with reported mild-moderate or severe pruritus after PEBD decreased compared to preop (ALGS: 0 = 100% with severe pruritus, >24 mos. = 9%; FIC1: 0 = 64% vs. >24 mos. = 10%; BSEP: 0 = 50% vs. >24 mos. = 20%, $p < 0.0001$ for all diagnoses, Figure 2). A trend toward greater freedom from xanthomata was also observed postoperatively in ALGS patients (0 = 50%, >24 mos. = 75%, $p = 0.125$). Prior to IE, 5 out of 5 ALGS patients experienced severe pruritus. At 6–12 mos., 2 out of 5 still experienced severe pruritus; none reported severe pruritus at 12–24 mos., suggesting some benefit surgically. None of the 5 ALGS undergoing IE experienced resolution of xanthomata postoperatively through 24 months.

In terms of medication usage (yes versus no) in patients with ALGS after PEBD, there were no significant changes in reported medication usage but there were trends toward decreases in the use of cholestyramine (47% preoperatively vs 14% >24 mos. postoperatively, $p = 0.09$) and rifampin (60% preoperatively vs 36% >24 mos. postoperatively, $p = 0.125$). There was no reported change in the use of ursodeoxycholic acid, opioid antagonists, Vitamin E, combination fat-soluble vitamins, or diuretics. There was a reported increase in usage of Vitamin K (33% preoperatively vs. 77% >24 mos. postoperatively, $p = 0.03$) and a trend toward an increase in usage of Vitamin D (53% preoperatively vs. 92%, >24 mos. postop, $p = 0.125$).

Eleven patients (5 ALGS, 1 FIC1, 2 BSEP, & 3 GGTP < 100) underwent IE. Five out of 5 ALGS patients had severe pruritus prior to IE and 1 out of 4 still had it at 12 months postoperatively; no change was observed in xanthomata (5/5 at both 0 mos. and 12 mos.). No clear trend in terms of severe pruritus was seen in FIC1/BSEP patients (0=3/5, 12 mos.=1/3, 24 mos.=1/2). Two patients with GGTP < 100 who had undergone IE subsequently underwent revision to PEBD due to persistent severe pruritus. Both had improvement of symptoms post-revision.

Seven patients (1 ALGS, 3 FIC1, 3 BSEP, 0 GGTP<100) underwent GBC diversion with evidence of reduced post-GBC pruritus (0=7/7, 12 mos.=0/6, 24 mos.=3/6).

There was one death reported within the network. Twelve patients underwent liver transplantation after surgical interruption of the enterohepatic circulation. Three out of 20 ALGS patients (2/15 following PEBD, 1/4 IE, 0/1 GBC) underwent transplant. Three out of 16 FIC1 (2/12 following PEBD, 1/2 IE, 0/2 GBC) underwent transplant. Six out of 18 BSEP

(3/13 s/p PEBD, 3/3 s/p IE, 0/2 s/p GBC) underwent transplant. There was no appreciable difference in the frequency of liver transplantation amongst ALGS, FIC1, and BSEP patients following non-transplant surgery.

Discussion

The indications for and outcomes of non-transplant surgical interventions for intrahepatic cholestasis are not well delineated. Most of the published literature is single-centered and subject to potential bias toward positive results (2, 5, 8, 9, 15, 16, 18–20, 27, 28). The current study was designed to be cross-sectional, multi-centered, and unbiased toward outcomes with an intent to give a real world view of this complicated area of surgical therapy. In this study, we analyzed retrospectively collected data on patients with ALGS or PFIC who underwent PEBD, IE, or GBC procedures for relief of pruritus and xanthomata at 14 centers with expertise in this area. Not surprisingly, there was considerable variability in the surgical approaches undertaken at the 14 centers. PEBD remains the most commonly used approach. A significant reduction in serum total bilirubin was observed following PEBD in FIC1 patients but not in ALGS or BSEP patients. Serum total cholesterol decreased in ALGS patients after PEBD. Symptomatically, ALGS, FIC1, and BSEP patients experienced less pruritus after PEBD. ALGS patients exhibited a trend toward reduced xanthomata burden as well. A reduction in the use of anti-pruritus medications was observed in ALGS after PEBD, consistent with improved symptomatology. There were insufficient numbers of patients undergoing IE or GBC procedures to draw any significant conclusions; however, there were trends towards improvements in symptomatology following each of these procedures as well. These results were consistent with but perhaps not as dramatic as the existing published literature. Incomplete and transient responses were reported in many cases.

There are a variety of complex unresolved issues that face clinicians considering the use of non-transplant surgery for the treatment of intrahepatic cholestasis. There are a number of surgical options available, and it is unclear if they are all equivalent in both the expected outcome and the potential risks associated with the procedures. PEBD is the classic approach and has the longest track record. It can be associated with excellent outcomes and appears to be relatively safe. The fraction of bile that is diverted to the ostomy is variable and not easily controlled. Excessive diversion can be associated with fluid and electrolyte issues along with nutritional problems related to decreased luminal bile acids. The increased use of vitamin K after PEBD in ALGS may reflect this issue. Inadequate diversion will likely be ineffective. Given low patient satisfaction with a permanent ostomy, alternative approaches have been developed including ileal exclusion and “internal” diversion to the colon. The relative efficacy of all these approaches remains uncertain and the current investigation was not adequately powered to provide a definitive answer. IE can be complicated by the potential for diarrhea due to uncertainty in determining the appropriate amount of ileum to be excluded. “Internal” diversion can also be complicated by diarrhea. Both alternatives have the potential of long-term cancer risk associated with bile flowing directly into the colon (29).

Differences in response to surgery in PFIC relative to ALGS in this study support the notion that disease specific responses exist. Likely, not all cholestasis is the same. In fact, there may be genotypic differences in response as more severe defects (nonsense and deletions) in *ABCB11* are less likely to respond to surgery compared to less severe missense mutations (30). One might hypothesize that the response to surgery relates to specific interruption of the enterohepatic circulation of bile acids. This hypothesis is currently being tested in on-going studies of a pharmacologic inhibitor of intestinal reabsorption of bile acids (e.g. NCT 01903460, 02057718, 02057692, 02160782). A significant amount of the published literature on non-transplant surgery predated the identification of the molecular basis of different forms of cholestasis and the routine use of relevant genotyping. In this analysis, genotyping was not readily available for most patients. In many instances, genotyping was likely not covered by insurance and, therefore, was not performed. Thus, a clear analysis of genotype and response to surgery was not possible. Assessing indications for and outcomes of surgery becomes remarkably complicated when one subdivides on the basis of 1) type of surgery, 2) genetic defect, 3) severity of the genetic defect, and 4) stage of disease at the time of surgery.

The current study suggests that outcomes are much more complicated than one might glean from the existing published literature. Emerick et al. demonstrated that ALGS patients at baseline had greater bile salt, cholesterol, phospholipid and chenodeoxycholic-to-cholic acid ratios than PFIC patients (31). They also showed that following successful PEBD, ALGS patients have higher biliary lipid concentrations than PFIC patients and that the FIC1 subtype of PFIC was associated with increased postoperative biliary phospholipic concentrations. Jericho et al. studied the kinetics of bile acid turnover in 5 PFIC patients with successful PEBD compared to 5 PFIC patients who underwent liver transplantation (32) and observed comparable bile acid transport kinetics between the two groups. The authors postulated that the PEBD causes a shift to a relatively more hydrophilic bile acid pool composition that is less damaging to liver parenchyma and, thus, alleviates cholestasis. In our study, we observed PEBD to be effective for some patients with either FIC1, BSEP, or ALGS. We posit that similar mechanisms of action result in relief of pruritus and xanthomata in ALGS. Our data suggest some efficacy as well with IE, and although the mechanism of action here is unstudied, there is likely a similarly bile acid turnover and pool composition change associated with relief of symptoms.

Conduct of a prospective, randomized trial comparing outcomes of children who have undergone non-transplant surgery for cholestasis will be nearly impossible. It is likely to be underpowered and unacceptable to providers, patients, and their families. The current investigation highlights the complexity of this question. Because liver transplantation can be problematic for many of these disorders, identifying the appropriate patient for the appropriate operation would be ideal (33–36). A prospective, multicenter multi-national registry would be most likely to provide further insights into this important issue. Such a registry will need to be multi-centered and will need to carefully account for the type of surgery, genotype of the disease, and stage of disease at the time of surgery. Prospective follow up of complications and outcomes is critical for a valid assessment.

In summary, we found that, in an experience representing multiple institutions specializing in the care of children with intrahepatic cholestasis, biliary diversion is an effective option for non-cirrhotic patients with pruritus who are refractory to medical management. Responses to therapy are complex, with variability in the completeness of the response. Further acquisition of prospective multi-centered data in a systematic manner study is required to better understand the full scope of the indications for and outcomes of non-transplant surgery for intrahepatic cholestasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Schematic of (A) partial external biliary diversion, (B) ileal exclusion, and (C) gallbladder-to-colon biliary diversion.

Figure 2. Distribution of severity of pruritus in ALGS, FIC1 and BSEP patients following partial external biliary diversion. Numbers within bars report the number of subjects reported with the various symptoms at each time point. * $p < 0.05$.

Figure 3.
Presence or absence of xanthomata in ALGS following partial external biliary diversion.

Table 1

Preoperative and postoperative serum laboratory data following partial external biliary diversion, *p<0.05.

(A)					
FIC 1		Surgery	0 mo (N)	6–12 mo (N)	12–24 mo (N)
	Total bilirubin (mg/dL)	PEBD	*8.1±4.0 (12)	*2.2±2.8 (10)	*2.9±4.1 (12)
		IE	8.7±0.7 (3)	10.2±14.2 (2)	8.4±10.4 (2)
	Cholesterol (mg/dL)	PEBD	132.67±54 (6)	101 (1)	96.5±5.0 (2)
		IE	150 (1)	127±39 (2)	139 (1)
	Albumin (g/dL)	PEBD	3.6±0.5 (12)	3.9±05 (10)	4.1±0.4 (11)
		IE	3.7±0.4 (3)	3.9±0.2 (2)	3.9±0.2 (2)
	Alk Phos (U/L)	PEBD	551±269 (12)	516±238 (10)	489±252 (11)
		IE	317±59 (3)	323±101 (2)	323±101 (2)
	ALT (IU/L)	PEBD	*113±134 (12)	*61±53 (10)	*56±32 (11)
IE		352±343 (3)	120±16 (2)	734±23 (2)	
(B)					
BSEP		Surgery	0 mo (N)	6–12 mo (N)	12–24 mo (N)
	Total bilirubin (mg/dL)	PEBD	2.7±2.9 (10)	4.0±7.4 (8)	2.1±2.5 (7)
		IE	1.5±0.9 (5)	4.0±7.4 (8)	6.8 (1)
	Cholesterol (mg/dL)	PEBD	160±36 (4)	134±60 (4)	-
		IE	186±40 (3)	-	-
	Albumin (g/dL)	PEBD	4.3±0.5 (10)	4.2±0.8 (8)	4.2±0.3 (7)
		IE	4.2±0.4 (5)	4.2 (1)	4.1±0.3 (2)
	Alk Phos (U/L)	PEBD	600±269 (10)	564±107 (8)	509±133 (7)
		IE	425±152 (5)	294 (1)	328±53 (2)
	ALT (IU/L)	PEBD	*123±112 (10)	*117±57 (8)	*99±83 (7)
IE		137±106 (5)	336 (1)	104±109 (2)	
(C)					
ALGS		Surgery	0 mo (N)	6–12 mo (N)	12–24 mo (N)
	Total bilirubin (mg/dL)	PEBD	5.3±5.4 (15)	5.5±4.6 (12)	4.9±4.1 (12)

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	IE	10.6±3.4 (5)	10.7±1.6 (4)	9.8±1.3 (4)
Cholesterol (mg/dL)	PEBD	*694±465 (9)	*365±152 (8)	*457±319 (9)
	IE	1050±127 (5)	825±134 (5)	786±152 (3)
Albumin (g/dL)	PEBD	3.8±0.7 (15)	4.0±0.6 (11)	4.1±0.6 (11)
	IE	3.9±0.6 (5)	4.2±0.3 (4)	4.0±0.0 (4)
Alk Phos (U/L)	PEBD	740±324 (15)	910±525 (12)	920±494 (11)
	IE	576±147 (5)	605±213 (5)	471±124 (4)
ALT (IU/L)	PEBD	182±70 (15)	235±111 (11)	260±73 (11)
	IE	134±36 (5)	140±43 (5)	150±59 (4)

(D)					
ggtp<100	Total bilirubin (mg/dL)	Surgery	0 mo (N)	6-12 mo (N)	12-24 mo (N)
		PEBD	13.4±10 (2)	4.6±6.1 (2)	0.6±0.3 (2)
		IE	4.1±5.9 (3)	0.8 (1)	0.4±0.3 (2)
	Cholesterol (mg/dL)	PEBD	-	-	-
		IE	143±9 (2)	-	-
	Albumin (g/0dL)	PEBD	3.7±0.7 (2)	3.1±0.2 (2)	3.6±0.1 (2)
		IE	4.8±1.0 (3)	4.1 (1)	3.5 (1)
	Alk Phos (U/L)	PEBD	4167±125 (2)	344±216 (2)	367±288 (2)
		IE	371±43 (3)	770 (1)	709±95 (2)
	ALT (IU/L)	PEBD	72±38 (2)	52±16 (2)	63±46 (2)
		IE	80±21 (3)	49 (1)	52±6 (2)