Biliary Atresia

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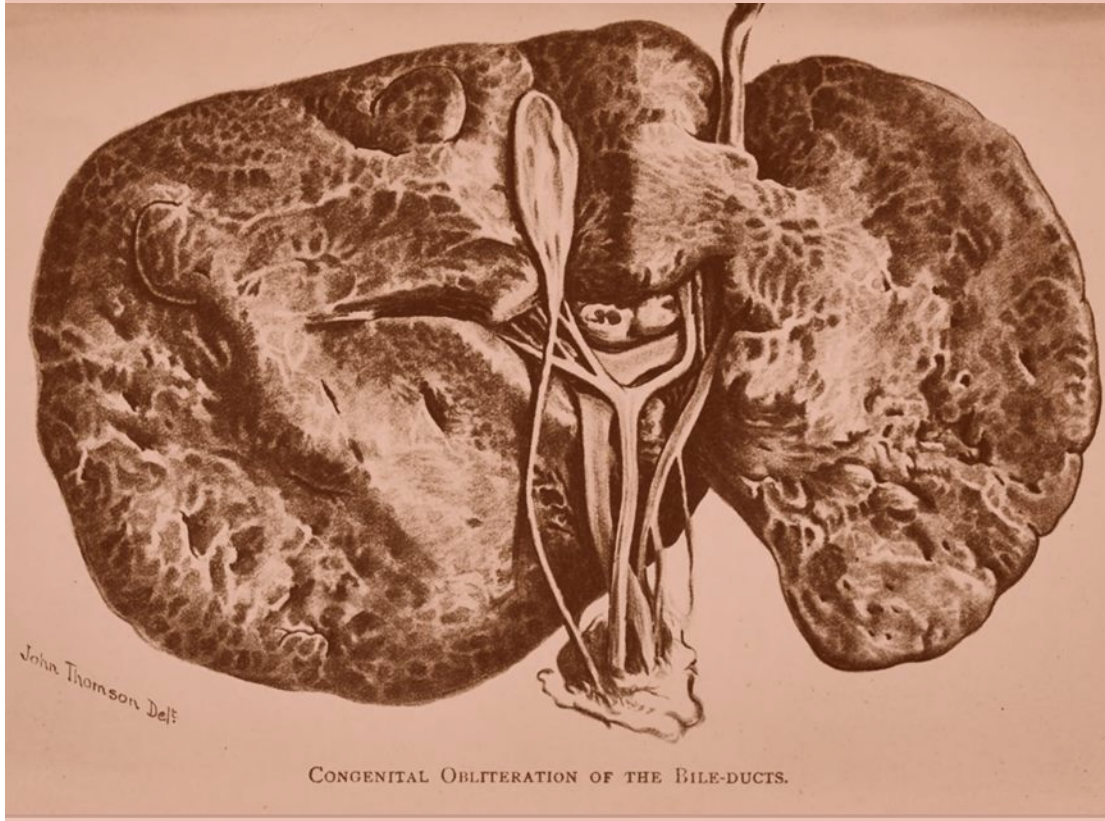
27 กุมภาพันธ์ 2563

Outline

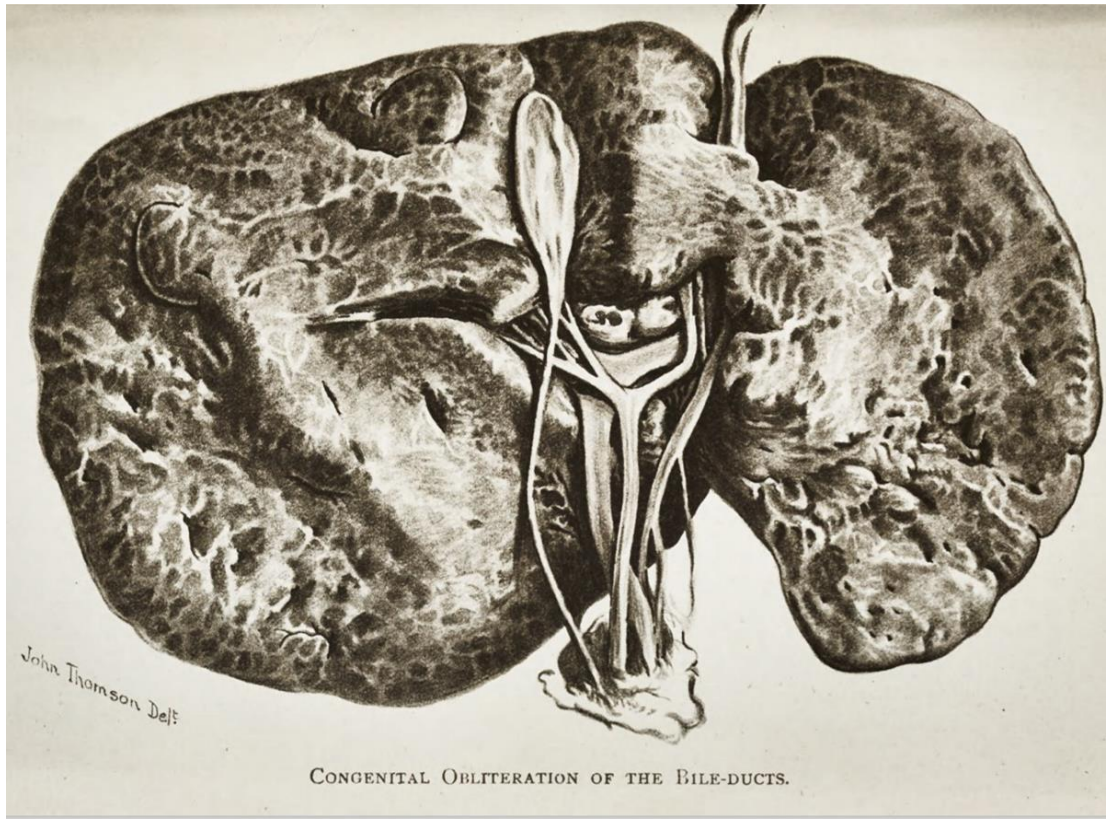
- Introduction
- Epidemiology
- Definition and Etiology
- Morphology classification
- Diagnosis
- Treatment
- Screening
- Post op management
- Outcome
- Role of livertransplant

1 Introducion



CONGENITAL OBLITERATION OF THE BILE-DUCTS.

Introduction



CONGENITAL OBLITERATION OF THE BILE-DUCTS.

- In 1891, John Thomson Edinburgh described infant dying from liver failure secondary from congenital biliary obstruction
- BA is the main cause of cholestatic jaundice in neonates

Thomson J.. Trans Edinb Obstet Soc 1892;17:17-49

2 Epidemiology

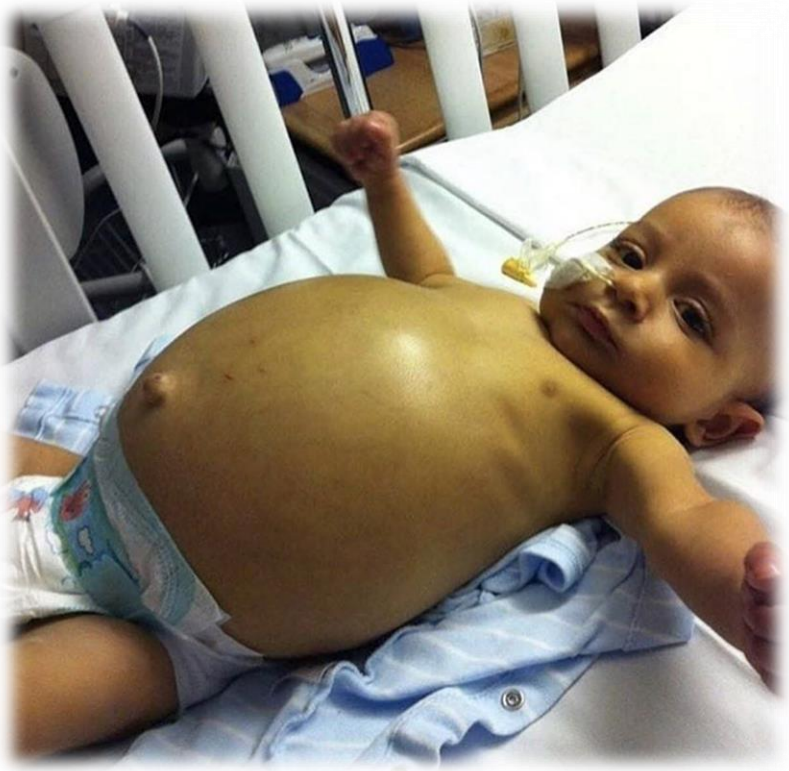
Epidemiology

- Higher incidence in Asia than in Europe
  - Europe 0.5-0.8 :10,000 , Japan 1.1:10,000, Taiwan 1:5,000
- Female > Male ratio of 1.4-1.7 : 1
- Preterm > Term
- Low birth weight > Normal birth weight

Yoon PW, Bresee JS, . Pediatrics 1997;99:376-82.
Sanchez-Valle A,. Adv Pediatr 2017;64:285-305.
Hsiao CH, et al. . Hepatology 2008;47:1233-40

3 Definition and Etiology

Definition

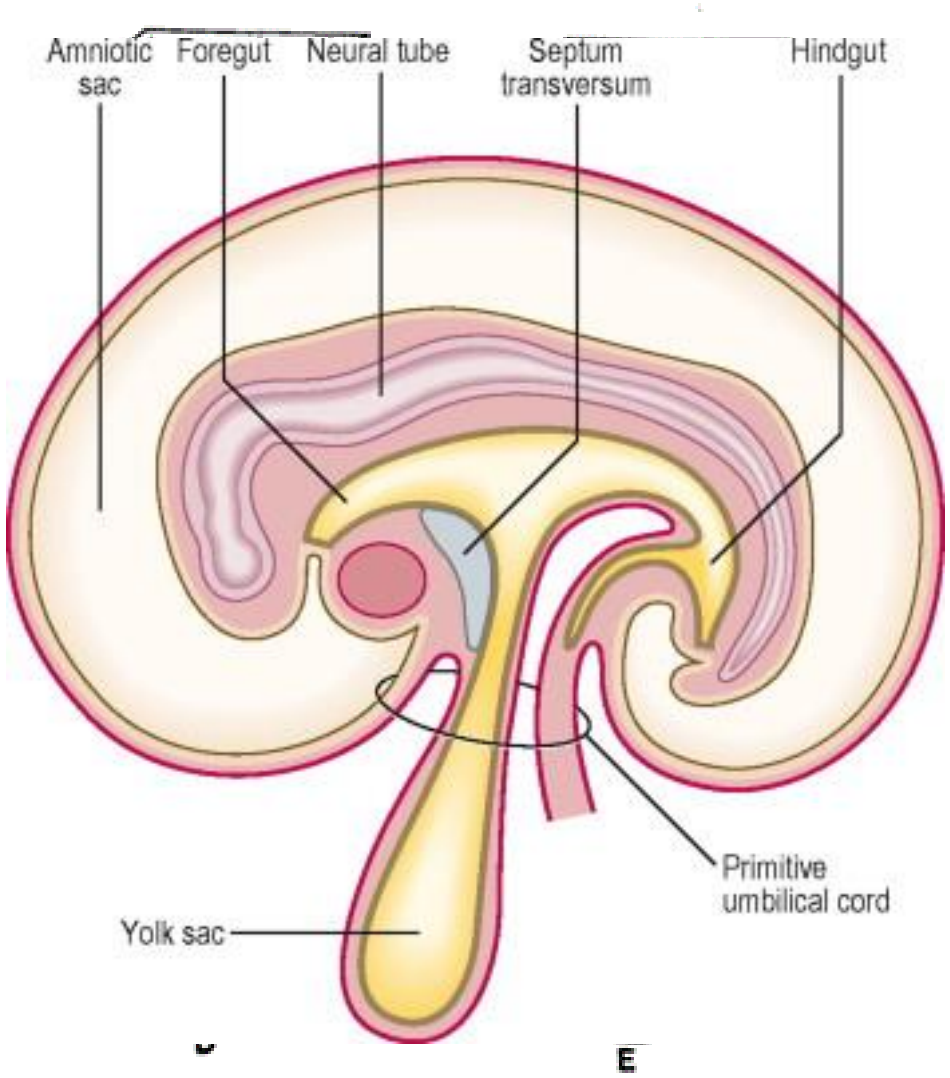


- Biliary atresia (BA) is severe inflammatory and obliterative cholangiopathy that affects both extra and intrahepatic bile duct

Nizery L et al. Biliary atresia: Clin Res Hepatol Gastroenterol 2016;40:281-7

Etiology

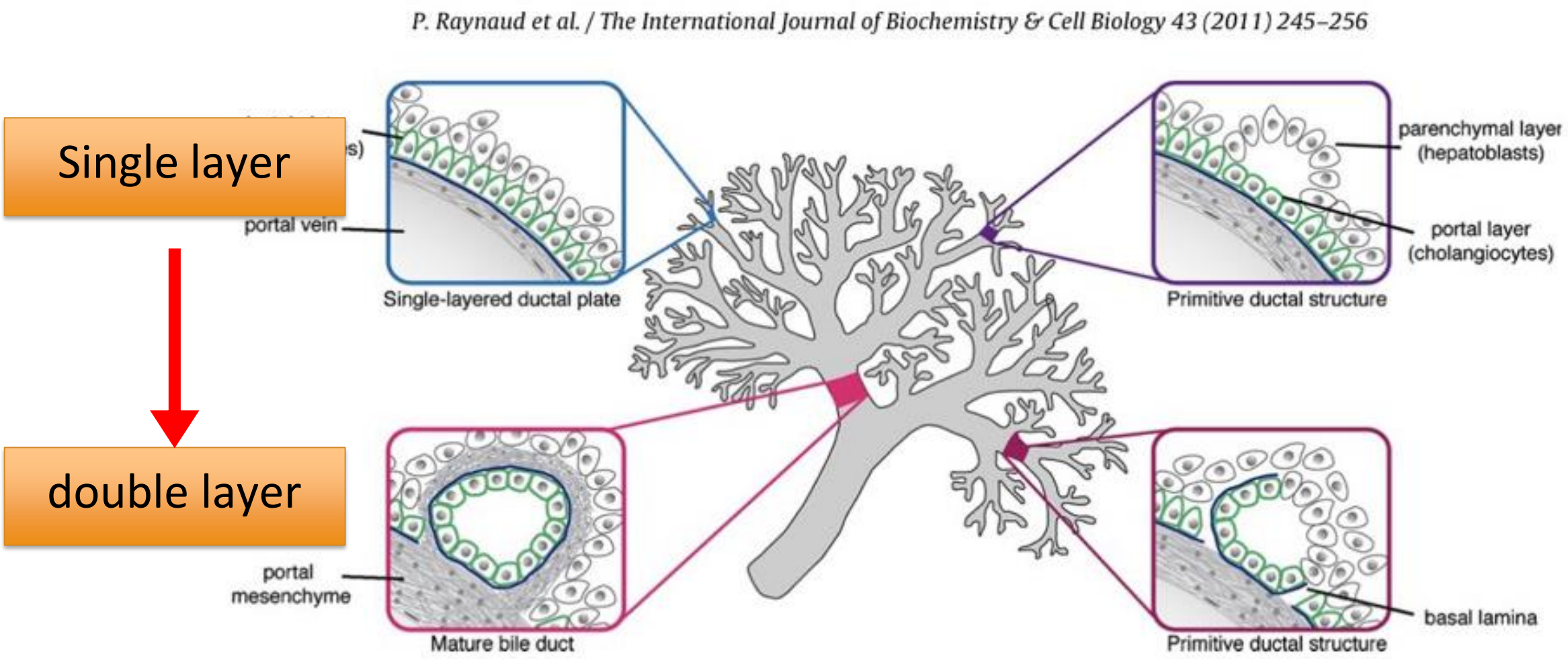
- In humans liver and biliary tree arise diverticulum of ventral fore gut endoderm
- Intrahepatic bile ducts
  - Cranial part
  - Begin at 8th week of gestation
  - "ductal plate" : sheath of primitive biliary epithelium around portal vein
  - At birth was immature will be completed during first year of life



Pediatr Surg 1994;29:808-14.

Strazzabosco M. J Hepatol 2012;56:1159-70

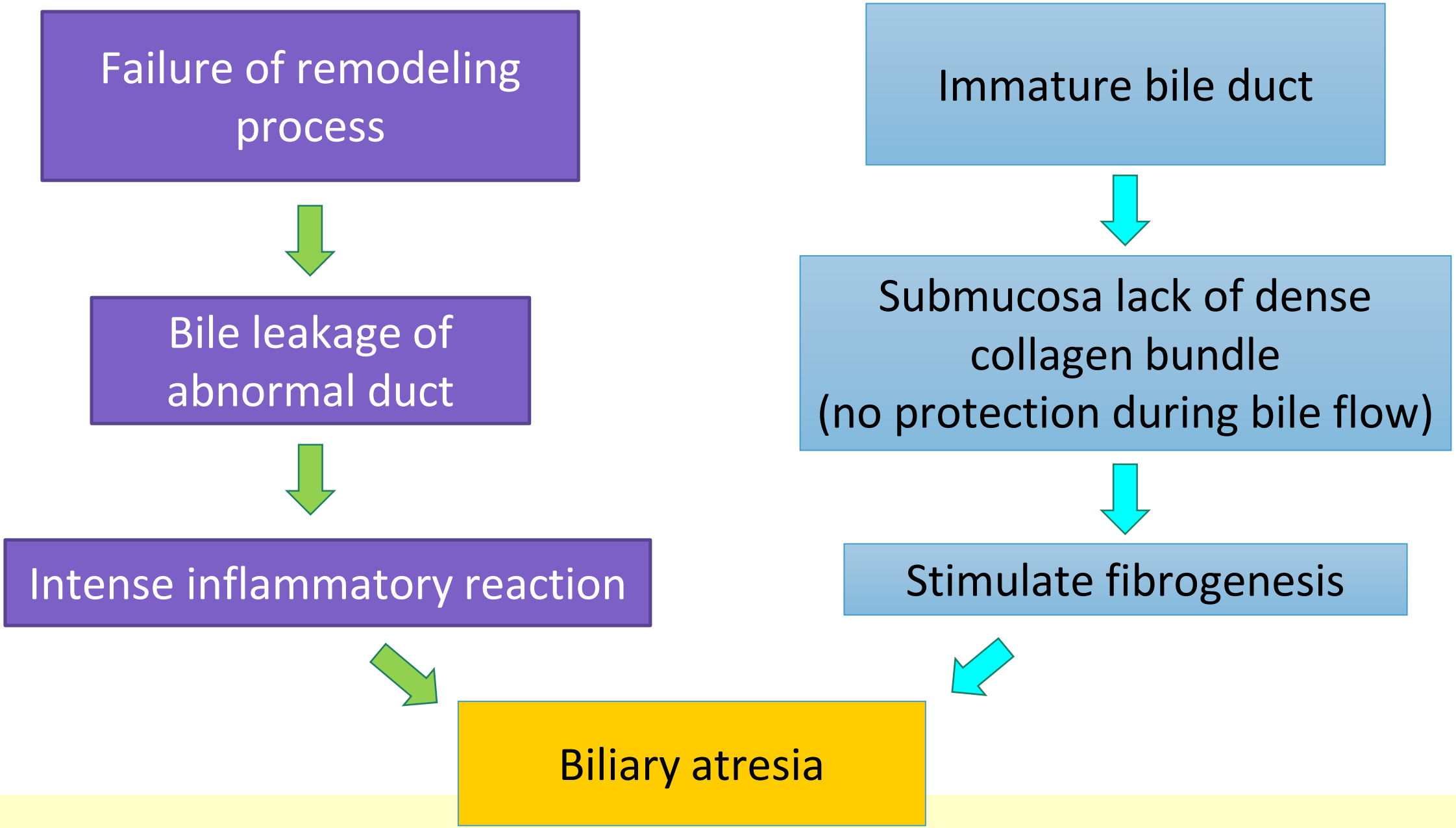
Intrahepatic bile duct formation

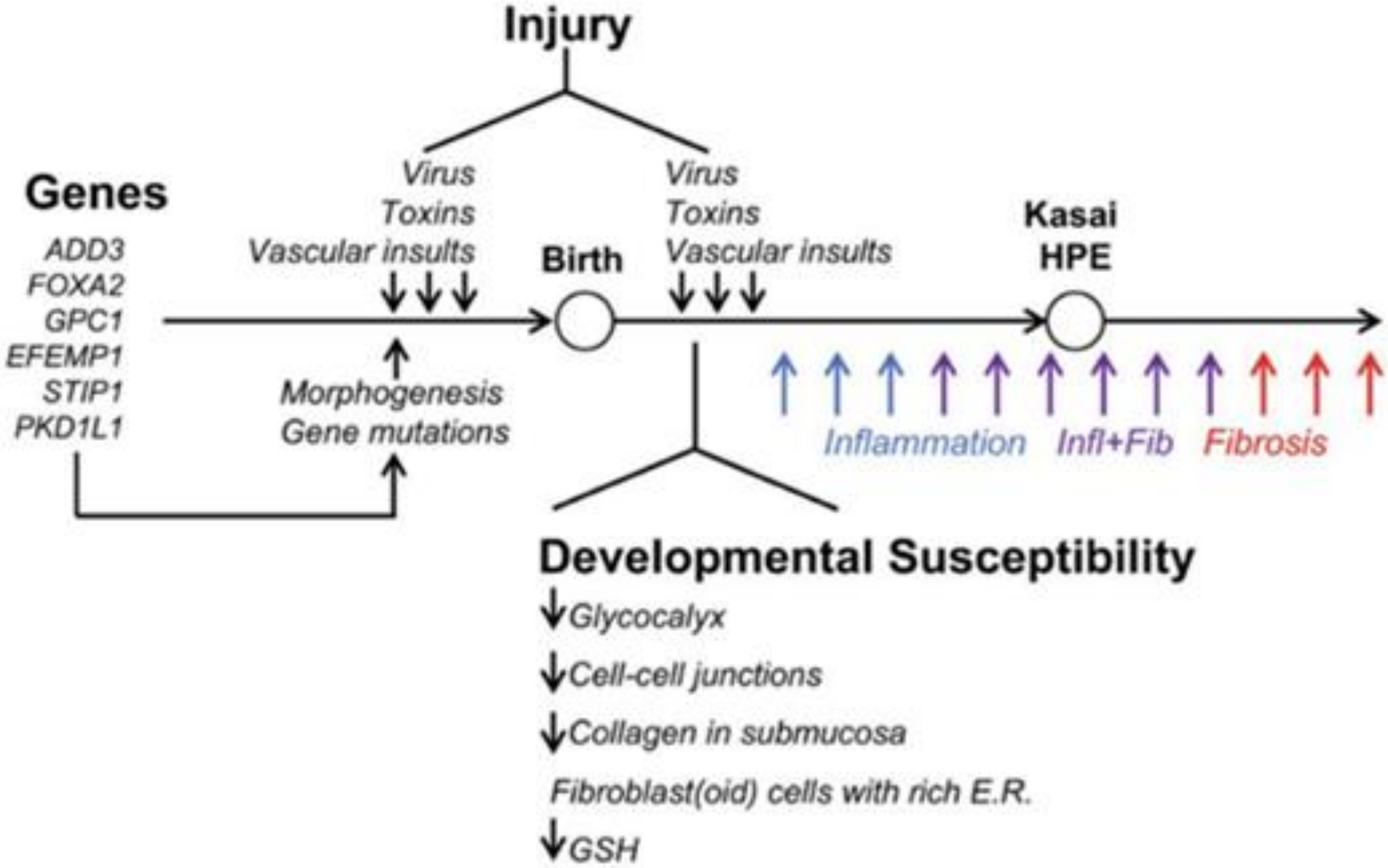


Strazzabosco M. J Hepatol 2012;56:1159-70

Etiology

- Extra hepatic biliary tree
  - Cholangiocyte derive from caudal part of ventral foregut
  - Develop before intrahepatic part
  - Merge at level of hepatic hilum


Failure of remodeling process
Bile leakage of abnormal duct
Intense inflammatory reaction
Immature bile duct
Submucosa lack of dense collagen bundle (no protection during bile flow)
Stimulate fibrogenesis
Biliary atresia



Bezerra JA, et al. Biliary Atresia:. Hepatology 2018;68:1163-73

Pathogenesis

1.Infection

- **Cytomegalovirus (CMV)**
- Liver biopsy CMV DNA was detect 60%
- Immunological study
    - Liver memory T cell response to CMV 56%
- **Other**
- Reovirus, rotavirus

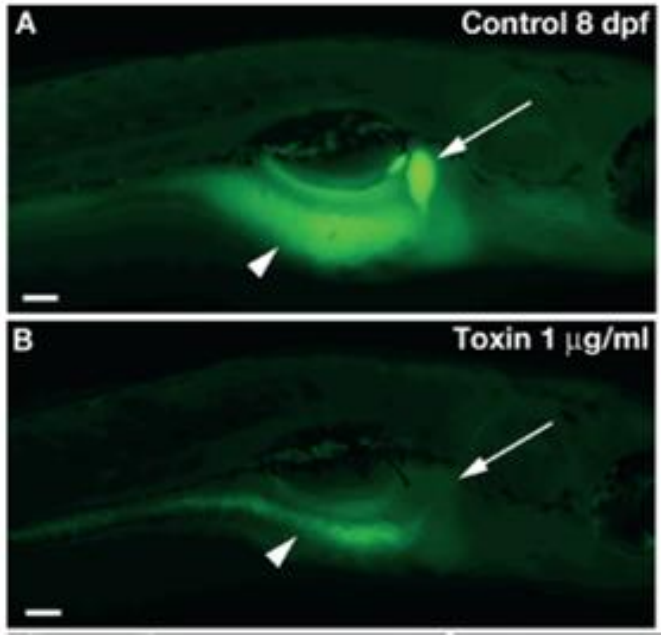
Xu Y, Yu J, et al. Clin Pediatr (Phila) 2012;51:109-13

Pathogenesis

2.Toxin

- Isoflavonoid biliary toxin “Biliatresone”
- Pregnant animals that eat Dysphania plant

  -> 14-100% of newborn were Biliary atresia
- Study in larva of zebrafish
  - •Larvae ingest the fluorescent lipid reporter PED-6 and Bodipy-C5 and Bodipy-C16
  - •Reduced fluorescence in the gallbladders and intestines in all larvae



Lorent K, Gong W, Koo KA, Waisbourd-Zinman O, Karjoo S, Zhao X, et al. Sci Transl Med 2015;7:2

Pathogenesis

3. Genetic

- Cripto, FRL-1, Cryptic family 1 (CFC1 gene)
- Intercellular Adhesion Molecule 1(ICAM1)
- Macrophage migration inhibitory factor

4. Immune dysfunction

- Autoimmune mechanism
- Decretion of regulatory T cell

Phenotypic classification

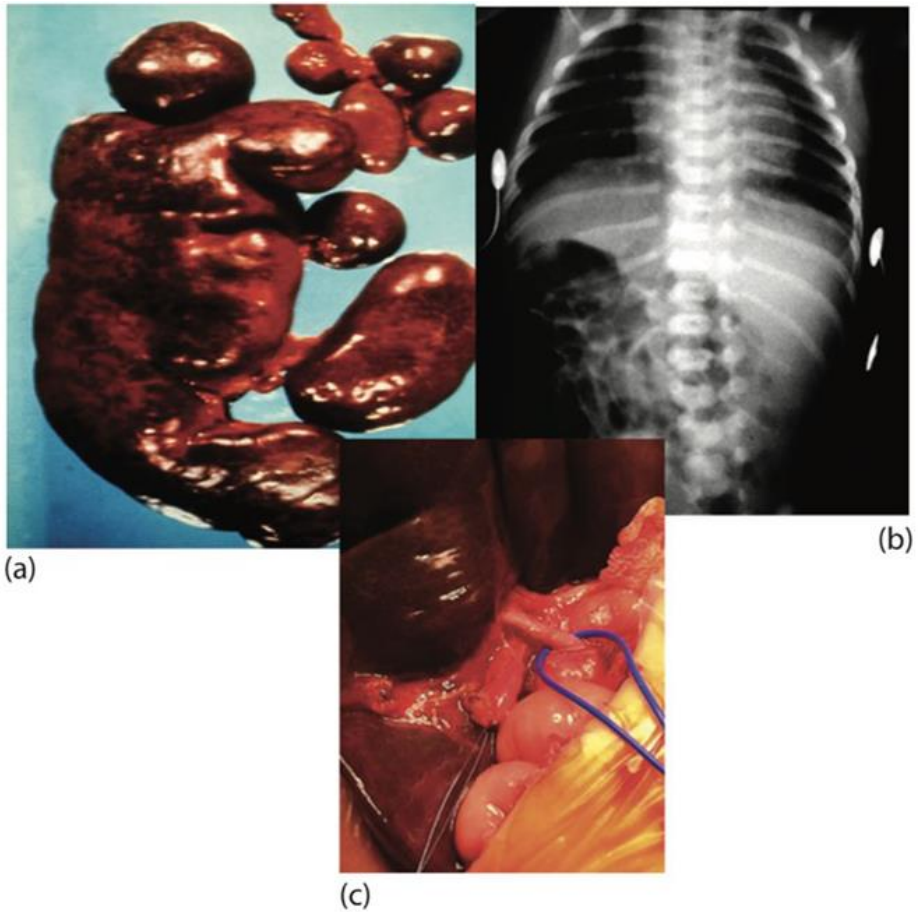


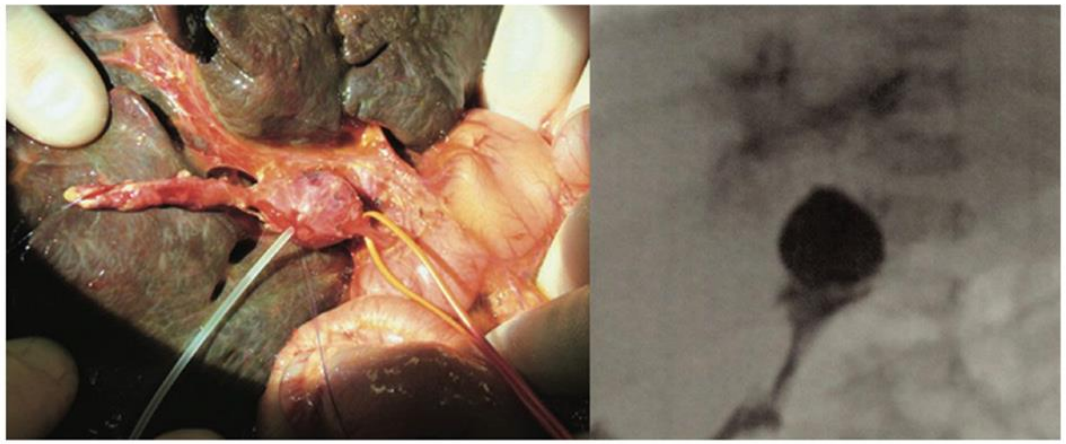
Figure 6.2 BASM syndrome. Typically, infants will have polysplenia (a), situs inversus (b) and a preduodenal portal vein (c).

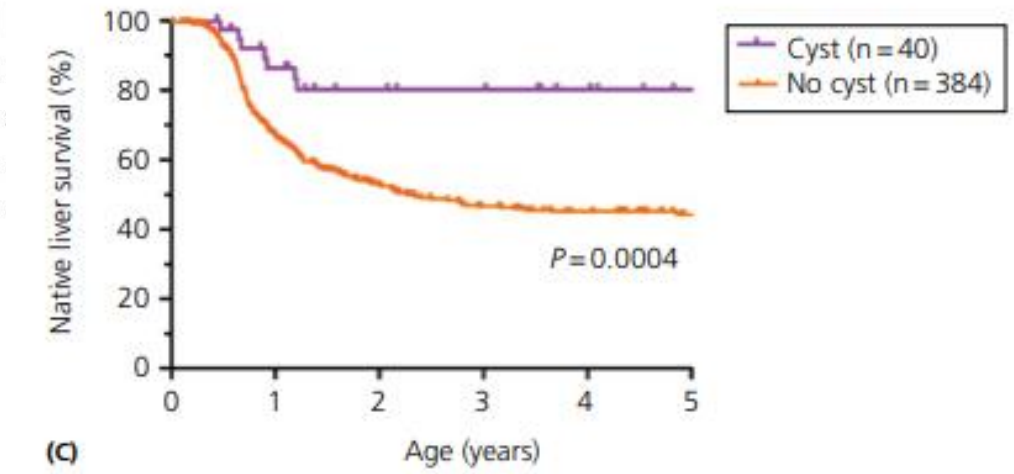
1.Syndromic BA and associated congenital malformation

- Syndromic congenital anomaly
  - BA splenic malformation (BASM) syndrome
  - Cat-eye syndrome
- Non syndromic congenital anomaly
  - esophageal atresia, jejunal atresia
  - Female predominant

M. Davenport. Surgery of the liver bile ducts and pancreas in children 2017

Phenotypic classification





2. Cystic biliary atresia

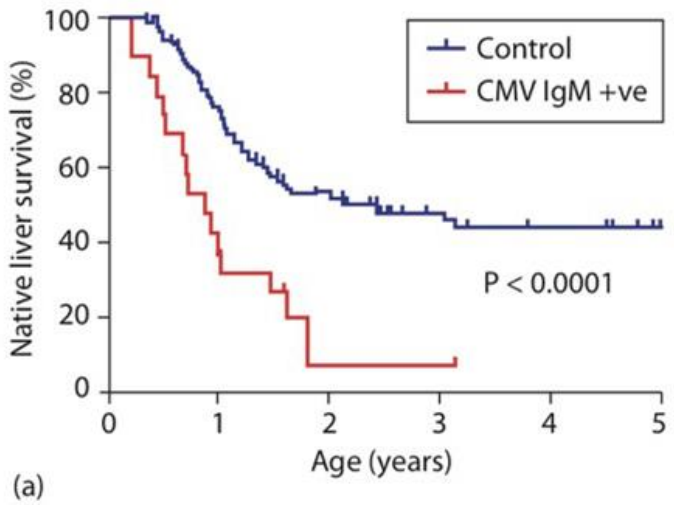
- 10% of all BA cases
- Can be confused with choledochal malformation -> confirm at surgery with cholangiogram
- Better outcome after KPE

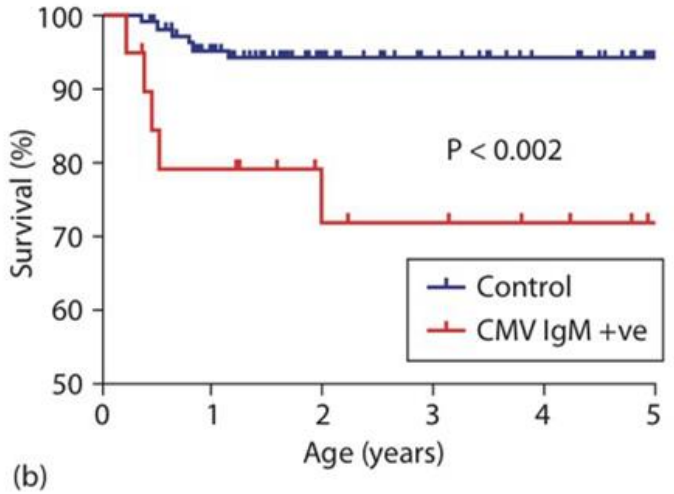
M. Davenport. Surgery of the liver bile ducts and pancreas in children 2017

Type of Biliary atresia

3. CMV -associated biliary atresia

- 10% of BA cases
- Majority in non Caucasian
- Outcome after KPE was less effective





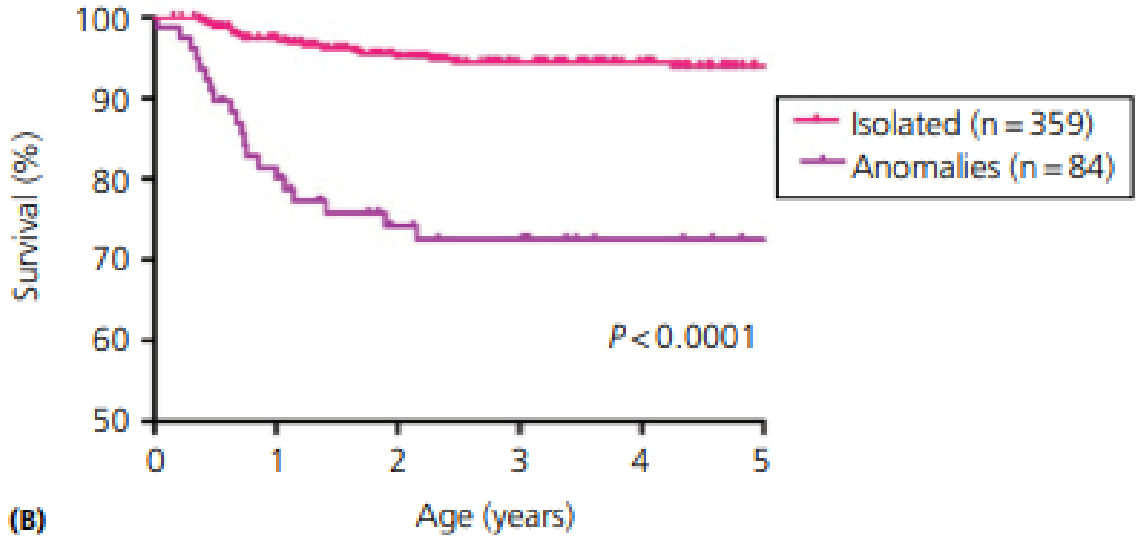
M. Davenport. Surgery of the liver bile ducts and pancreas in children 2017

M. Davenport. Surgery of the liver bile ducts and pancreas in children 2017

Phenotypic classification

4.Isolated biliary atresia

- Largest group 70-80%
- 2 theories
  - 1st trimester arrested
  - obliteration during perinatal period



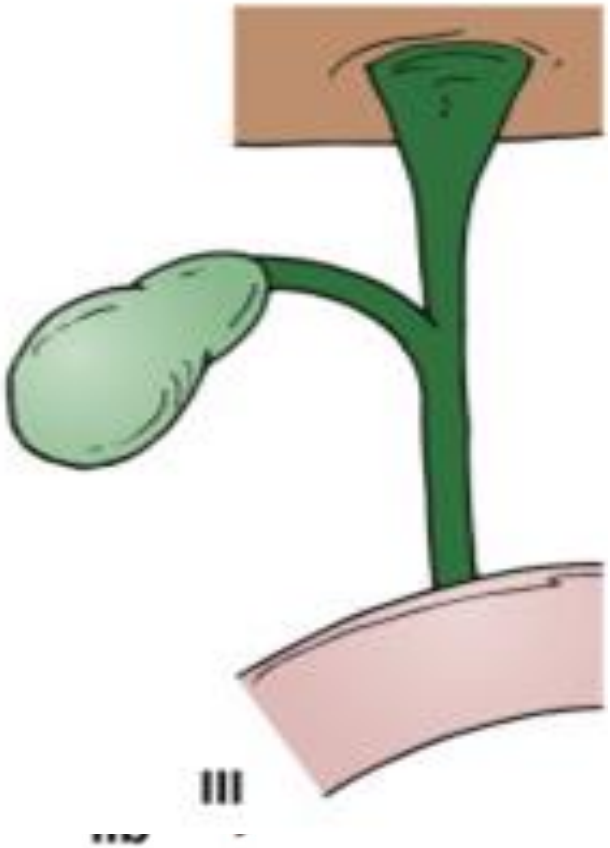
M. Davenport. Surgery of the liver bile ducts and pancreas in children 2017

4 Morphological classification

Morphologic classification

"Japanese classification of Pediatric Surgeons"

- **Type I (5%)**
  - Obliteration of commom bile duct
- **Type II (2%)**
  - IIa – atresia of common hepatic duct , cystic duct patei
  - IIb – atresia of cystic duct, common hepatic duct, common bile duct
- **Type III (90%)**
  - Atresia at right and left hepatic duct
  - Worst prognosis due to atresia



Hartley JL, Davenport M, Kelly DA. Biliary atresia. Lancet 2009;374:1704-13

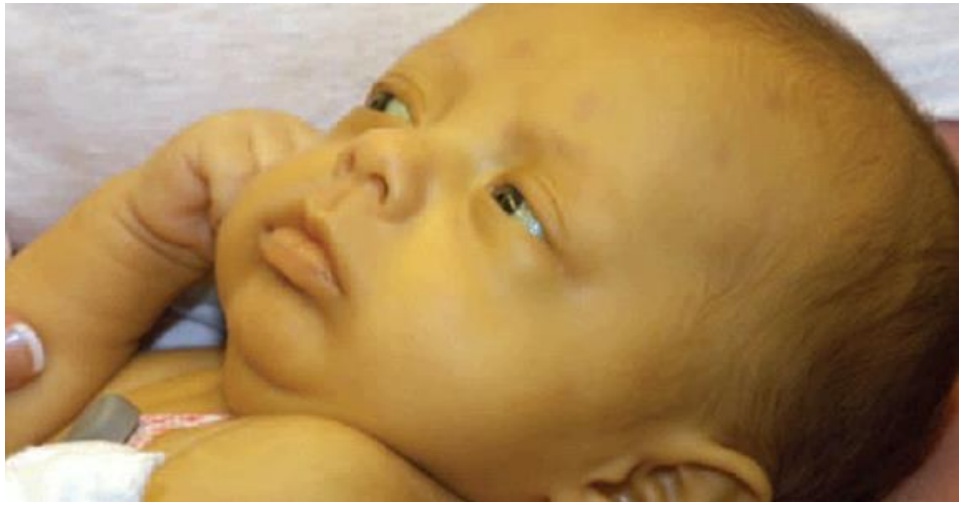
Cazares J, Ure B, Yamataka A. Biliary atresia. In: Holcomb GW, Murphy JP, Peter SDS, editors. Pediatic surgery. 7 ed. Edinburgh: Elsevier; 2020. p. 679-94.

5 Diagnosis

Diagnosis

- **History**

- Jaundice
- Dark urine
- Pale, acholic stool
- Onset – usually after 2-3 week of life
- Bleeding tendency
- Failure to thrive



Davenport M. Biliary atresia: clinical aspects. Semin Pediatr Surg 2012;21:175-84.

Diagnosis

- **Physical exam**
  - Jaundice
  - Hepatomegaly
  - Spleenomegaly
  - Cardiac murmur

Davenport M. Biliary atresia: clinical aspects. Semin Pediatr Surg 2012;21:175-84.

Laboratory Investigation

- CBC, UA, LFT
- Hepatitis A, B, C serology
- TORCH titer (Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes simplex virus)

- Direct hyperbilirubinemia
- AST, ALT normal to high normal
- High ALP and GGT
- GGT > 300 IU/L
  - specificity 98% sensitivity 38%
- Serum matrix metalloproteinase (MMP-7)
  - sensitivity 98% specificity 95%

Tang KSet al.. Acta Paediatr Taiwan 2007;48:196-200.
Yang L, et al.. Hepatology 2018;68:2069-77.

Direct hyperbilirubinemia

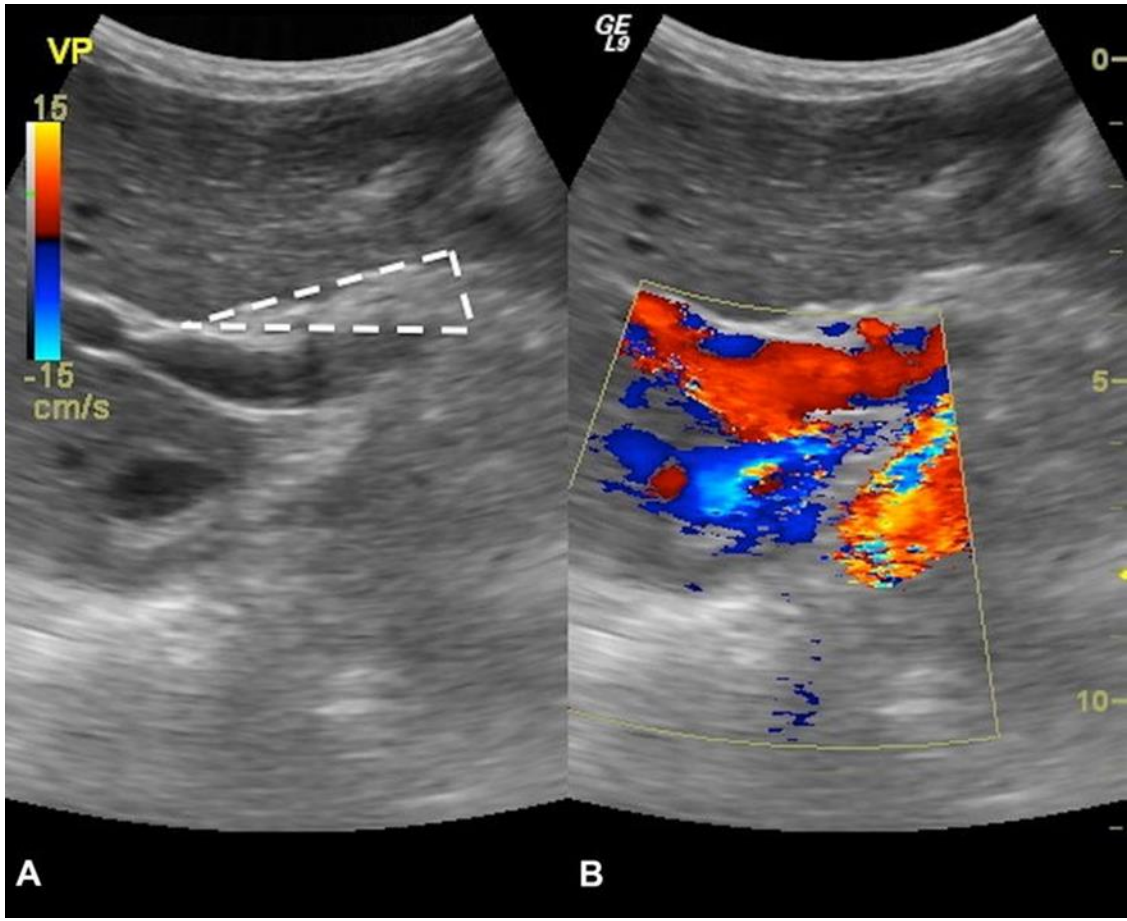
Hepatocellular jaundice	Metabolic	Obstructive jaundice

• Neonatal hepatitis from
  • Idiopathic giant cell hepatitis
  • TORCH infection
  • Sepsis
	• Galactosemia
	• Alpha-1 antitrypsin deficiency
	• Parenteral nutrition related cholestasis
		• BA
		• Choledochal cyst
		• Inspissated bile syndrome
		• Alagille syndrome

Imaging

- **Ultrasonography**
- Non invasive
- Exclude specific anomalies of biliary tract eg. Choledochal cyst

- ***"Triangular cord sign"***
  - •triangular echogenic density seen cranial to the portal vein bifurcation
  - •Fibrotic ductal remnant at portal vein
  - •sensitivity 23-100% specificity 94-100%



Choi SO, Park WH, Lee HJ, Woo SK. J Pediatr Surg 1996;31:363-6

Pediatr Radiol (2003) 33: 311–315
DOI 10.1007/s00247-003-0867-z

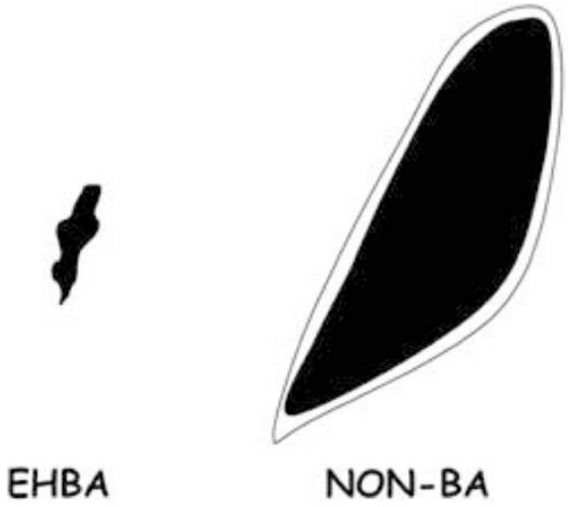
ORIGINAL ARTICLE

Anne Poh Ann Tan Kendrick
Kong Boo Phua
Boo Chye Ooi
Carolyn Eng Looi Tan

Biliary atresia: making the diagnosis by the gallbladder ghost triad

"Gallbladder Ghost triad"

- **A** : Atretic gallbladder length <1.9cm
- **T** :thinned or lack of smooth/complete echogenic mucosal lining and indistinct wall
- **K :** knobby, irregular gallbladder contour



	BA (31)	Non-BA (186)
GB ghost triad	30	0
GB length	0–1.82 cm	1.6–4.82 cm
GB thick wall	0	46 (mean 0.19 cm)
TC	26	0
Diffuse PPE	4	22
Hepatic artery	0.20–0.29 cm	0.20–0.25 cm

Specificity 100%

If the ultrasounds are negative

Re-evaluate in 1-2 weeks

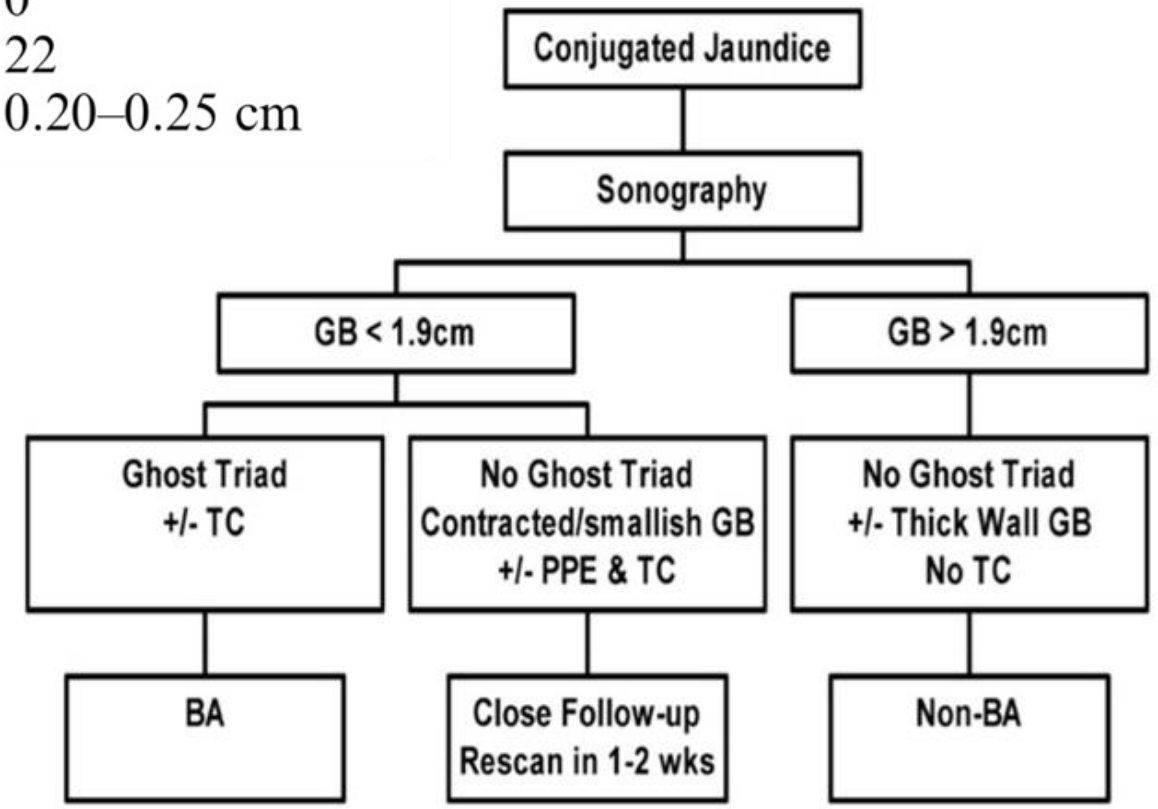


Fig. 6 Flowchart illustrating our protocol for evaluating babies with cholestastic jaundice on sonography

Tan Kendrick AP, Phua KB, Ooi BC, Tan CE. Pediatr Radiol 2003;33:311-5

AJR FOCUS ON:

Ultrasound for the Diagnosis of Biliary Atresia: A Meta-Analysis

TABLE 3: Outcomes of Meta-Analysis of Different Ultrasound Features in Diagnosis of Biliary Atresia

Ultrasound Feature	No. of				AUC
GBA					.94 (0.91–0.95)
TC					.97 (0.95–0.98)
TC + GBA					.94 (0.92–0.96)
HA enlargem					.83 (0.80–0.86)

Note—Values … rmality, TC = triangular cord sign, TC + GBA = TC and GBA combined, HA = hepatic artery.

Highest sensitivity combining triangular cord sign and gallbladder abnormality

Zhou L, Shan Q, Tian W, Wang Z, Liang J, Xie X. AJR Am J Roentgenol 2016;206:W73-82.

Hepatobiliary scintigraphy

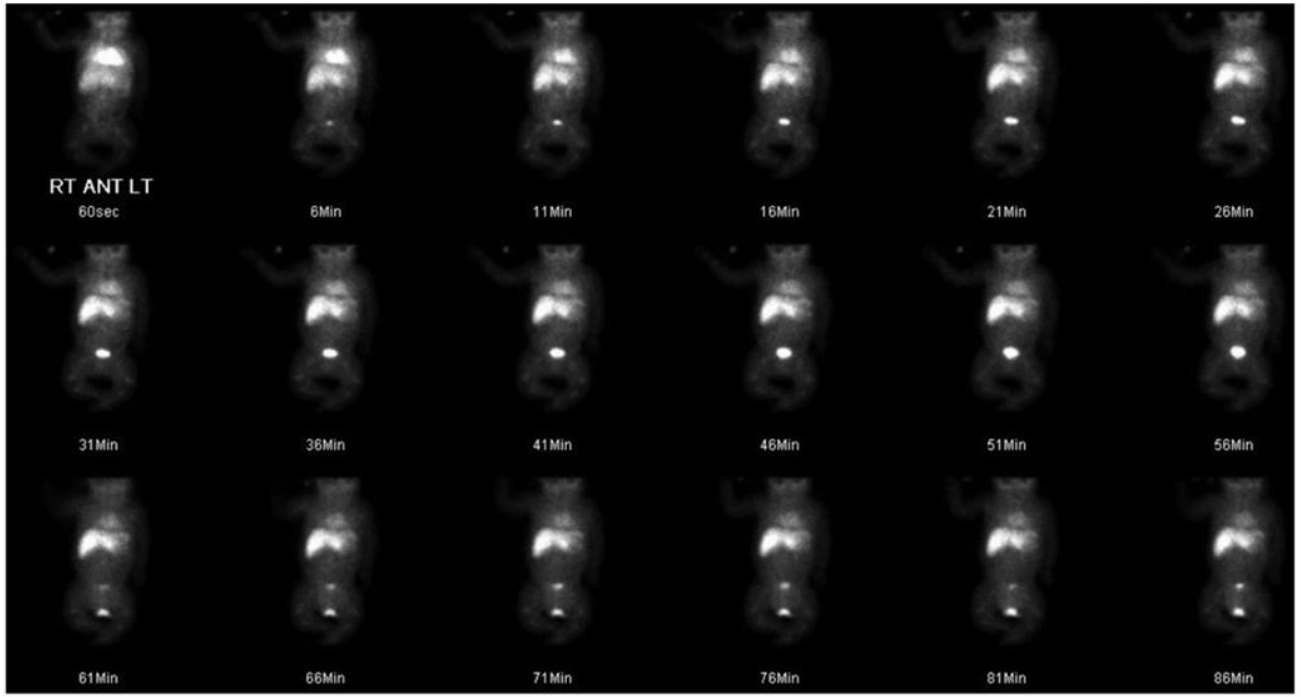


Fig. 3. Abnormal HIDA imaging in an infant later confirmed to have biliary atresia. After injection of radioisotope, there is uniform distribution of activity within the liver. Even at 24 hours, on delayed images, there is neither visualization of the gallbladder nor excretion in the gut.

- Using technetium-labeled diisopropyl iminodiaceticacis (DISIDA) nuclear scintiscan
- Failure of excretion suggest BA
- Sensitivity 98% specificity 70%

Mandelia A, Lal R, Mutt N. Indian J Pediatr 2017;84:685-90

Hepatobiliary scintigraphy

- Using phenobarbital (5 mg/kg/day for 5 days) per oral can enhance radioisotope excretion

Increase sensitive100%, specific 93%

Kwatra N .Pediatr Radiol 2013;43:1365-75

Intraoperative cholangiogram

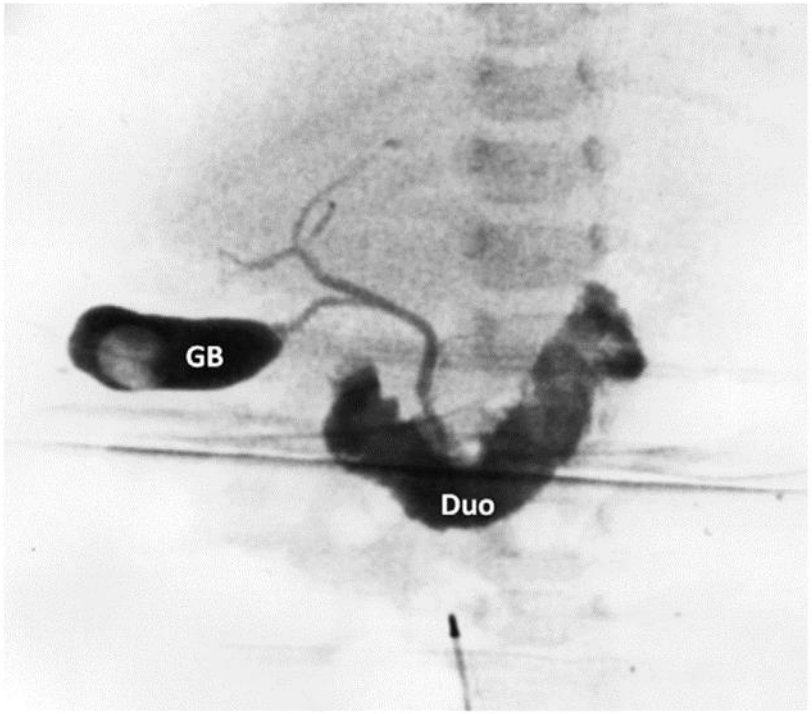


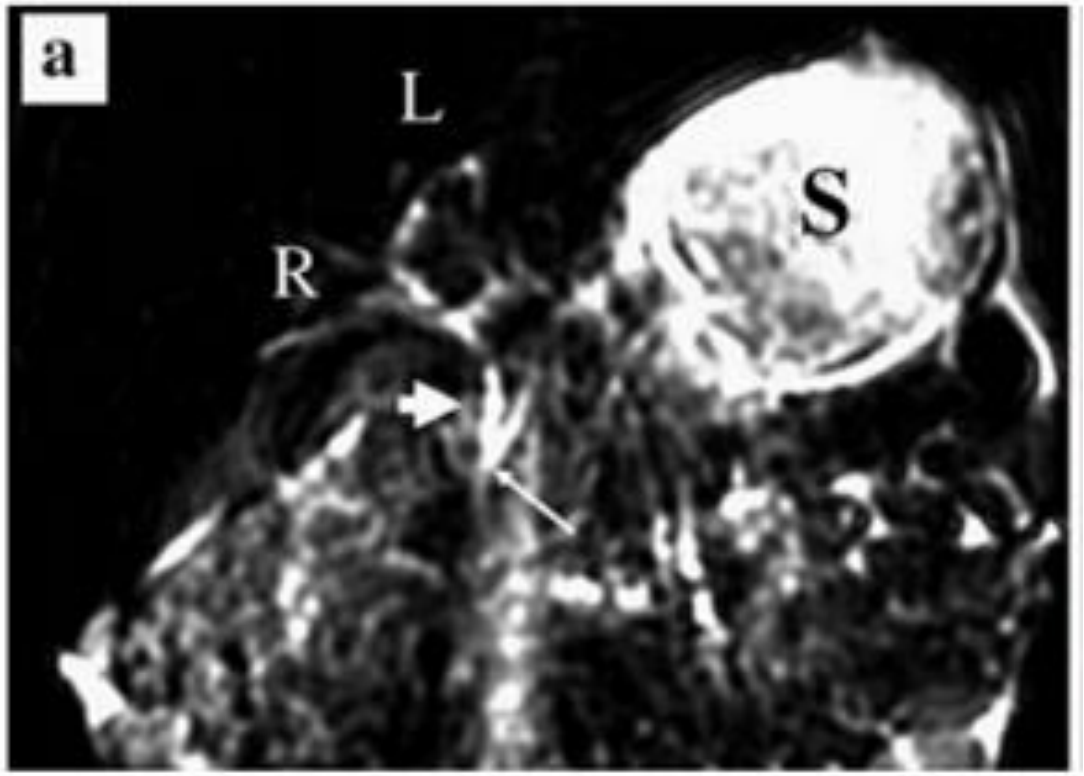
FIGURE 105-4 Cholangiogram obtained during abdominal exploration for presumed biliary atresia. The gallbladder (*GB*) appeared normal, and an intraoperative cholangiogram revealed patency of the intrahepatic ducts to the duodenum (*Duo*). A liver biopsy was performed, and the procedure was concluded.

- Gold standard diagnosis of BA
- Demonstrate anatomy and patency of the extrahepatic biliary tract
- Percutaneous operative cholangiogram

  Reduce unnecessary surgical exploration 47%

Cowles RA. In: Coran AG, editor. Pediatric surgery. 7 ed. Philadelphia2012. p. 1321-30

Magnetic resonance cholangiopancreatography (MRCP)



- Morphology of bliary tree
- Differentiated with neonatal hepatitis
- Sensitivity 90-100%, specificity 77-96%
- Limit interpretation

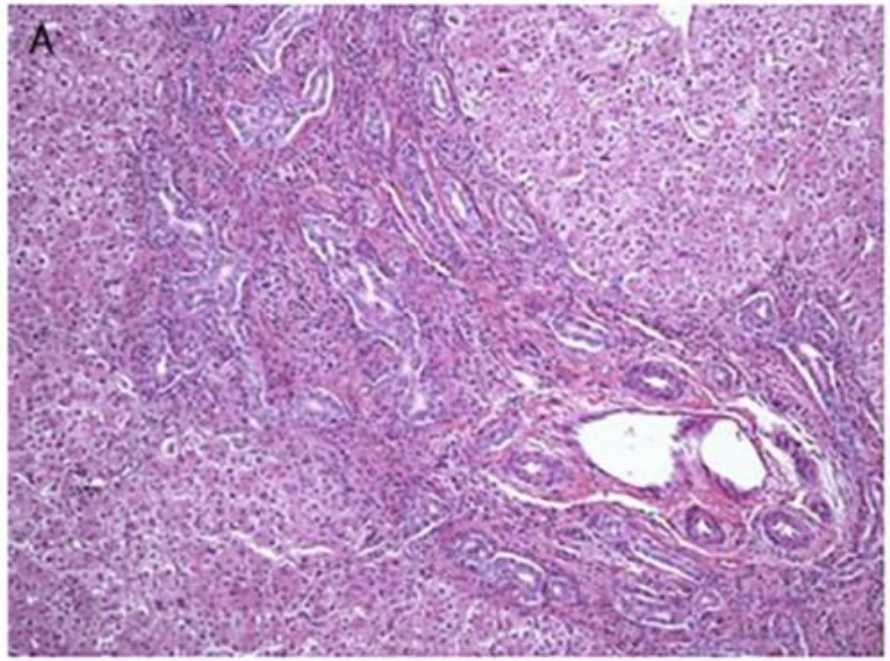
Percutaneous liver biopsy

- Disease other than BA that cause cholestasis can be determined via histologic examination
- Sensitivity 91.2%, specificity 93%, accuracy 91.6%
- limitation
  - Experienced of pathologist
  - Not adequate biopsy
  - Age of biopsy : < 6 week of age can miss diagnosis
  - Overlapping of histopathological feature

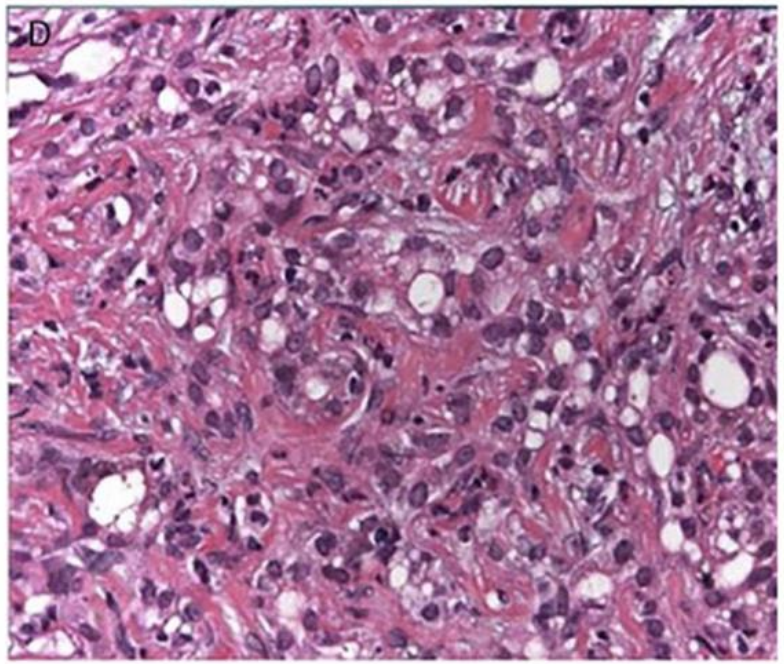
Histology

- Inflammation and fibrous cells surrounding minuscule duct
- Bile duct proliferation
- Ductal plate malformation
- Portal stroma edema
- Higher stage of portal fibrosis (stages 3 and 4)
- Prominent pseudorosette formation
- Moderate to marked peribiliary neutrophilic infiltrate
- Bile duct injury
- Giant cell transformation

Cazares J, Ure B, Yamataka A. The jaundiced infant : biliary atresia. In: Coran AG, editor. Pediatric surgery. 7 ed. Philadelphia2012. p. 1321-30



Proliferation of centrally located bile duct



Extensive bile duct injury (Marked vacuolization)

- *Russo P, et al. Am J Surg Pathol 2016;40:1601-15.*

5 Key Histological features in BA

1. Bile plugs in ducts/ductules
2. Portal stromal edema
3. No bile duct paucity
4. Absent to rare giant cell transformation
5. Absent to rare extramedullary hematopoiesis(EMH)

Resulted in a concordance index of 0.89 (95% CI: 0.84, 0.93) for the diagnosis of BA vs non-BA.

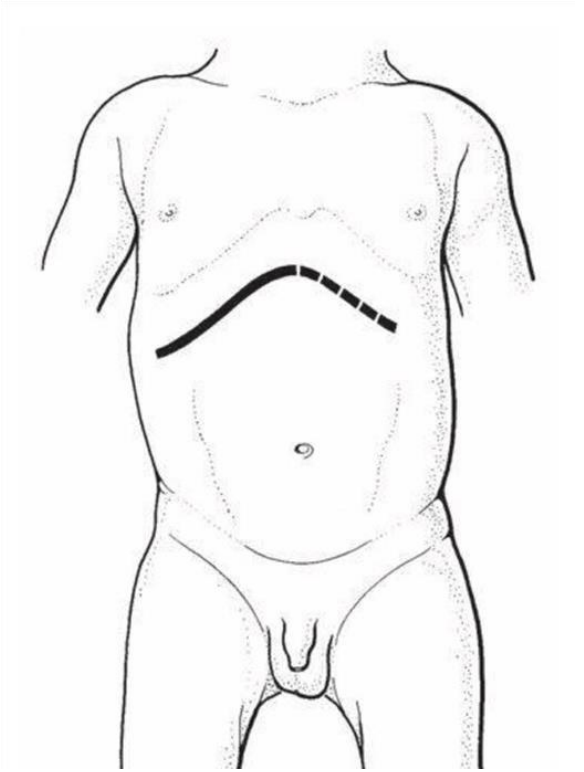
6 Treatment

Treatment

- The Roux-en-Y hepatic portoenterostomy (**“Kasai procedure”)** is the standard initial operation
- Aim to allow drainage of bile from liver via microscopic ductules into intestine

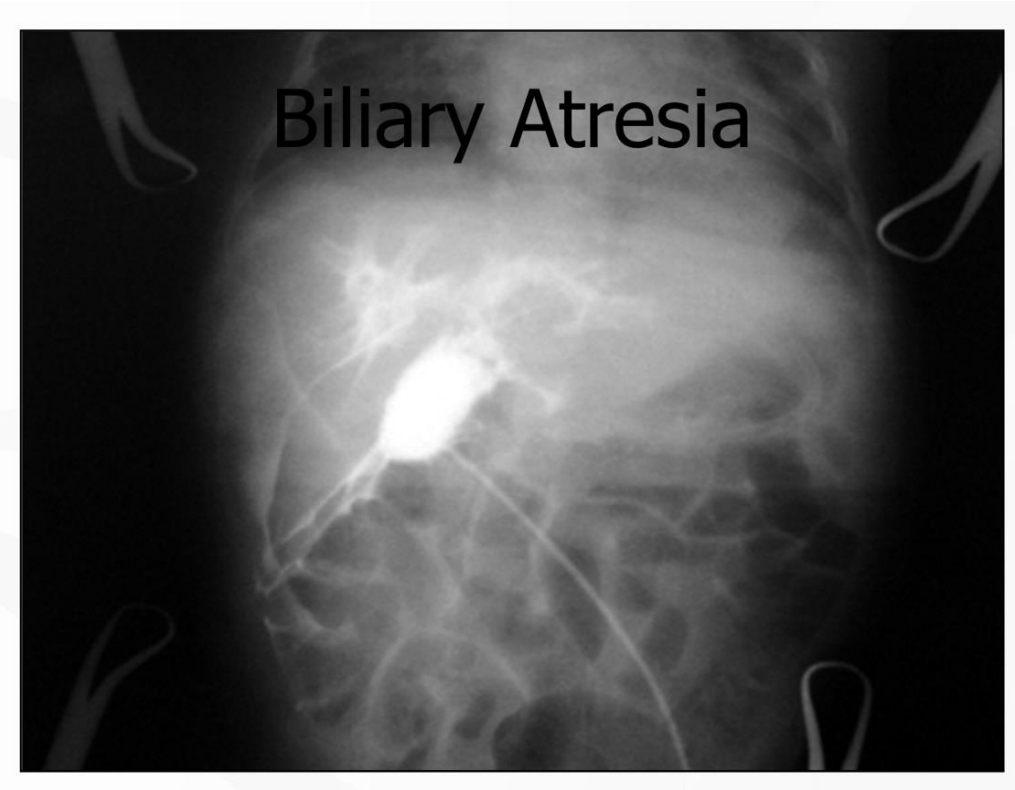
Treatment

- **Incision**
  - Extended right subcostal incision



Operative Pediatric surgery 7th ed

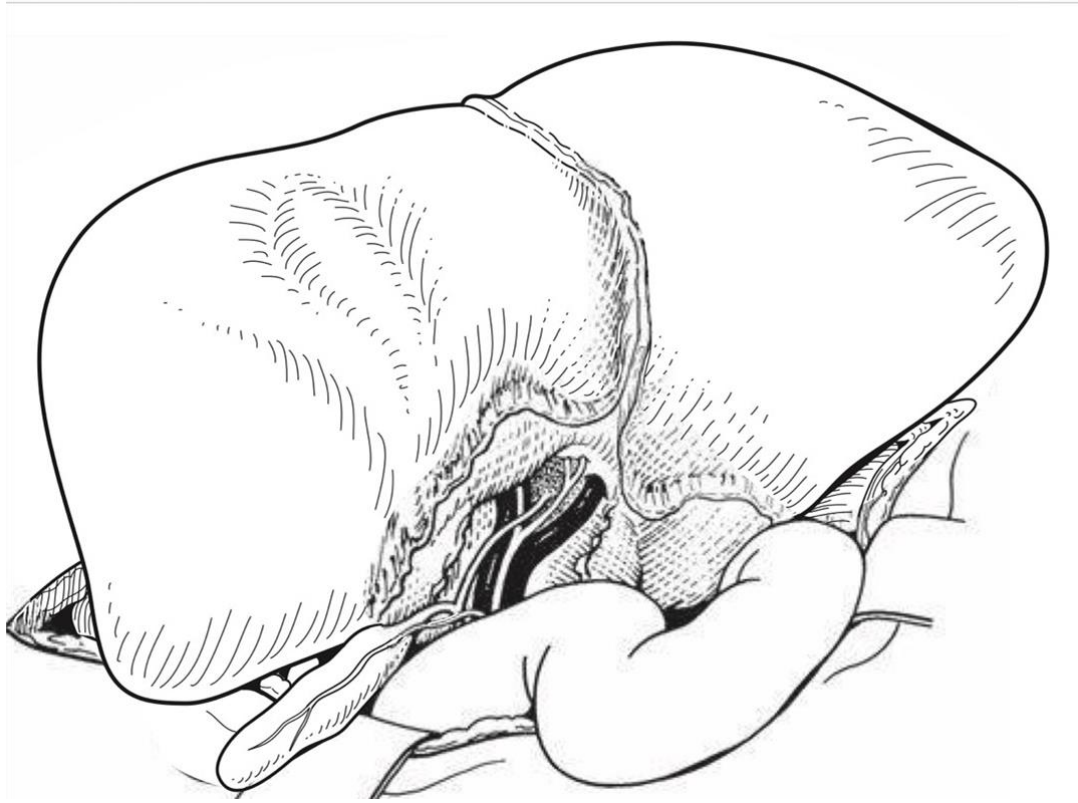
Confirm diagnosis



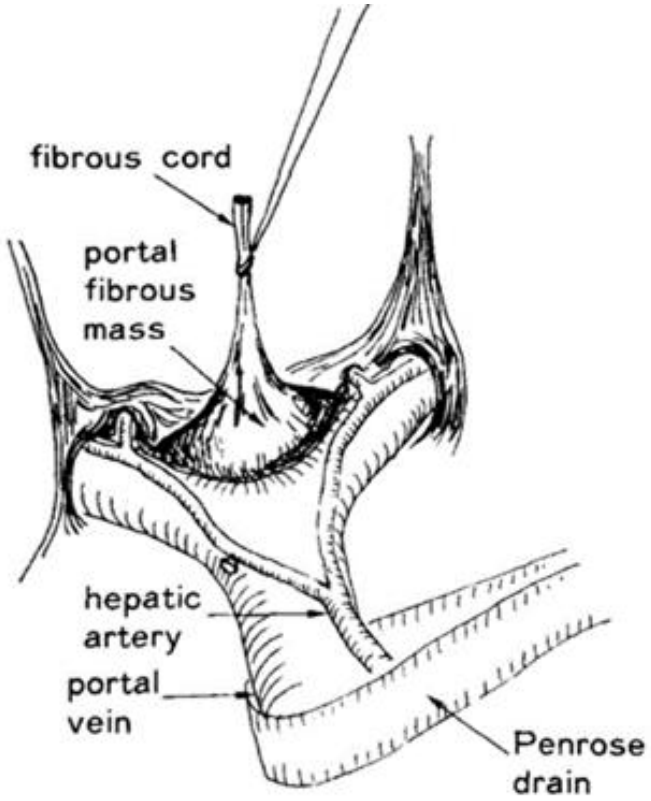
- Inspection
  - no bile or only clear mucus in gallbladder
- Intraoperative cholangiogram
- Presence of other anomalies
- Assess degree of liver
- Liver biopsy

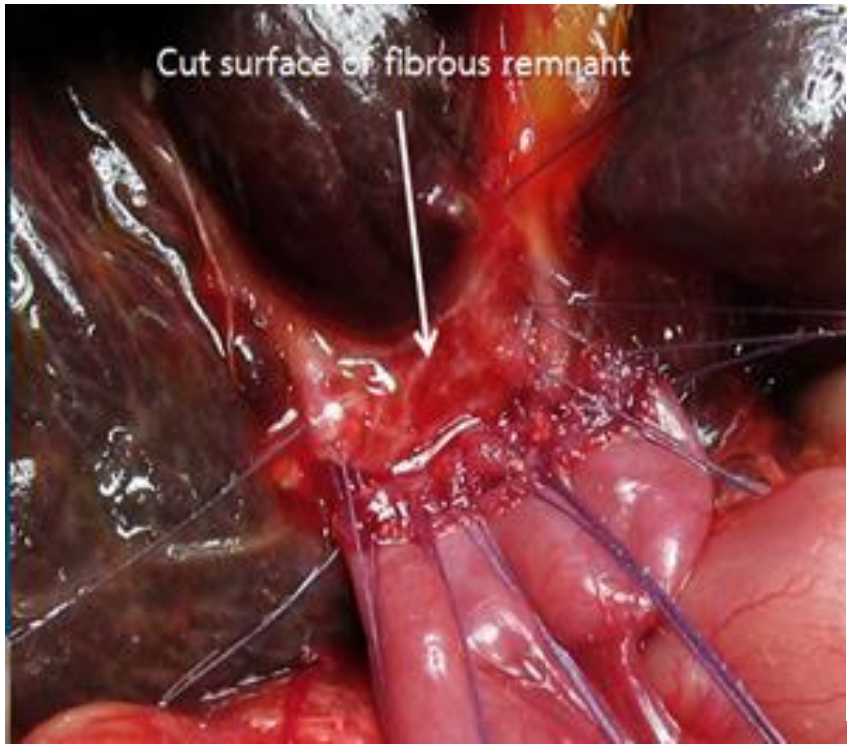
Mobilisation of liver

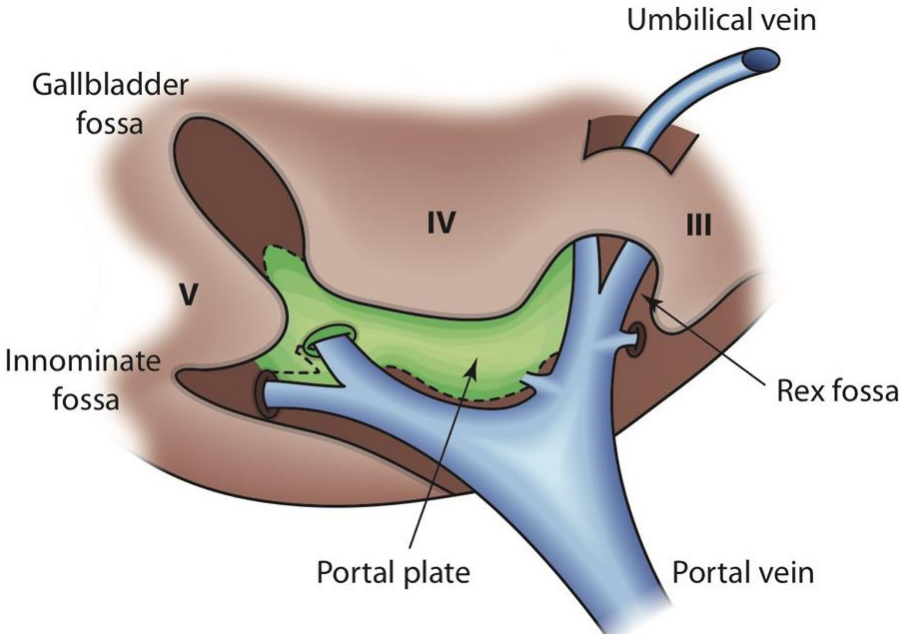
- **Divide**
  - Falciform ligament
  - Left triangular ligament
  - Deliver and evert liver into wound



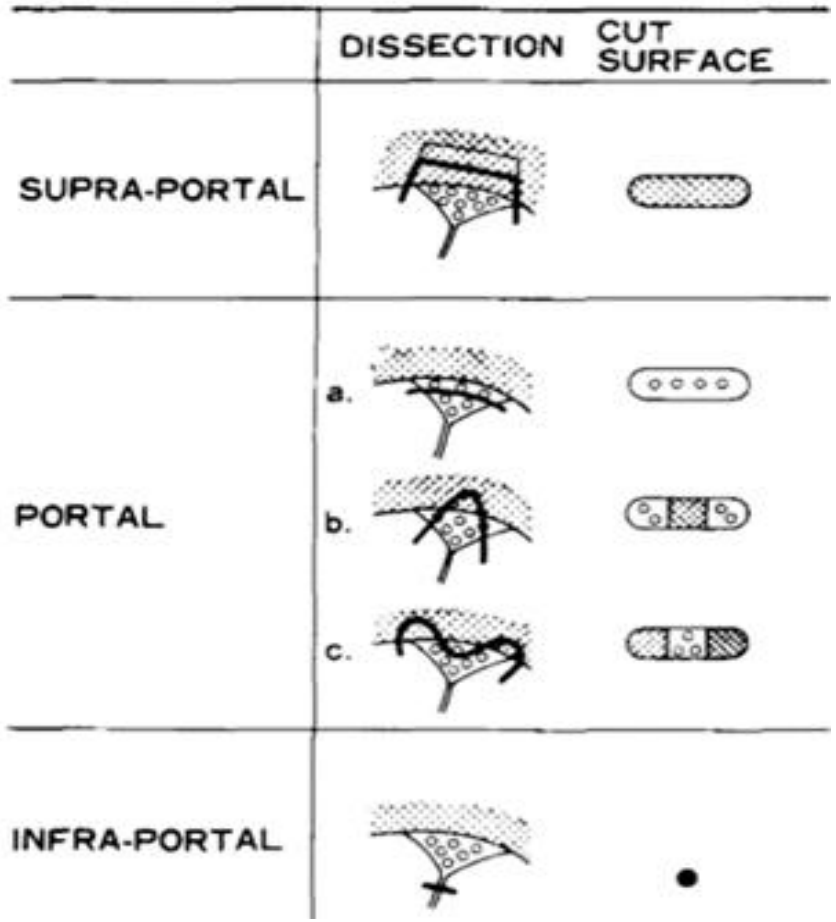
Portal dissection : to expose portal fibrous mass







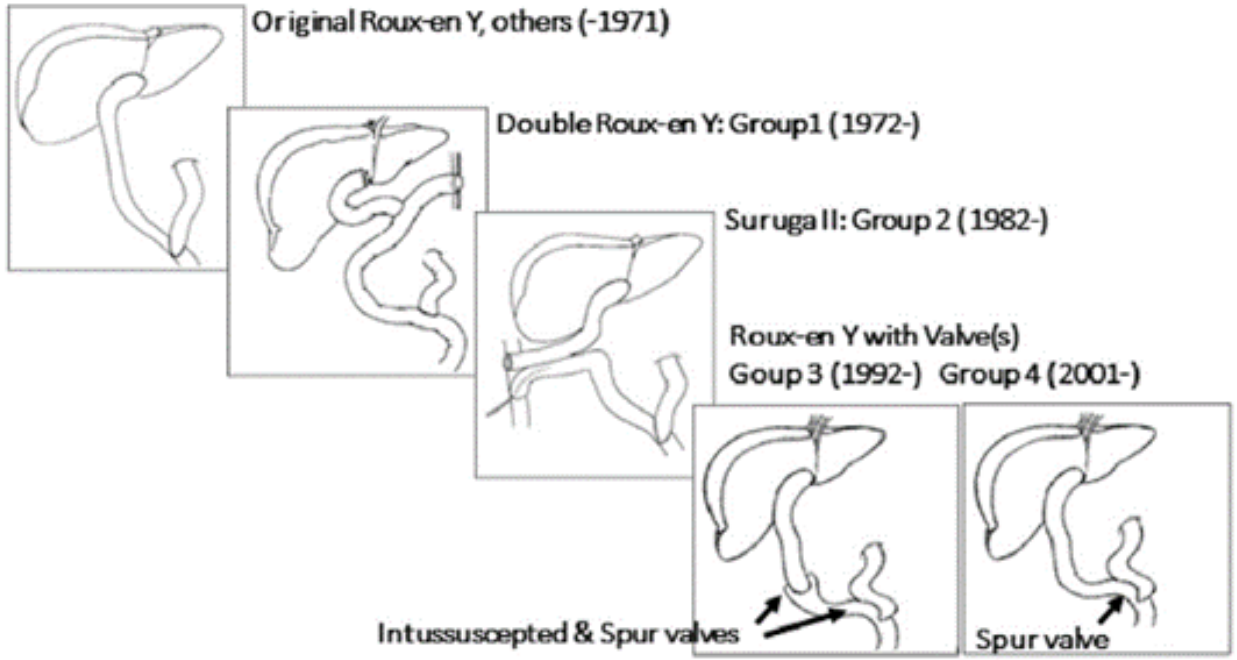
Porta hepatic dissection



1979 Kimura : n 37 BA patient

Hepatic portal disection	Success bile drainage	2 year Survivor
Supra portal	11%	0/9
Portal	76%	8/25
Infra portal	0%	0/3

Kimura K. J Pediatr Surg 1979;14:27-32



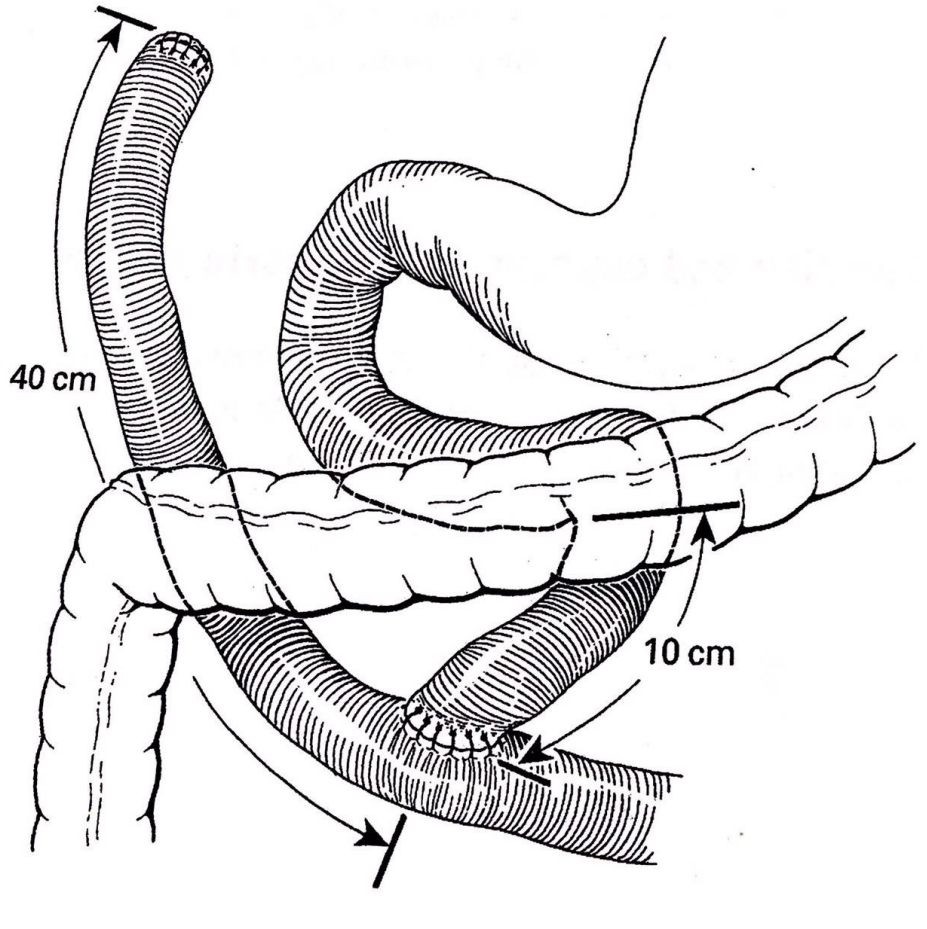
Rox-en Y with moderately deep dissection best result

	Group 1	Group 2	Group 3	Group 4	P value
jaundice clearance rate	65.9%,	77.5%	63%	87.2%	0.042
incidence of early chonlangitis	60.4%	53.8%	37%	23.1%	0.0002

Nio M, Wada M, Sasaki H, Kazama T, Tanaka H, Kudo H. . J Pediatr Surg 2016;51:2105-8

Roux loop preparation

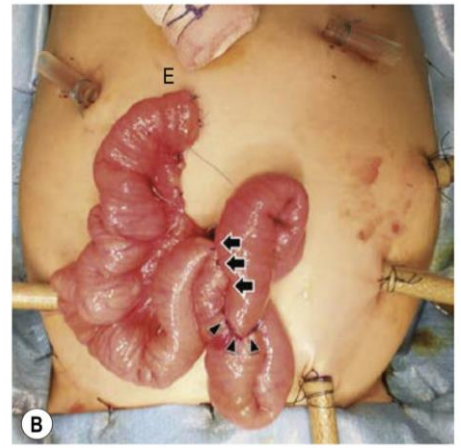
- Identify point 10 cm from duodenojejunal junction
- Divided bowel using stapled linear cutter
- Roux loop measured 40 cm
- End to side jejunal anastomosis



	Con-sensus	No con-sensus
Kasai procedure/technical aspects		
Transverse laparotomy	+	
Liver mobilisation	+	
Separation and looping of hepatic arteries and portal vein		+
Exposure of the Rex fossa	+	
Extensive dissection of the fibrotic plate to portal bifurcation	+	
Transection plane/not into liver	+	
Ligation of additional arteries		+
Portoenterostomy with end-to-side anastomosis		+
Placement of retrocolic Roux-en-Y loop	+	
40 cm length of the Roux-en-Y loop	+	
Stoma		+
Antireflux valve		+
Laparoscopic cholangiography		+
Laparoscopic Kasai (trial mandatory)	+	

- *Davenport M, Ure BM, Petersen C, Kobayashi H. Surgery for biliary atresia--is there a European consensus? Eur J Pediatr Surg 2007;17:180-3*

Roux loop preparation



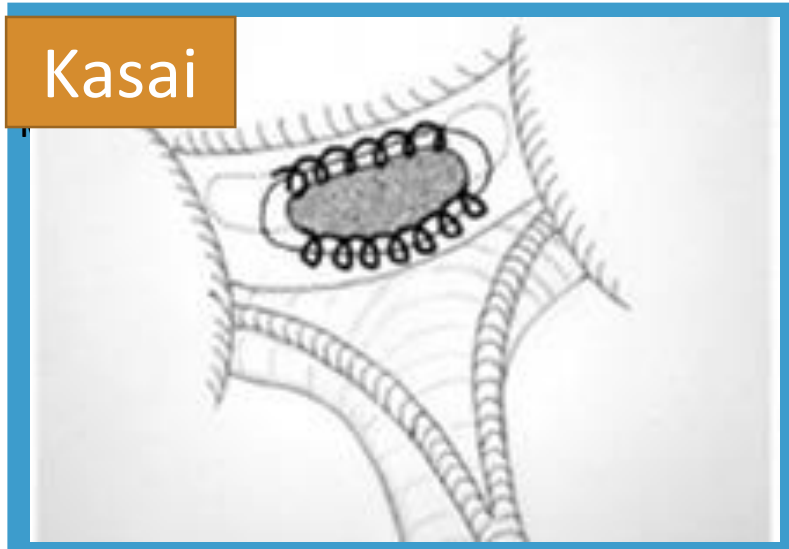
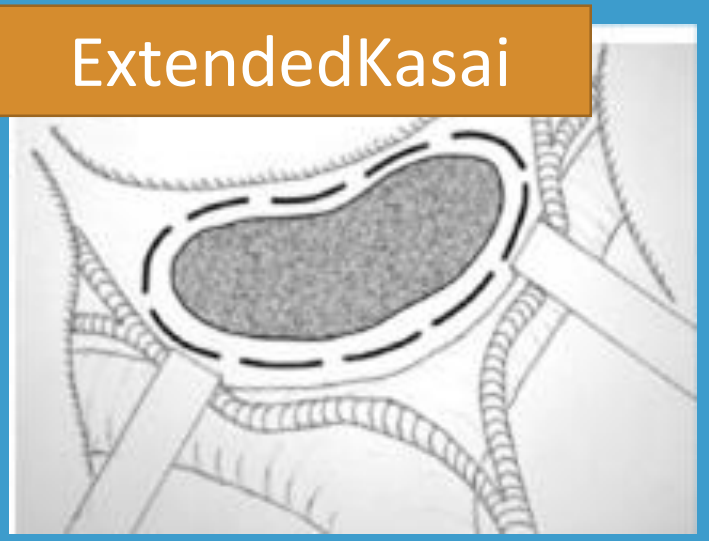
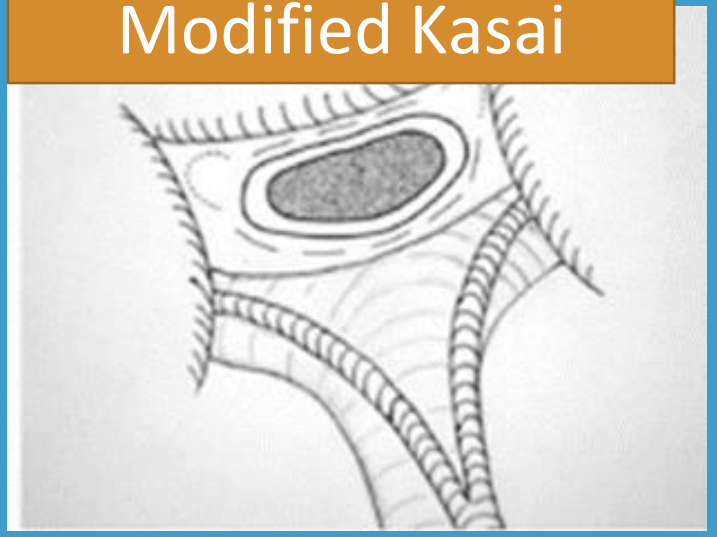
2018, Xiao : Prospective RCT

Table 2 – Outcomes of the two groups after Kasai portoenterostomy

	LRLG (91)	SRLG (75)	P
Clearance of jaundice	45.1% (41/91)	50.7% (38/75)	0.47
Total postoperative cholangitis	42.9% (39/91)	46.7% (35/75)	0.62
Intestinal obstruction	2	3	
Esophageal variceal bleeding	1	1	
Bile/pancreatic leaks	1	0	
Anastomotic stenosis	0	1	
Overall complication rate (%)	4.4% (4/91)	6.7% (5/75)	0.76
Reflux of Roux loop	3/35	2/30	1.00
rowheadNative liver survival rate			
1 y	87.9% (80/91)	90.7% (68/75)	0.57
2 y	80.2% (73/91)	78.7% (59/75)	0.81

Xiao H. J Surg Res 2018;232:492-6

Portoenterostomy

Kasai	ExtendedKasai	Modified Kasai
		
continuous suture	deep interrupted suture	shallow interrupted suture
Suture except 2 and 10 o clock , continuous suture at edge biliary remnant	Suture are necessary at2 and 10 o clock	Suture except 2 and 10 o clock ,suture outer edge of transected biliary remnant
Dissected around base biliary remnant	Extensive transected surface of fibrous cone	Dissected around base biliary remnant

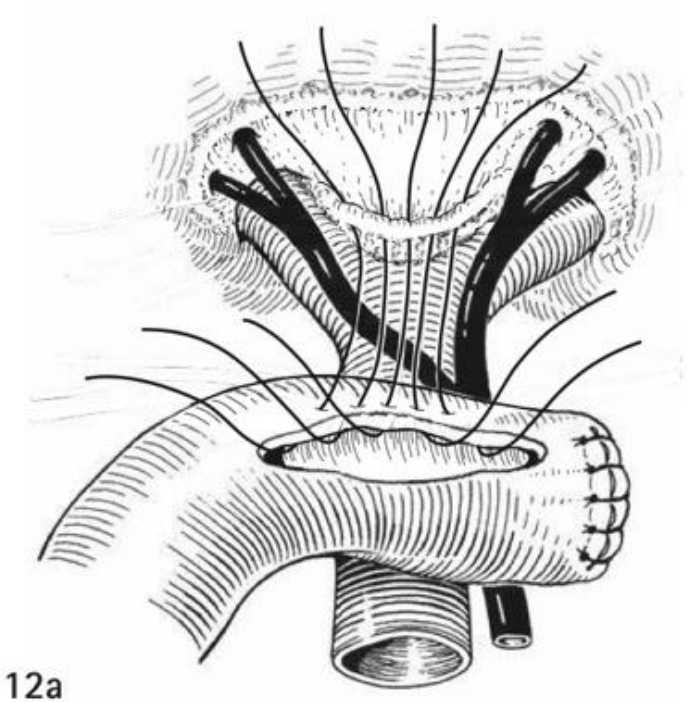
- *Yamataka A, Lane GJ, Cazares J. Semin Pediatr Surg 2012;21:201-10.*

Portoenterostomy

	Modified Kasai	Extended Kasai	value
Body weight (kg)	4.1 ± 0.9	5.4 ± 1.8	0.05
Age at PE (days)	66.9 ± 24.1	63.8 ± 22.8	0.8
Jaundice-clearance ratio (%)	90.9 (10/11)	46.2 (6/13)	0.02*
Time taken for jaundice clearance (days)	45.2 ± 14.6	41.3 ± 18.2	0.65
Steroid dosage required for jaundice clearance (mg/kg)	52.2 ± 32.5	73.5 ± 22.6	0.7
Survival rate of cases with native livers (%)	90.9 (10/11)	30.8 (4/13)	0.003*
Survival rate of cases with native livers after jaundice clearance (%)	72.7 (8/11)	30.8 (4/13)	0.04*
Incidence of cholangitis (%)	36.4 (4/11)	28 (5/13)	0.9
Liver transplantation ratio (%)	9.1 (1/11)	69.2 (9/13)	0.003*

- *Yamataka A, Lane GJ, Cazares J. Laparoscopic surgery for biliary atresia and choledochal cyst. Semin Pediatr Surg 2012;21:201-10.*

Portoenterostomy



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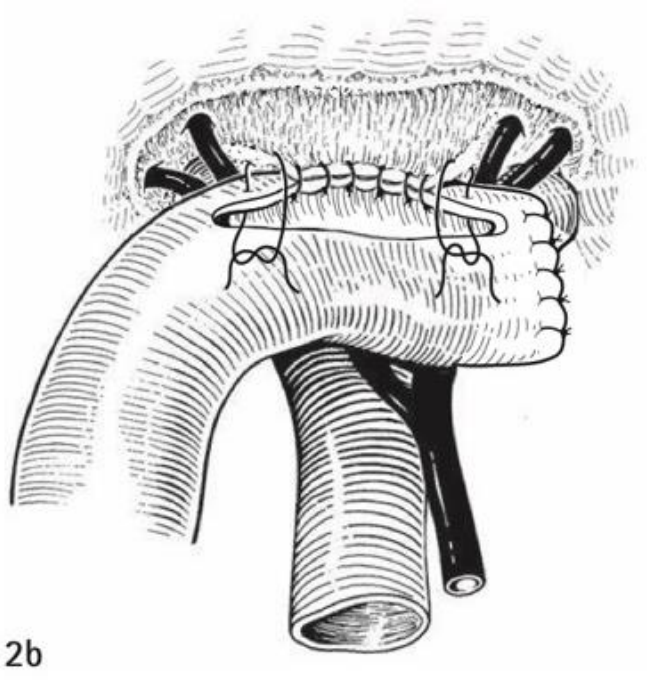


12b

6 Post op management

Post operative management

Cholagogue

Oral cholagogues;

1. Ursodeoxycholic acid
2. Aminoethylsulfonic acid

Ursodeoxycholic acid 15-30 mg/kg/day

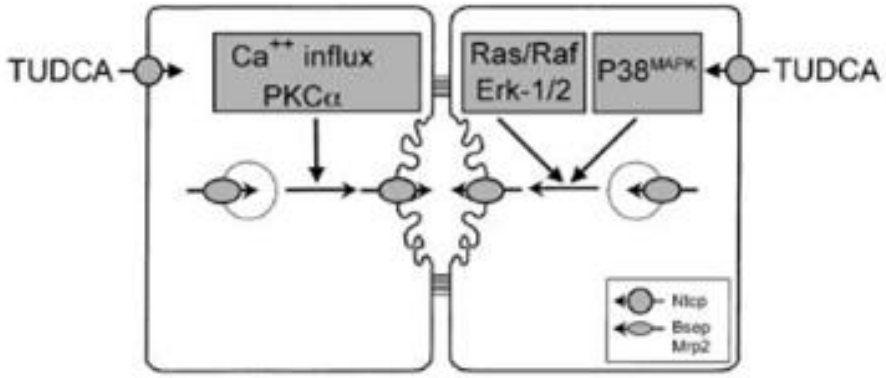
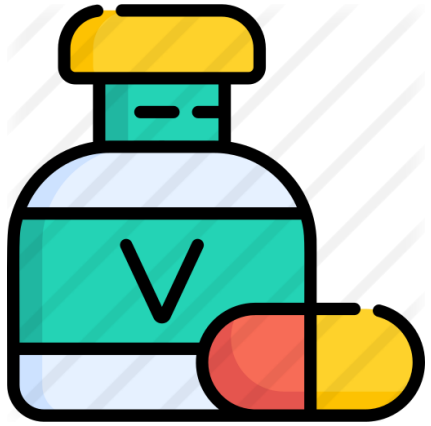


Fig. 1. Experimental model of TUDCA-induced stimulation of hepatocellular secretion. TUDCA, taken up into the hepatocyte by the Na^+-taurocholate cotransporting polypeptide (Ntcp), stimulates apical vesicular exocytosis and insertion of key canalicular transporters such as the conjugate export pump, Mrp2, and the bile salt export pump, Bsep, via Ca^{2+}- and PKCα-dependent mechanisms[15,17] or via activation of $p38^{MAPK}$ and Ras-, Raf-, Erk-1/2-dependent mechanisms[24,26] (for details, see text).

Paumgartner G, Beuers U.. Hepatology 2002;36:525-31.

Fat soluble Vitamin

- Fat-soluble vitamins (A, D, E, and K) must be supplemented
- These vitamins are usually deficient in cholestatic infants



Role of Corticosteroid

- 2007 :Davenport. Randomized control trial

Table 2. Measures of the Primary Outcome

	Prednisone (n = 34)	Placebo (n = 37)	P
6 months			
Transplantation	4 (12%)	5 (13%)	0.99*
Normal bilirubin	16 (47%)	18 (49%)	0.89
12 months			
Transplantation	9 (26%)	13 (35%)*	0.47
Normal bilirubin	17(50%)	15 (40%)	0.35

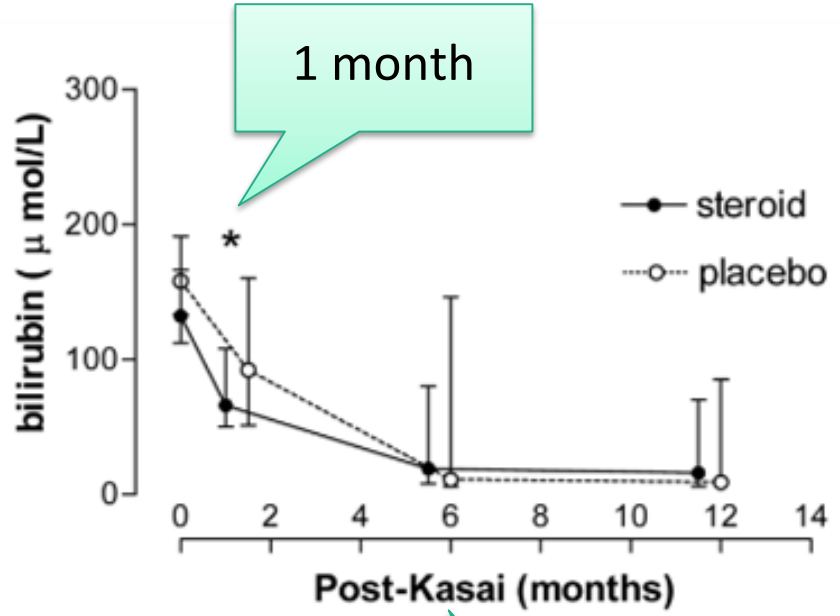


Fig. 1. Postoperative median (interquartile) bilirubin in the steroid group (n = 34) versus the placebo group (n = 37). *P = 0.06.

No significant difference between the low dose steroid and placebo groups

Davenport M. J Hepatol 2013;59:1054-8

Role of Corticosteroid

2014 : Bezerra Randomized control trial

No significant difference between the high dose steroid and placebo groups

Table 3. Primary and Secondary End Points

	No. (%) of Participants				
	Steroids (n = 70)	Placebo (n = 70)	Adjusted RR (95% CI)	Adjusted HR (95% CI)	*P* Value
At 6 mo posthepatoportoenterostomy[a]					
Total bilirubin <1.5 mg/dL and survival with native liver	41 (58.6)	34 (48.6)	1.14 (0.83-1.57)[b]		.43
Total bilirubin <1.5 mg/dL	43 (61.4)	38 (54.3)	1.14 (0.82-1.58)[c]		.44
Survival with native liver	55 (78.6)	52 (74.3)	1.06 (0.82-1.36)[c]		.66
Alive	68 (97.1)	68 (97.1)	1.00 (0.94-1.06)[c]		.98
At 24 mo posthepatoportoenterostomy[d]					
Survival with native liver and total bilirubin <1.5 mg/dL	49.4%	39.8%		0.8 (0.5-1.2)	.29
Survival with native liver	58.7%	59.4%		1.0 (0.6-1.8)	.99

Bezerra JA, et al. JAMA 2014;311:1750-9

Role of Corticosteroid

- 2018, Alonso : Impact of Steroid therapy on early growth
  - Steroid therapy associated with lower length, head circumference, weight
  - Unsuccessful HPE
    - growth trajectory for length, and weight were abnormal but not significantly impact by steroid
  - Successful HPE
    - Strong effect of steroid in length and weight
    - Improve growth velocity at 3-6 month
    - Expose to steroid will effect recovery of growth

Alonso EM, et al. J Pediatr 2018;202:179-85.e4

Role of Corticosteroid

- American association for the study of liver Disease(AASLD) 2014 recommend

Steroid can be use but High-dose corticosteroid therapy initiated within 72 hours of HPE is not recommended.

Squires RH, et al. J Pediatr Gastroenterol Nutr 2014;59:112-31

7 Outcome

Outcome and Result

- The earliest measurable outcome is **“Clearance of jaundice”**

Successful Kasai : resolved from jaundice

Failed Kasai: Total bilirubin remain more than 2 mg/dL at 6 months

Outcome and Result of Kasai

1. Good outcome (40-60%)

Resolved from jaundice TB < 2 mg/dL, Normal growth

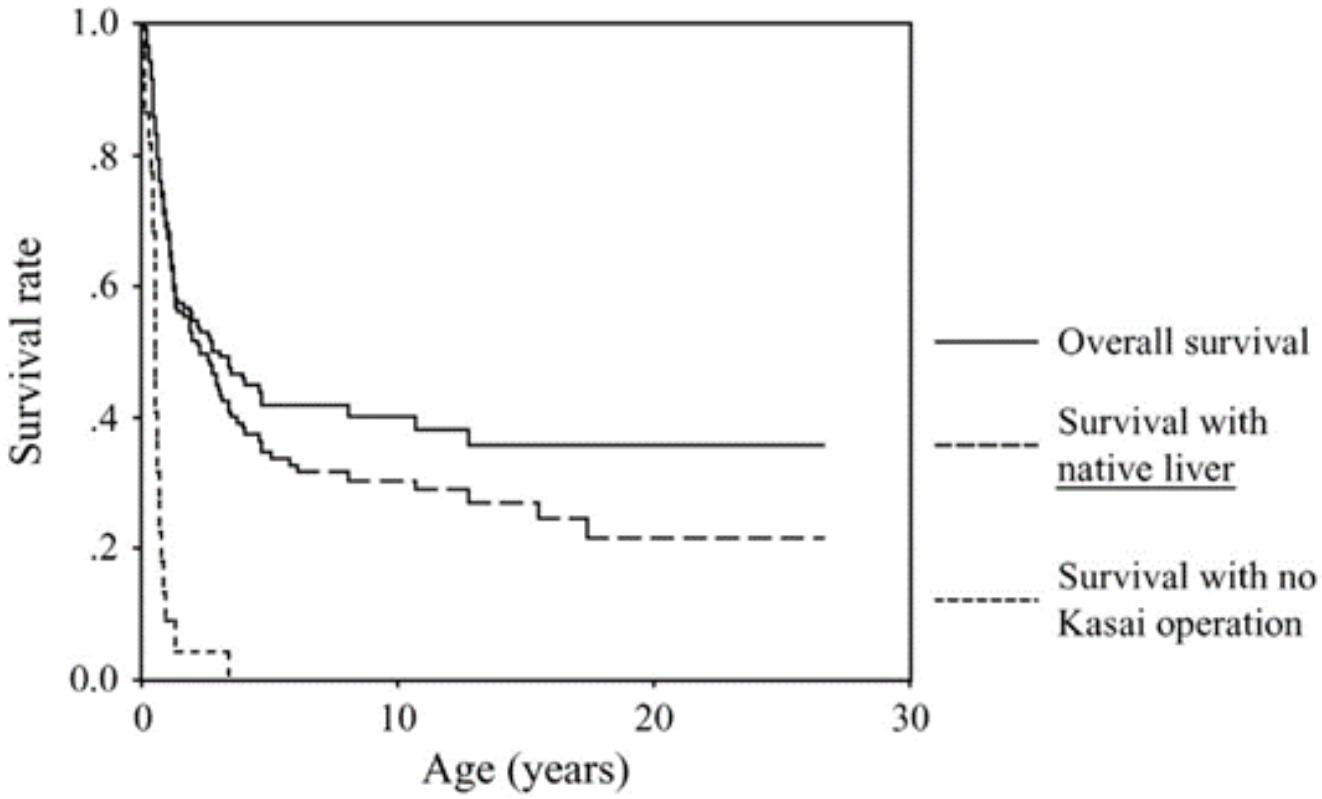
2.Fair outcome (20-30%)

- Able to clear bile but remain jaundice TB > 2 mg/dL
- Chronic Liver inflammation >> decompensated liver cirrhosis (2-5 Y)
- Need liver transplant later

3. Poor outcome (20-30%)

- Liver cirrhosis with no response to surgery
- Need early liver transplant

Outcome and Result



- BA without surgery lived < 2 years due to biliary system inflammation
- After biliary drainage the inflammation continues >> liver cirrhosis
- 20-40% of BA with Kasai operation lived for > 20 yr with native liver

Hung PY, et al. J Pediatr Gastroenterol Nutr 2006;42:190-5

Outcome and Result

- 2013, Bijl :Long term outcome Kasai operation

Table 2. *Analysis of the population*

	Number
Total population >20 years	184
Death	8 (4.3%)
Alive with Ltx	14 (7.6%)
Alive without Ltx	162 (88%)
Without complications	64 (39.5%)
With complications	98 (60.5%)
Cholangitis	98 (100%)
Portal hypertension	78 (80%)
Gastrointestinal bleedings	35 (45%)
Hepatocellular carcinoma	1 (1.3%)

Ltx = liver transplantation.

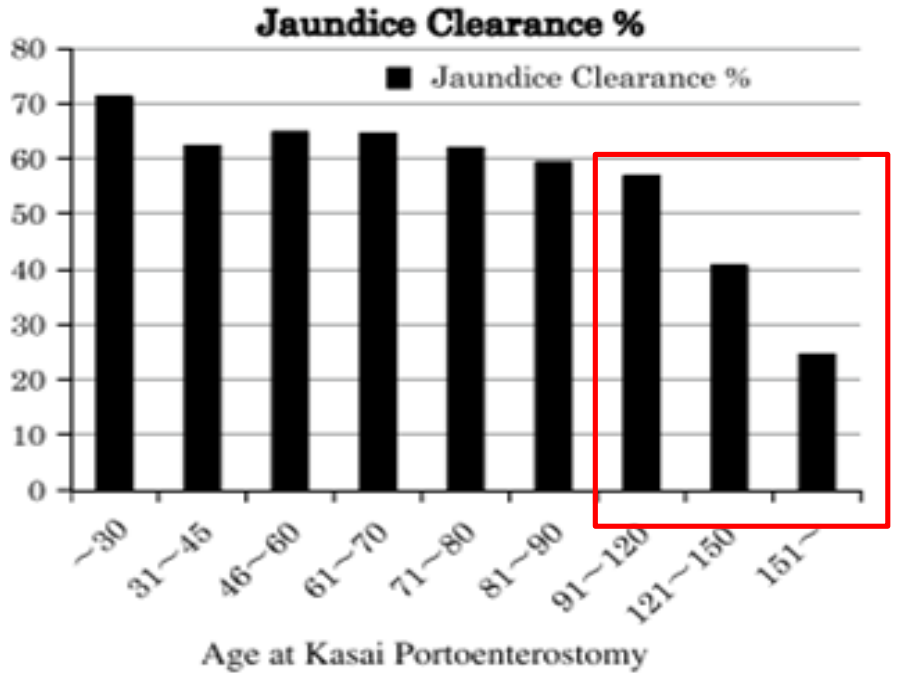
Bijl EJ, Bharwani KD. Neth J Med 2013;71:170-3

Factors that affect outcome

1. Age at initial operation

Age less than 60 day has better outcome

2013 Japanese biliary atresia society
: BA N= 2600



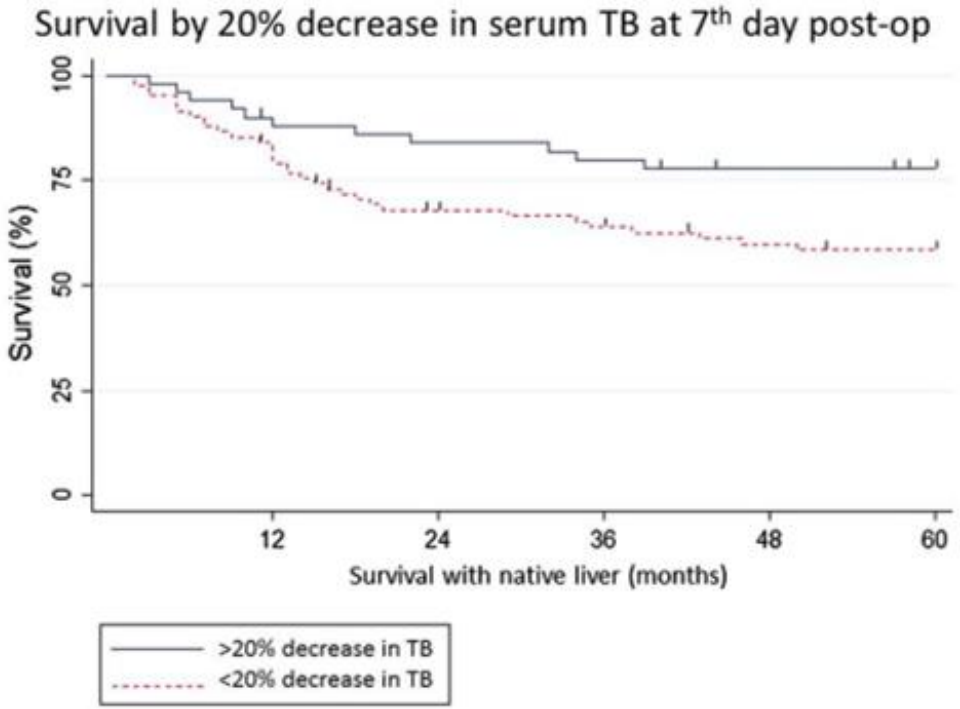
Japanese biliary atresia society. Jpn J Pediatr Surg. 2013;49:277–89

Factors that affect outcome

2. Serum bilirubin after 7 day after surgery

- 2016, Chusilp : Prognostic values of serum bilirubin at 7th day

20 % decrease in serum TB at 7th day post-Kasai predict good outcome



Chusilp S, et al. Pediatr Surg Int 2016;32:927-31

Factors that affect outcome

3. **Experience of the institute** ; > 5 cases/ year
4. **Size of bile canaliculi at portal plate**; > 150 micron
5. **Type of BA** ;

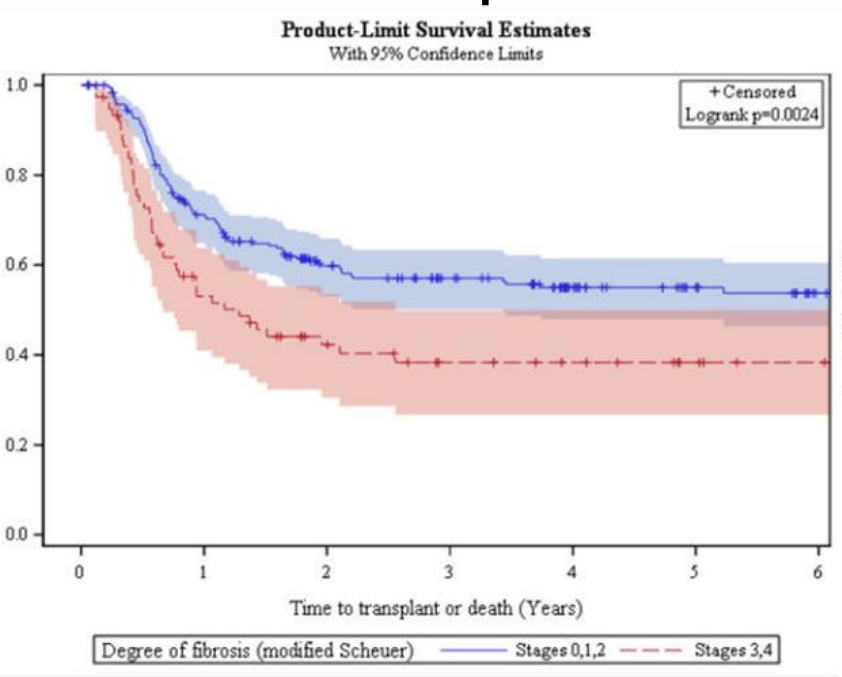
    Type I,II has better prognosis in jaundice clearance and survival

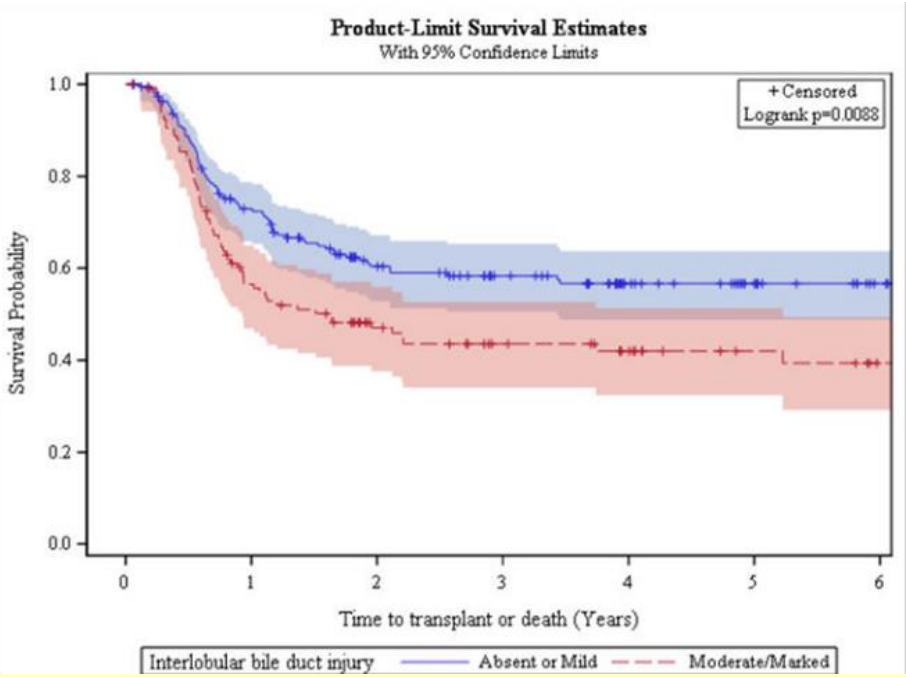
Pediatic surgery. 7*th ed*. *Edinburgh*: *Elsevier;* 2020

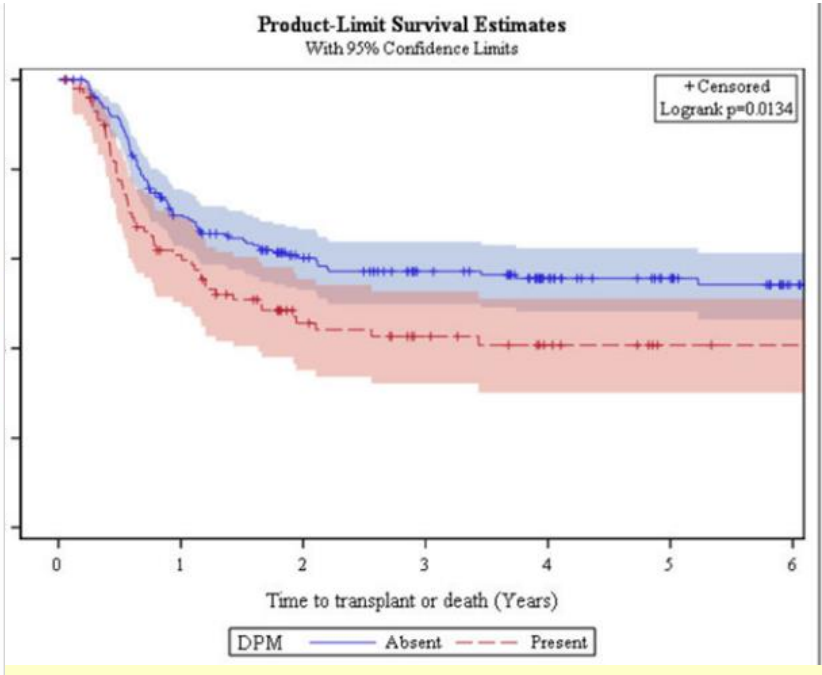
Factors that affect outcome

6. **Pathology;** Higher Hazard Ratio in

- Fibrosis stage 3,4
- Moderate to marked interlobular bile duct injury
- Ductal plate malformation







Russo P, et al.. Am J Surg Pathol 2016;40:1601-15

Factors that affect outcome

2004 Davenport : retrospective review

Table 1. Relationship of Histologic Criteria to Outcome

Histologic Feature	Alive	Dead/OLT	Significance	PPV	NPV
Fibrosis					
4	4	7			
<4	4	7	$P = .67$	-	
Cholangiolar bile duct destruction					
3	0	4			
<3	8	10	$P = .13$	100%	56%
Parenchymal cholestasis					
3	2	3			
<3	6	11	$P = .62$		
Bile duct destruction					
Yes	5	9			
No	3	5	$P = .64$		
Giant cell transformation					
Yes	5	6			
No	2	9	$P = .18$	55%	88%

No histologic criteria had any bearing on outcome either in terms of clearance of jaundice

Davenport M. J Pediatr Surg 2004;39:575-81

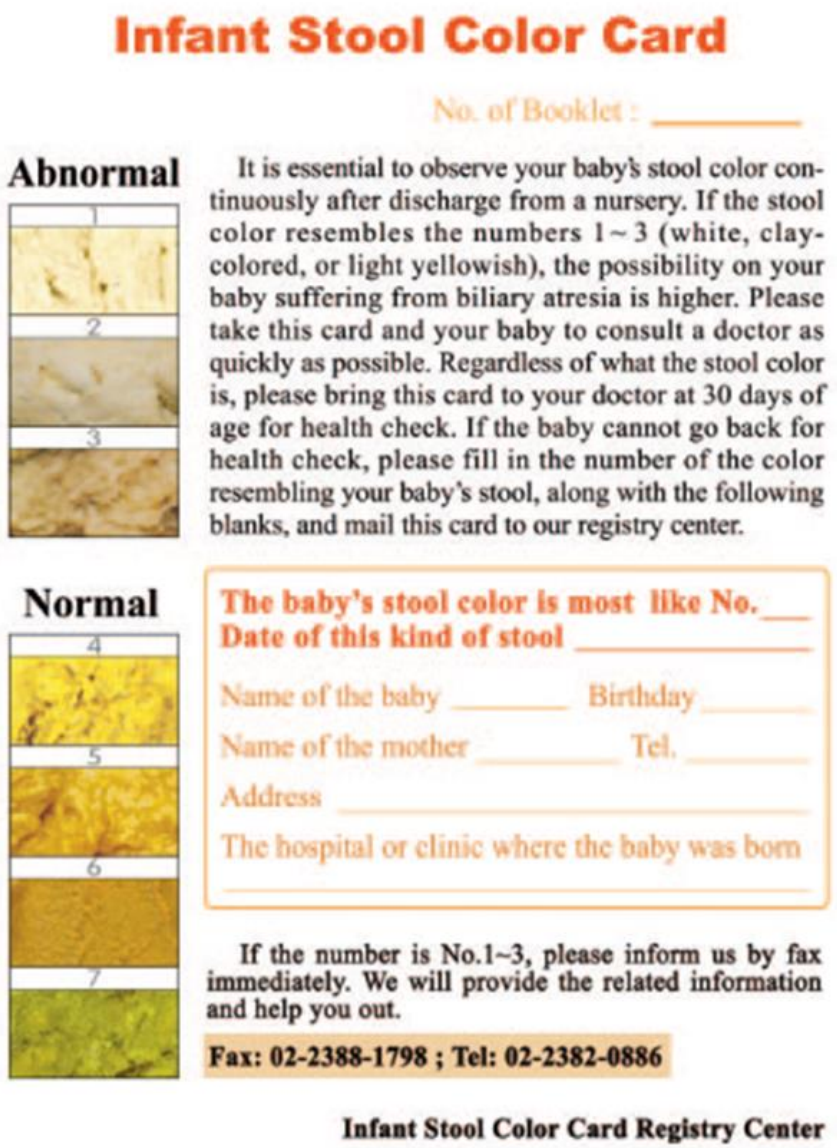
8 Screening

Post natal screening

- **Stool color card**
- Use series of stool picture for early screening
- Observe stool for 1 month

Sensitivity 88%

Specificity 99%



Infant Stool Color Card

No. of Booklet : _____

Abnormal

1

2

3

It is essential to observe your baby's stool color continuously after discharge from a nursery. If the stool color resembles the numbers 1 ~ 3 (white, clay-colored, or light yellowish), the possibility on your baby suffering from biliary atresia is higher. Please take this card and your baby to consult a doctor as quickly as possible. Regardless of what the stool color is, please bring this card to your doctor at 30 days of age for health check. If the baby cannot go back for health check, please fill in the number of the color resembling your baby's stool, along with the following blanks, and mail this card to our registry center.

Normal

4

5

6

7

The baby's stool color is most like No.___
Date of this kind of stool _____

Name of the baby _____ Birthday _____

Name of the mother _____ Tel. _____

Address _____

The hospital or clinic where the baby was born _____

If the number is No.1~3, please inform us by fax immediately. We will provide the related information and help you out.

Fax: 02-2388-1798 ; Tel: 02-2382-0886

Infant Stool Color Card Registry Center

Chen SM, et al.. Pediatrics 2006;117:1147-54.

9 Complication

Complications of hepatic portoenterostomy

- **Cholangitis**
  - Most common 33-60%

- Prompt treatment with Intravenous broad-spectrum antibiotic
- Recurrent attack cause progressive liver cirrhosis

Decharun K, Leys CM, West KW, Finnell SM.. Clin Pediatr (Phila) 2016;55:66-72.

Postoperative Cholangitis Prevention

- 2016 Katawaetee Decharun : systematic review
- Prophylactic antibiotic for prevention of Cholangitis
- No study to date provides satisfactory evidence for its benefit.
- Prospective studies determining the value of antibiotic prophylaxis are needed.

Katawaetee D. Cliin Pediatric 2016

Postoperative Cholangitis Prevention

- 2003, Ling Nan Bu :Prophylactic antibiotic in prevention of recurrent cholangitis
  - 19 BA in 1997-2000 who had one episode of cholangitis
    - 9 cases: TMP/SMZ (TMP 4mg/kg/d and SMZ 20mg/kg/d, divided in 2 dose)
    - 10 cases: neomycin(25mg/kg/d, qid)
  - 18 BA in 1991-1196 who had cholangitis but not put on long-term prophylaxis,

Table 2. Comparisons of the Recurrence Rates of Cholangitis in the Three Groups

Group	RRR	*P* Value	95% CI
Control	1		
TMP/SMZ	0.52	.042	0.28-0.98
Neomycin	0.42	.011	0.22-0.82

Abbreviations: RRR, recurrence rate ratio; CI, confidence interval.

TMP/SMZ decreased Cholangitis recurrence and prolonged the next Cholangitis event

10 Role of liver transplant

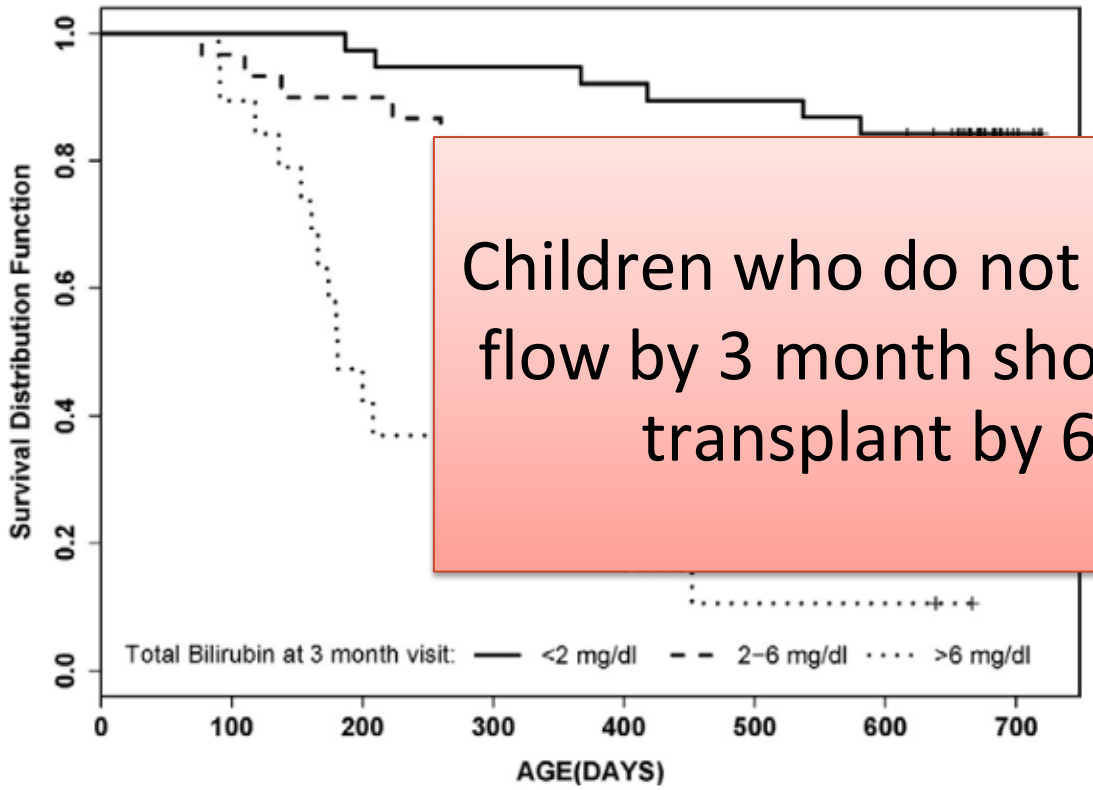
Role of liver transplant

- Biliary atresia is the most common cause of liver transplant in children

Indication for liver transplant

1. Failed Kasai portoenterostomy
2. Primary liver transplant
3. Recurrent bacterial cholangitis
4. Failure to thrive
5. Liver Cirrhosis and complication of cirrhosis
6. Hepatic malignancy

Failed Kasai



TB < 2 mg/dL 2year transplant free surviaval 84%

Children who do not demonstare good bile flow by 3 month should evaluate for early transplant by 6-9 month of age

ar transplant
%

Shneider BL, Brown MB, Haber B, Whitington PF, Schwarz K, Squires R, et al. J Pediatr 2006;148:467-74

Recurrent bacterial cholangitis

- 40–80% of patients with KPE experience at least one episode of bacterial cholangitis before the age of 2 years

- repeated cholangitis increased 3-fold risk for early failure after KPE

Liver transplant should be considered in
recurrent cholangitis despite aggressive antibiotic, multi-resistant bacterial organisms, episodes of life-threatening sepsis, severely impaired quality of life

Failure to thrive

- Children with poor bile drainage develop significant malabsorption, protein-energy malnutrition, growth failure and developmental delay
- The presence of failure-to-thrive requiring aggressive nutritional support or unremitting bone disease should prompt liver transplant evaluation

Liver Cirrhosis and complication of cirrhosis

- Inflammation still progress after Kasai opearation
- Some patient turn cirrhosis with complication
  - Variceal bleeding
  - Hepatorenal syndrome
  - Hepatopulmonary syndrome

Hepatic malignancy

- Hepatocellular carcinoma (HCC)

  ~1% of children with BA

  can occur as early as infancy
- Complete surgical resection is the only curative option
  chemotherapy may be more effective in children than adults
- Transplant should be considered in the absence of radiological evidence of extrahepatic disease regardless of size

Primary liver transplant

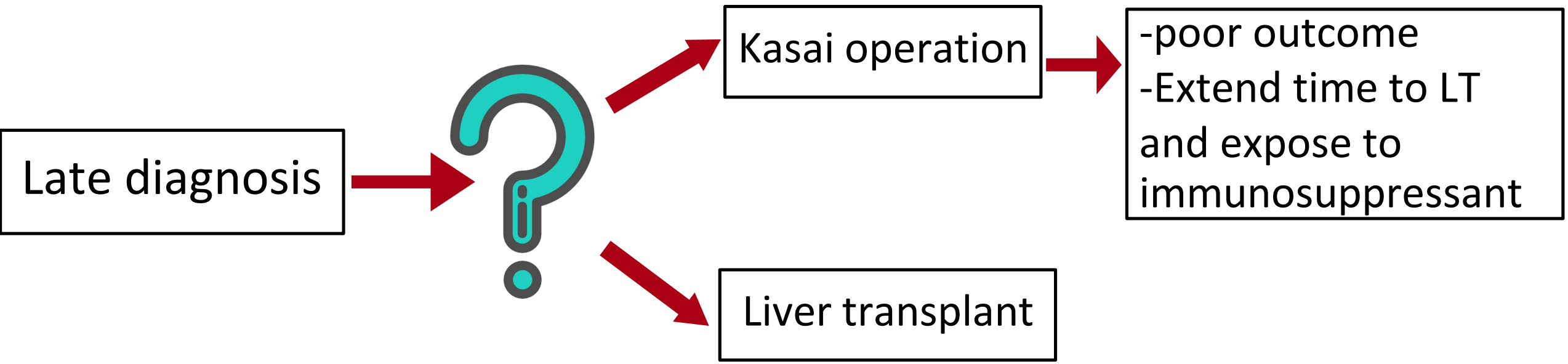
- Patient who deliver liver transplant without doing Kasai

Cirrhosis

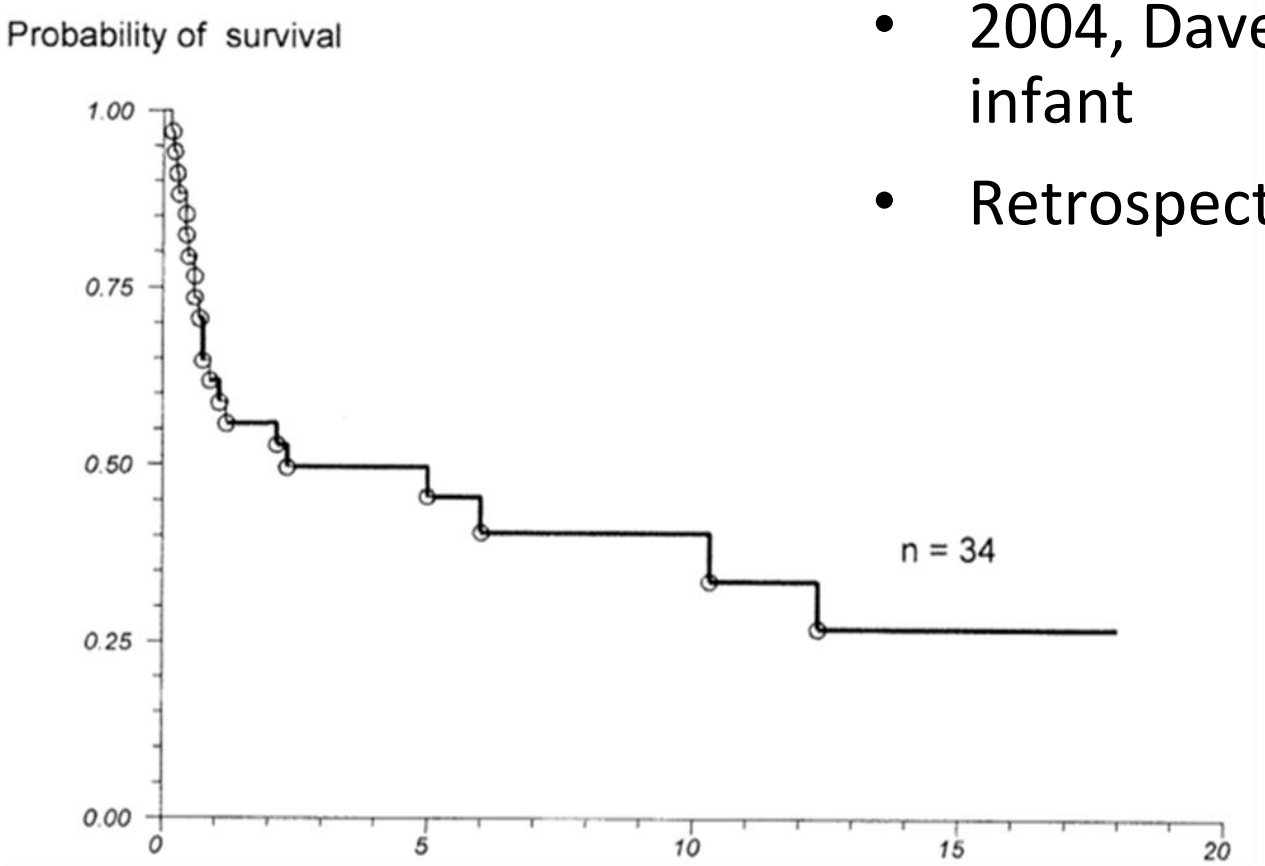
Primary liver transplant

Primary liver transplant

- Patient who deliver liver transplant without doing Kasai



Primary liver transplant



- 2004, Davenport : Outcome of older(>100 days) infant
- Retrospective review 422 BA , 35 pt age >100 day

5 year survival 45%
10 year survival 40%

Davenport M, et al. J Pediatr Surg 2004;39:575-81.

Primary liver transplant

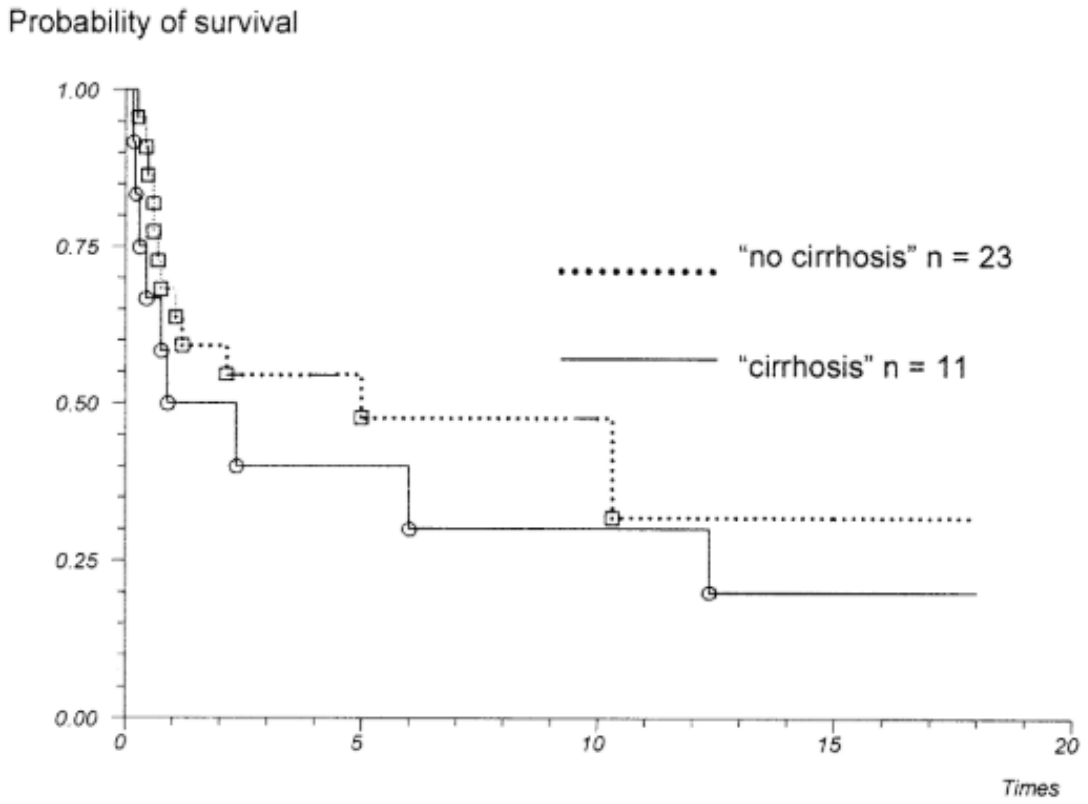


Fig 3. Effect of "cirrhosis" perceived at time of laparotomy.

There was no significant survival disadvantage in cirrhosis

Davenport M, et al. J Pediatr Surg 2004;39:575-81.

Primary liver transplant

- 2012, Alexopoulus : Impact of HPE on LT
  - Retrospective review 134 BA patient

Early failure (needed LT within 1st year of life)

Late failure (needed LT beyond 1st year of life)

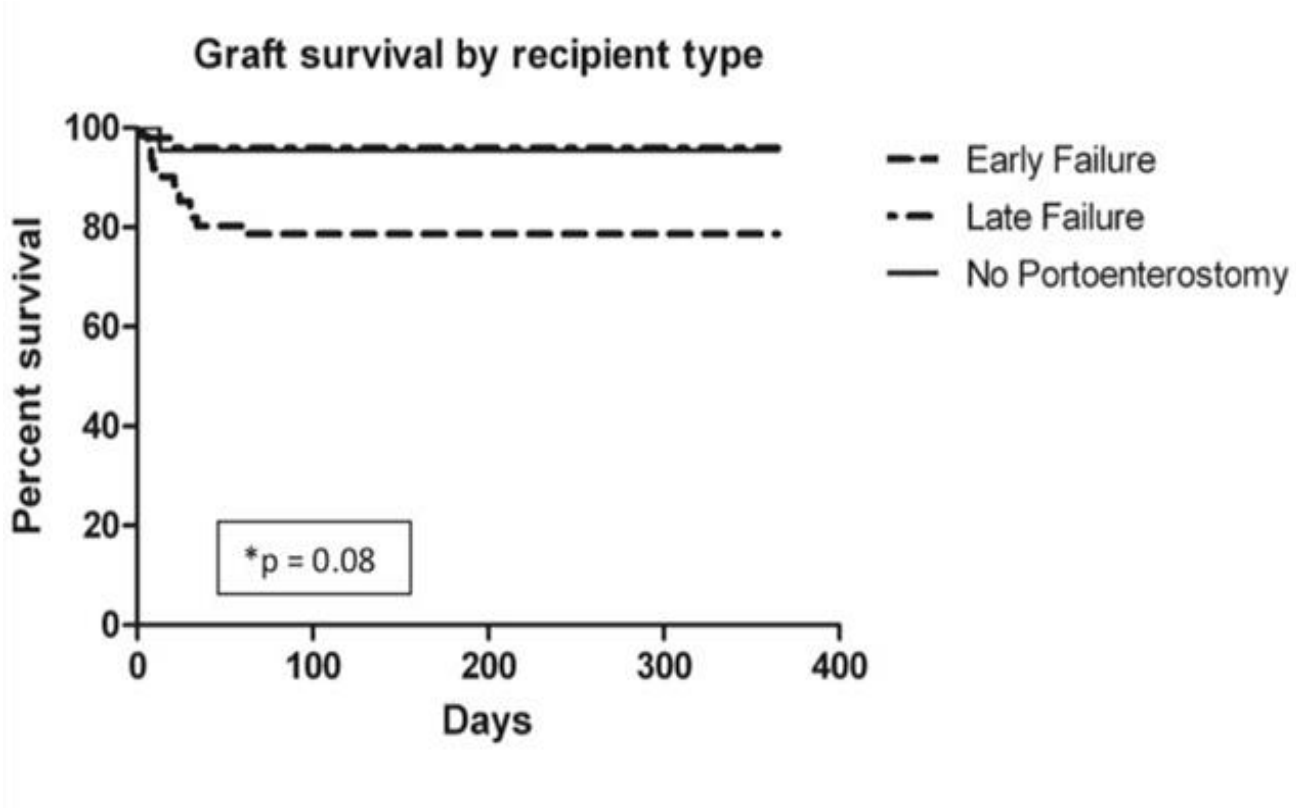
NPE (no Portoenterostomy)

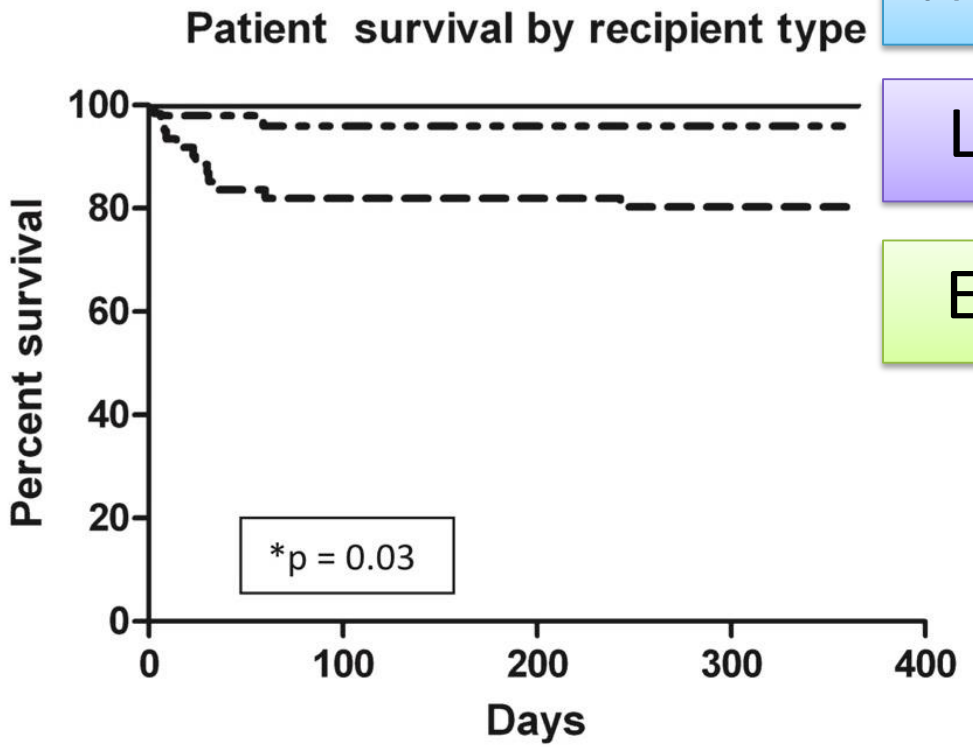
Table 1. Pre- and peri-operative characteristics by recipient type

	EF	LF	No portoenterostomy
Number	63	49	22
Age at portoenterostomy (days)	73 ± 36	75 ± 42	NA
Previous cholangitis (%)	41.7	42.9	NA
Median age at listing (days)	171*	269	158*
Age at transplant (days)	246 ± 59*	1076 ± 1270	333 ± 149*
Median time listing to transplants (days)	58*	261	76*
Height (cm)	64.2 ± 5.4*	87.3 ± 25.9	64.7 ± 4.6*
Weight (kg)	7.0 ± 1.5*	14.0 ± 11.2	7.3 ± 2.0*
Laboratory PELD	11.5 ± 8.4*	5.5 ± 9.0	13.6 ± 6.0*

Alexopoulos SP, et al. Pediatr Transplant 2012;16:373-8.

Primary liver transplant





NPE

LF

EF

EF has worst graft survival rate

EF significant lower one-year patient survival rate

Alexopoulos SP, et al. Pediatr Transplant 2012;16:373-8.

Primary liver transplant

Table 2. Post-operative outcomes by recipient type

	EF	LF	No portoenterostomy
Infectious complications			
Surgical site			
Intra-abdominal infection (%)	22.2	18.4	22.7
Soft tissue infection (%)	3.3	6.1	0.0
Blood stream			
Bacteremia (%)	23.0	8.2	4.5*
Sepsis (%)	11.5†	0.0	0.0

EF had significant incidence of bacteria , sepsis

EF has benefit in primary transplant

Alexopoulos SP, et al. Pediatr Transplant 2012;16:373-8.

Primary liver transplant

- 2015, Neto : Impact of Kasai on LT
- Retrospective cohort 347 BA patient
- 94 EF, 115 LF, 138 no HPE

TABLE 2. Posttransplant Outcomes in Patients With BA According to the Studied Groups

Variables	K-EF (n = 94)	K-LF (n = 115)	No-K (n = 138)	*P* Value
Biliary complications, n (%)	18 (19)	21 (18.3)	12 (8.7)	0.03
HAT, n (%)	6 (6.4)	4 (3.5)	8 (5.8)	0.62
Portal vein complications, n (%)	15 (16)	13 (11.3)	20 (14.5)	0.61
Reoperation for intestinal perforation, n (%)	5 (5.3)	9 (7.8)	2 (1.4)	0.04

Kasai operation increase risk of biliary complication and intestinal perforation

Neto JS, et al.. Liver Transpl 2015;21:922-7

Primary liver transplant

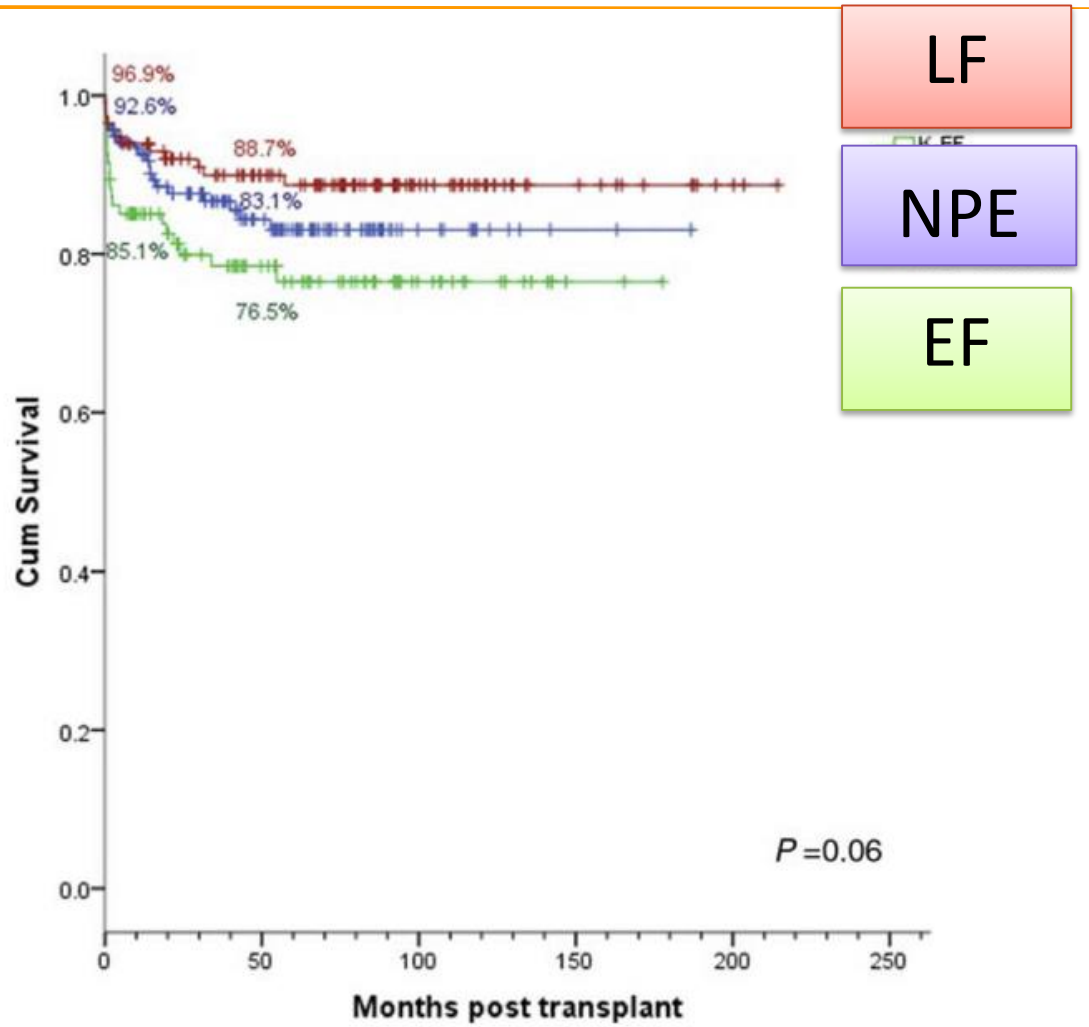


TABLE 5. Multivariate Cox-Regression Analysis: Effect of Kasai-PE on Patient Survival

Variables	HR	95% CI	*P* Value
Kasai-PE			
No Kasai-PE	-		
K-EF	1.21	0.57-2.58	0.61
K-LF	0.16	0.03-0.73	0.02
IOBT	1.01	1.0-1.02	0.06
WIT	0.95	0.91-0.99	0.04
HAT	6.11	2.4-15.58	<0.001

Neto JS, et al.. Liver Transpl 2015;21:922-7

11 Outcome of liver transplant

Outcome of liver transplant

- 2017, Kasahara
- 2085 case of BA in Japanese Liver transplant society 1989-2005

Number BA	Graft survival			
	1y	5y	10y	20y
2085	90.4%	87.9%	84.6%	82%

Kasahara M, et al.. Am J Transplant 2018;18:659-68

Conclusion

- Kasai Portoenterostomy is the main treatment for Biliary atresia
- Better prognosis in operations done before 60 days of age
- Early diagnosis and treatment is key factor
- Failed kasai , cirrhosis -> liver transplantation


Thank
you