The efficacy of surgical shunts to treat severe portal hypertension after a Kasai procedure for biliary atresia

Florent Guérin, Lionel Charre, Stéphanie Jasienski, Mathieu Duché, Stéphanie Franchiabella, Olivier Bernard, Emmanuel Jacquemin, Hélène Agostini, Frédéric Gauthier, Sophie Branchereau

LEVEL OF EVIDENCE:

Type of study: Therapeutic

Level of evidence III

ABREVATIONS :

BA: Biliary atresia

LT: Liver transplantation

PH: Portal hypertension

TIPS: Transjugular intrahepatic portosystemic shunts

SS: Surgical shunts

HE: Hepatic encephalopathy

HPS: Hepatopulmonary syndrome

PPH: Portopulmonary hypertension

OS: Overall survival

TFS: Transplant free survival

cBL: Conjugated bilirubin

tBL: Total bilirubin

GI: Gastrointestinal

EL: endoscopic ligation

INTRODUCTION:

Biliary atresia (BA) is the commonest indication for liver transplantation (LT) in children.The Kasai procedure is the treatment of choice of BA. Ten year survival with native liver following the Kasai procedure ranges from 35% - 46% (1,2). When the Kasai fails, liver transplantation is associated with a ten year overall survival ranging from 82% - 85%, whilst the ten year overall survival for the whole BA cohort ranges from 80 - 90% (1–4). Infection, rejection, non-observance, secondary malignancies and renal failure due to immunosuppressive drugs are associated with a poor outcome in children undergoing LT. The rate of second LT for BA at ten years is reported to range from 10 - 15%, and mortality in this subgroup is around 31% (4,5). In order to avoid the complications associated with LT, several strategies to increase the survival of BA patients with their native liver have proven to be effective. These include performing a Kasai procedure even with late presentations, and revising the Roux-en-Y when necessary (6,7).

Portal hypertension (PH) is a common complication occurring even after an initial successful Kasai procedure. The main risk associated with PH is upper gastrointestinal (GI) bleeding, which can be fatal or may lead to an acute liver failure necessitating an urgent LT. Management of PH and GI bleeding includes the use of beta blockers, endoscopic therapy, Transjugular Intrahepatic Portosystemic Shunts (TIPS), surgical shunts (SS), and LT (8-12). Prior to the era of transplantation, SS was commonly used for the patients with BA and PH. Following the establishment of paediatric liver transplant programs worldwide, many teams abandoned this technique. As a consequence, reported SS outcomes are scarce, despite the recommendation that this technique is employed in jaundice-free patients with BA and PH (11,13). SS may be considered either as a bridge or a definitive treatment to avoid LT. We wanted to assess the outcome of SS used to treat PH following a Kasai procedure, both before

and after the establishment of our transplant programme. We also sought to compare these results with TIPS and endoscopic treatment of varices, in order to determine when SS is indicated.

METHODS:

We collected data retrospectively between 1974 – 2014 for BA patients who had undergone a Kasai procedure, and who developed PH with either GI bleeding or high-grade oesophageal varices for which SS was performed. SS was performed in another centre by adult surgeons from 1974 - 1984, but were followed-up by our team. From 1984 SS was performed by paediatric surgeons at our centre. We decided to stopour SS for BA after 2014, waiting for the results of this present study. Data collected included demographics (age, gender, age at Kasai), symptoms of PH (GI bleeding, splenomegaly, oesophageal, gastric or stoma varices), platelets and liver function tests at diagnosis of PH. We also recorded the type of SS performed, and any short-term complications. All children received systematic heparin therapy for 10 days (100 UI/kg/day) and were maintained on a protein-restricted diet (1g/kg/day) for 6 months following SS. Assessment of SS patency was determined routinely at 6 months post-procedure using a combination of liver function tests, ultrasound and upper GI endoscopy in all patients, and vascular imaging (angiography before 2000 or angio-CT scan after 2000) in patients selected for SS . Recurrence of PH was defined by development of GI bleeding, recurrence of high-grade varices on upper gastrointestinal endoscopy or evidence of shunt thrombosis on imaging. Hepatic encephalopathy as long-term complication of SS was defined clinically by loss of attention, fatigability, irritability, deterioration in school performance, and daytime somnolence. Portopulmonary hypertension was detected on cardiac echography and confirmed by cardiac catheterization. Hepatopulmonary syndrome was identified by the presence of hypoxaemia, and confirmed by pulmonary scintigraphy with Tc99m labelled-Albumin macro aggregate. Transplant-free survival (TFS) defined by survival with native liver and overall survival (OS) were calculated according to the Kaplan Meier method. We included factors that may have influenced the outcome of SS; conjugated BL (cBL) with a cut-off value of 20 umol/l, Child- Pugh score at the time of SS, type of shunt,

and whether SS was performed before or after establishment of the LT program (1984). We compared OS and TFS with that of TIPS performed in our institution from 1992 and endoscopic ligation (EL) of varices from 1989.

Statistical methods:

Results are expressed as median and range. Comparison between groups was performed using Fisher's exact test for qualitative data, and Mann Whitney for quantitative data. TFS and OS were compared using the Logrank test between the groups. $P<0.05$ was considered significant.

Our local institutional review board approved this study and exempted us from requiring consent for patients due to its retrospective nature, and all data included complies with the Commission Nationale Informatique et Liberté and bio-ethic laws.

RESULTS:

Population

We performed SS in 38 patients (25 males) for PH occurring after a Kasai procedure (30 Portoenterostomies, 8 Portocholecystostomies). On average, in our centre, 20-25 children underwent a Kasai Procedure each year. Thirty (78%) patients had a cBL below 20 µmol/l 6 months after Kasai. Onset of signs of PH occurred after 24 months [1-96] following the Kasai procedure. Thirty one patients38 (82%) had a median of 2 episodes [1-7] of GI Bleeding. Seven patients did not bleed prior to SS, all of whom had cBL <20 µmol/l at time of SS. In 6/7 of these patients the indication for SS was high-risk varices (defined as grade 3 esophageal varices, grade 2 varices with red wale markings and/or gastroesophageal varices)(8), and one patient had SS in 1980 for major splenomegaly with low platelet count (45 G/l) **.** Liver function tests and Child-Pugh score at the time of SS are displayed in the Table.1. At time of SS, 24 patients had cBL<20 µmol/l, and the remaining fourteen had a median cBL of 34 µmol/l [22-85].

Eleven patients had SSprior to 1984, before the establishment of the paediatric LT program in our country. Since 1984 we have recorded systematically 614 Kasai procedure in our centre, therefore the estimated percentage of SS after Kasai is 27/614=4.3%: Patients characteristics before and after 1984 are displayed in Table2.. The median age of patients at the time of SS was 5.5 years [2-13.5]. Four patients had a concomitant splenectomy with a direct (without graft interposition) splenorenal shunt performed prior to 1980. For the other procedures, conduits were jugular grafts apart from one performed witha PTFE-graft interposition (Fig.1)..

Post-operative mortality and morbidity

One patient died of peritonitis due to the perforation of the Roux-en-Y during the dissection, he was Child-Pugh: B9 at time of SS. Other immediate and non-lethal post-operative complications consisted of wound abscess, peritoneal bleeding, hematemesis and acute pancreatitis: each of these in distinct patients. Three patients developed transient ascites. One patient (Child-Pugh B8 with cBL<20umol/l) developed a mild hepatic encephalopathy (EH) requiring low protein diet. No patient developed acute hepatic failure following the procedure requiring an urgent LT.

6 month Shunt patency/PH recurrence

Endoscopic assessment at 6 months identified either resolution of varices, or grade I varices in 34/38 patients (shunt patency 89 %). Shunt thrombosis or stenosis occurred in 4 (11%) patients. Two patients with splenorenal shunts had an immediate thrombosis. One underwent a successful portacaval shunt 7 years later, the other was treated with endoscopy and was alive at 20 years of follow-up. One patient with a stenosis of a splenocaval shunt was successfully dilated and stented at 6 months post SS. Another patient with a mesocaval shunt had an early shunt thrombosis, successfully cleared with surgery on day 2.

6 month hepatic function assessment

At 6 months post-SS, the Child Pugh score by a median of 1 unit [-4 to +6] (P=0.004), whereas either the factor V or Prothromin Time remained stable (P=0.850 and P=0.810). The Child-Pugh score changes before and after SS are displayed in Fig.2

SS related specific adverse events

Thirteen patients (34%) developed SS-related complications. Nine (23%) developed clinical hepatic encephalopathy at a median of 10 years [0-27] following SS. All were Child Pugh B-C at time of SS. Six underwent a LT, and two died following their LT. Five still have their

native liver, two due to non-observance, two because of mild hepatic encephalopathy without hepatic failure, and another was lost to follow-up after 20 years.

Three patients (8%) developed hepatopulmonary syndrome within a median of 11 years [6-16] following SS. Two were Child Pugh B, one was A at the time of SS. All had undergone transplant at time of diagnosis of hepatopulmonary syndrome. One child died 7 years after his transplantation as a result of chronic rejection. No patient developed portopulmonary hypertension. Liver nodules occurred in 4 (10.5%) patients at a median of 5 years [3-7], and one of them underwent a LT.

SS-related adverse events was not influenced by cBL at the time of SS (P=0.486), the type of shunt (P=0.999), or the shunt being performed prior to 1984 (P=0.714). SS-related adverse events were lower in the Child-Pugh A group (N=1, 6%) vs. Child-Pugh B-C group (N=12, 57%) (P=0.001).

Liver transplantation and long term outcome:

Median follow-up was 15 years [1-32 years]. Four patients died without LT: one patient of a procedure–related event (see postoperative mortality) and this patient is included in the survival analysis. Another patient died of sepsis, 25 months after a splenorenal shunt with a concomitant splenectomy performed in 1974. Two patients died after returning to their native country. One died 22 years following his splenorenal shunt, refusing LT on religious grounds. The other patient died whilst on the waiting list for a LT 19 years after his SS.

Ten patients (27%) were alive with their native liver at their last follow-up ranging from 4 to 30 years. One was lost to follow-up after four years with a tBL at 134 µmol/l and prothrombin time of 64%, she went back to Africa, and is probably dead since. Six had a total bilirubin level between 16 -60 µmol/l and prothrombin time above 70%, and three had a hepatic encephalopathy considered but not listed for LT due to compliance issues. Twenty-four

patients (63%) had a LT within a median of 11 years [1-30] following SS. Indication for transplantation was available for 15/24 patients (Table3).

Median age at LT was 18 years [6-30].. Four patients underwent a second LT. Of these, one patient had liver failure following the first LT due to failure of closure of SS. Six patients (25%) died following their LT. 5 after a first LT, One died after a combined heart and LT for a cirrhotic cardiomyopathy unrelated to portopulmonary hypertension, one from peritoneal sepsis following a difficult adhesiolysis, another due to peritoneal bleeding unrelated to the SS, and two due to unknown causes. One patient died after his second LT (immune rejection) from peritoneal sepsis.

The overall survival (OS) and transplant-free survival (TFS) are displayed in Table4 and Fig3. Median transplant-free survival was 13 years after SS. OS and TFS at 5 and 10 years were neither statistically different according to the year of SS, tBL, or the type of shunt. On univariate analysis the OS but not TFS was better if the cBL was below 20 µmol/l at the time of SS (Table 4). The TFS was statistically improved if the SS was performed in a Child-Pugh A patient (Table 4 and Fig 3). OS was not impacted by the presence of a complication (shunt thrombosis or extrahepatic adverse events).

Trans-jugular intra hepatic shunts (TIPS):

We implemented the TIPS program in 1992. Out of 39 patients who underwent TIPS in our institution, 7 were performed on patients with PH after a Kasai procedure for BA. Four had immediate technical failure due to a hypoplastic intrahepatic network. Three were successful, but one patient died after the procedure, which was palliative. Among the two who survived with a patent TIPS, one developed hepatic encephalopathy and is on the waiting list for LT 4 years after the TIPS, and the other was transplanted one year after the TIPS.

Prophylactic endoscopy of high-risk varices:

From 1989 - 2014, 734 patients with BA underwent an upper GI endoscopy at our institution, and 266 (36%) developed high-risk varices. Excluding those who had SS during their follow-up, 60 had tBl<85 µmol/l. We displayed in Table 5 the Prothrombin time and tBL of the EL and SPS groups. Twenty-one (35%) were transplanted during their follow-up at a median of 3 years [0-12] after the first endoscopic procedure. Five (8%) died; one before LT, the others within a range of 0 -12 years following LT. Comparisons of OS and TFS at 5 and 10 years after first endoscopic procedure and SS are displayed in Table 6. OS was not statistically lower although the TFS was clinically lower for endoscopic treatment than SS. Over a 10 year span risk of LT was 25% less in the SS than in the EL group. Relative risk of patients for LT at 10 years for SPS compared to EL is 0.468[0.217-0.963], which is consistent with the better EFS for SS than for EL

DISCUSSION

This study is the largest series of SS for severe portal hypertension following a Kasai procedure, and the first to demonstrate that a satisfactory long-term survival without LT can be achieved in patients with an initial successful Kasai procedure, and among those with cBL<85 µmol/l. A total of 35 out of 38 (92%) patients maintained a patent shunt, reducing the risk of GI bleeding, 86% and 70% of patients were alive with their native liver at 5 and 10 years respectively, following SS. Of note, half of the transplants were performed in patients older than eighteen years, considering that the onset of symptoms of portal hypertension was at a median of 5,5 years (4). SS for BA patients with low cBL may overcome issues related to small graft and organ accessibility in this subset of patients, and bring half of them to adult teams without a previous transplantation in childhood and therefore without the long term adverse events of immunosupressors on kidneys, infection or secondary tumours.

Worldwide, the majority of patients with BA with PH are managed by either endoscopic treatment of varices or by TIPS followed by liver transplantation (12). In our study, the median delay and age at transplantation were lower for patients with endoscopic management compared to SS.. Although we accept that patients without GI bleeding could be managed by endoscopy, some of these could be amenable to SS in case of failure of repeated endoscopic treatments. There is potentially a significant bias in this comparison, as we may have selected patients with high-risk varices and failure of endoscopic management for SS, rather than patients with high risk-varices alone. However, SS seems to be effective in avoiding the need for LT in the long-term. To our knowledge, there are no other studies which have attempted to compare either endoscopic treatment or TIPS to SS in children. Our experience is that TIPS does not seem to offer a long-term reliable alternative to treat PH in BA patients with low cBL despite our experienced interventional radiologist team. This is due to the technical difficulties and lack of long-term patency. Ultimately these patients usually undergo LT.

These findings are supported by other studies which include a few BA patients (10). Our conservative surgical approach is confirmed by a recent retrospective comparative study, supported by randomized trials, in adults, showing long term benefits of SS compared to TIPS, prior to transplantation (14). This conservative approach on children is also supported by the Baveno consensus advocating SS over TIPS or LT, in patients with a previous Kasai and failure of endoscopic therapy and tBL<60 µmol/l (13, 15).Given possible surgical adverse events following SS we also believe that SS should be an option in case of previous gastrointestinal bleeding and either a failure of endoscopic therapy or high risk varices. Another question is whether an additional procedure after a Kasai might impair the outcome of the LT. In our series, the OS after SS is comparable to the OS of 82% at 5 and 10 years reported in our patients transplanted for BA during the same period, and is comparable to the OS of LT for BA reported in more recent series(4,16). Moreover, other studies have shown that additional procedures after a Kasai procedure (i.e. to restore a bile flow) in order to avoid an early or unnecessary LT in the context of shortage of donors, have had a positive impact.Despite these technical difficulties, and the possibility of complications occurring after SS, the benefits of avoiding a LT for a significant period should be considered in the small subset of Child-Pugh A or low cBL patients who develop PH after a Kasai procedure. Because of the serious life threatening effects of LT in infancy (operative mortality, post-operative adverse events, lymphoproliferative disease, and long term nephrotoxicity), and the negative impact of multiple LT in childhood, we opted to perform SS rather than LT in this group of patients (4). This conservative approach could also be useful in countries without an established liver transplantation program. The adverse effect of cBL on OS for SS has not been reported in the children literature so far, but is intuitive, as cBL is highly correlated to the Child-Pugh score and reflects the extent of liver damage at time of surgery. cBL may therefore impact survival and outcome of SS, as demonstrated in adult literature(16). Our

analysis in table 4, showed that despite t and cBL must be linked, tBL<20 µmol/l did not impact the outcomes. This absence of significant difference is probably due to a fewer amount of patients in the tBL<20µmol/l group than in the cBL<20 µmol/l group , which may have excluded patients with low but above 20 µmol/ tBL , and therefore with good prognosis. In our study, the Child-Pugh score was a significant prognostic factor both for late extrahepatic complications and for the long-term efficacy of SS, as it includes cholestasis (tBL) as well as signs of liver failure (hepatic encephalopathy, ascites, increased prothrombin time, and albumin). The effect of Child-Pugh score on the outcome of SS has been reported in adult series. SS as an elective procedure can be performed on Child-Pugh A patients, although the use of distal splenorenal shunts may be used to treat acute GI bleeding, even in Child-Pugh C patients (17). The main disadvantages of SS are its specific complications and the most common is hepatic encephalopathy, which occurred in 23% of our patients, followed by portopulmonary syndrome, and liver nodules. Apart from the nodules, all these complications are considered an indication for LT, even though some patients in our series with hepatic encephalopathy were not transplanted. The most concerning issue is the risk that hepatic encephalopathy impacts the enrollment of these patients for LT, especially when they reach the age of 18, which is the age of civic responsibility in France. This is why we should consider LT once mild signs of hepatic encephalopathy are detected. However, most of these complications occurred in Child-Pugh B-C patients, which supports the idea of selecting either Child-Pugh A or anicteric patients for SS after a Kasai procedure.. With respect to the various techniques used in our series, splenorenal shunts compared to MC shunts were not associated with a higher risk of complications. However, splenectomy, which may increase the risk of sepsis, is no longer recommended because it led to a fatal complication in one patient and was therefore abandoned in our series from 1980.

The main bias in our series is a result of the small number of patients, the extended period of our study, and follow-up of our patients under the care of adult clinicians. Our study spans two eras (before and after the establishment of LT in our country), which may have resulted in heterogeneity in the selection of patients, and impact complication rates, although without significantly affecting OS. Another issue is the quality of data collection for complications. Even if our follow–up was standardized, we found that when patients were transferred to the care of adult clinicians, follow-up information regarding portopulmonary hypertension/hepatopulmonary syndrome or hepatic encephalopathy was less easily identified. Moreover, evaluation of hepatic encephalopathy during the follow-up was not systematic, and usually subjective. Hepatic encephalopathy is difficult to assess given that neither brain MRI features nor blood ammonia correlates with the degree of clinical hepatic encephalopathy (18).

In conclusion, there is a downward trend in surgical intervention for PH in cirrhotic patients, which is likely due to a fear of precipitating the need for LT, or concern that prior surgical intervention will make LT technically more challenging (16). However, we have demonstrated successful outcome in SS, and we advocate application of this practice in non-icteric BA patients who develop severe PH following a Kasai procedure, or in countries without a LT program. We therefore resumed our program of surgical shunts in non-icteric, Child A patients who had a previous Kasai and have previous GI bleeding or intractable high risk varices.

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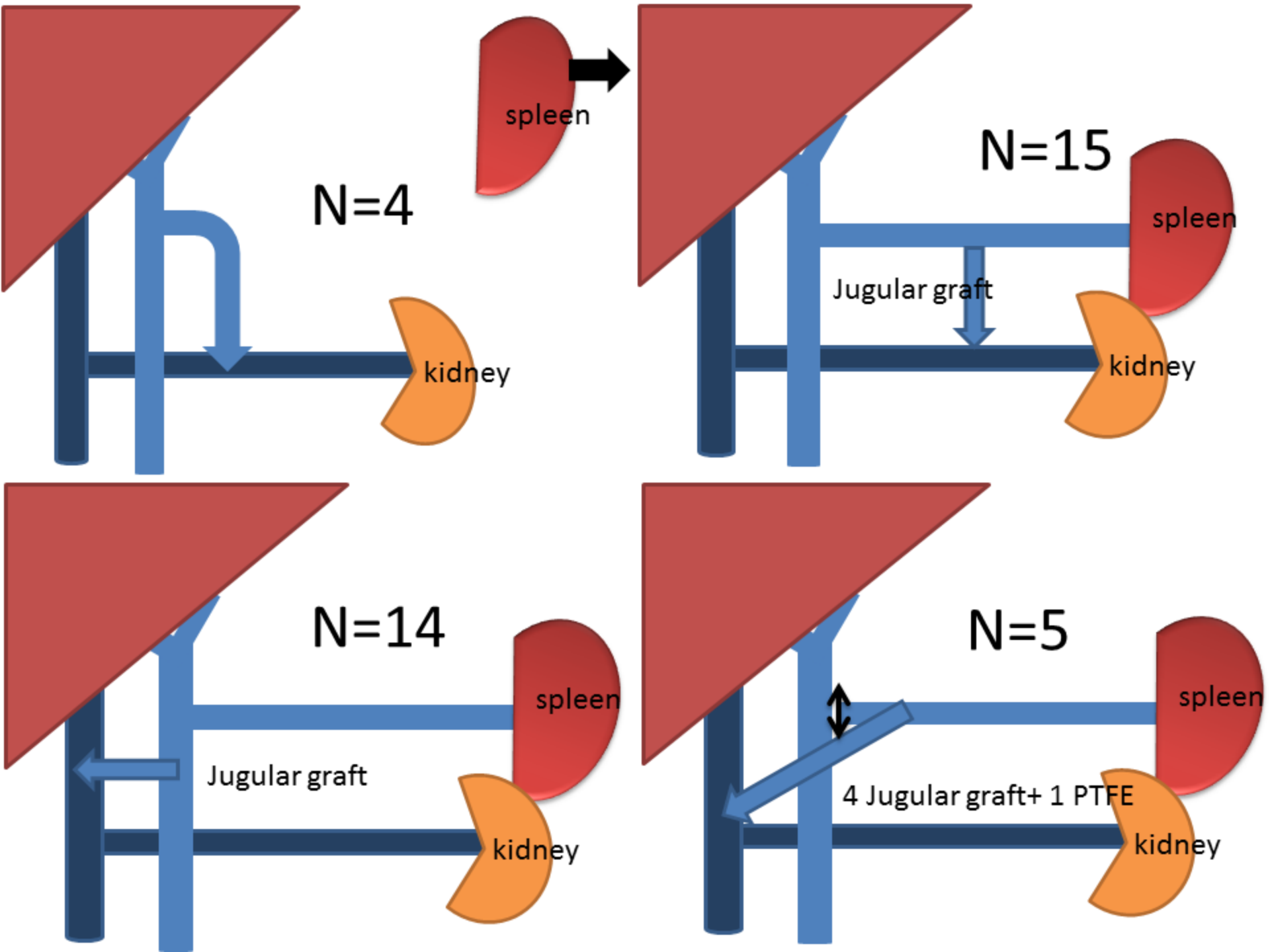
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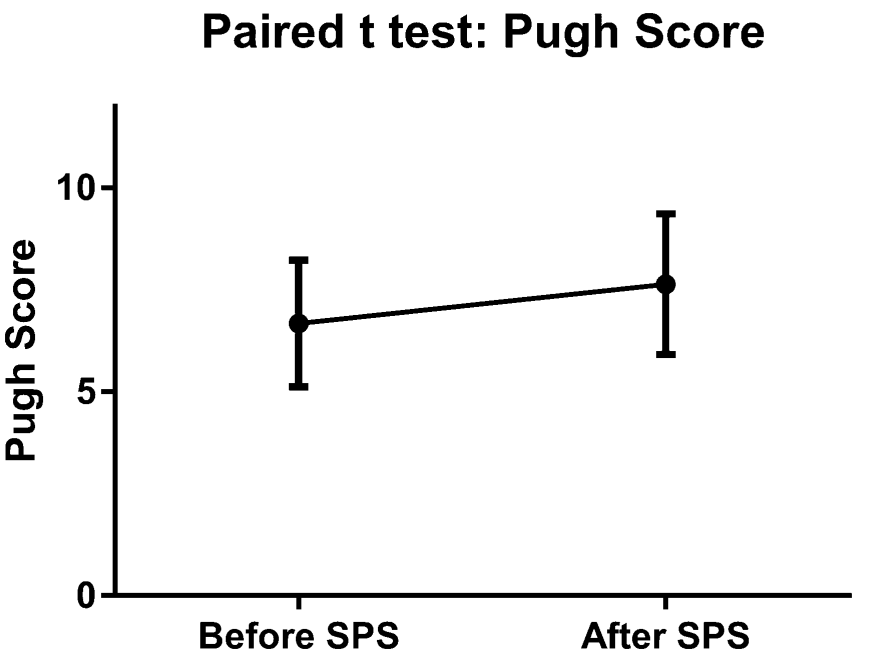
4 Jugular graft+ 1 PTFE
kidney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Pugh Score
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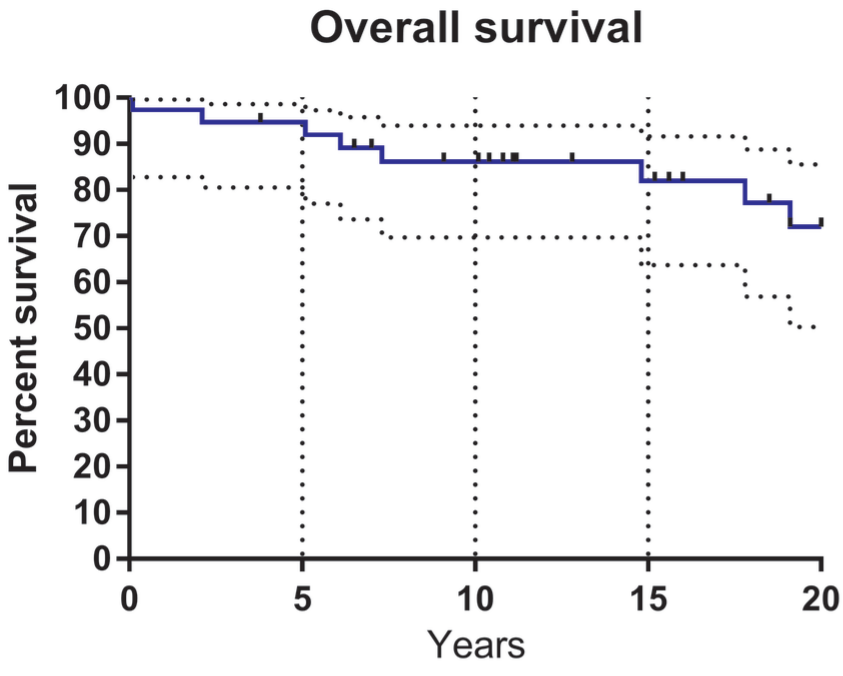
Before SPS
After SPS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Percent survival
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90
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50
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10
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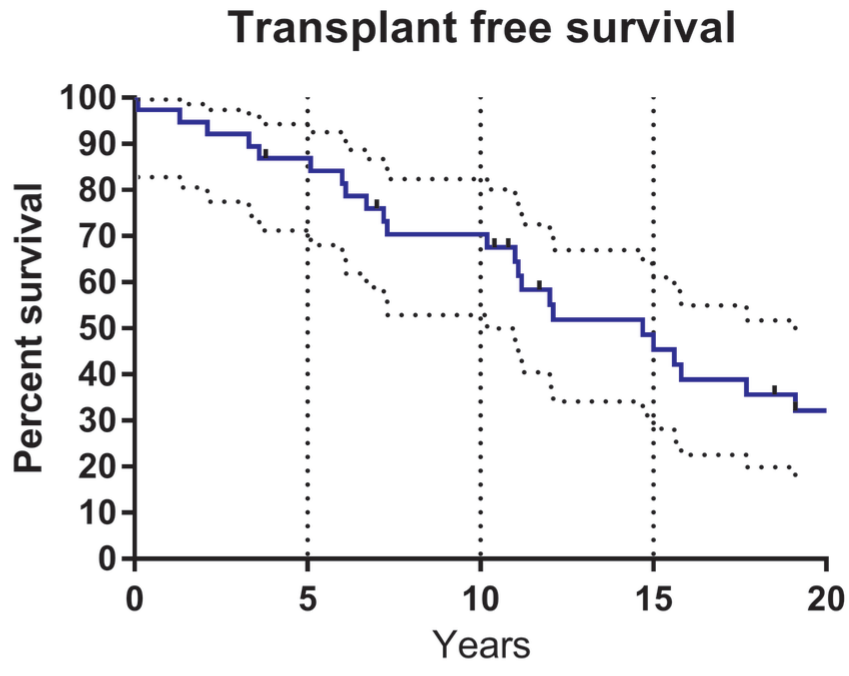
Years


Transplant free survival
Percent survival
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90
80
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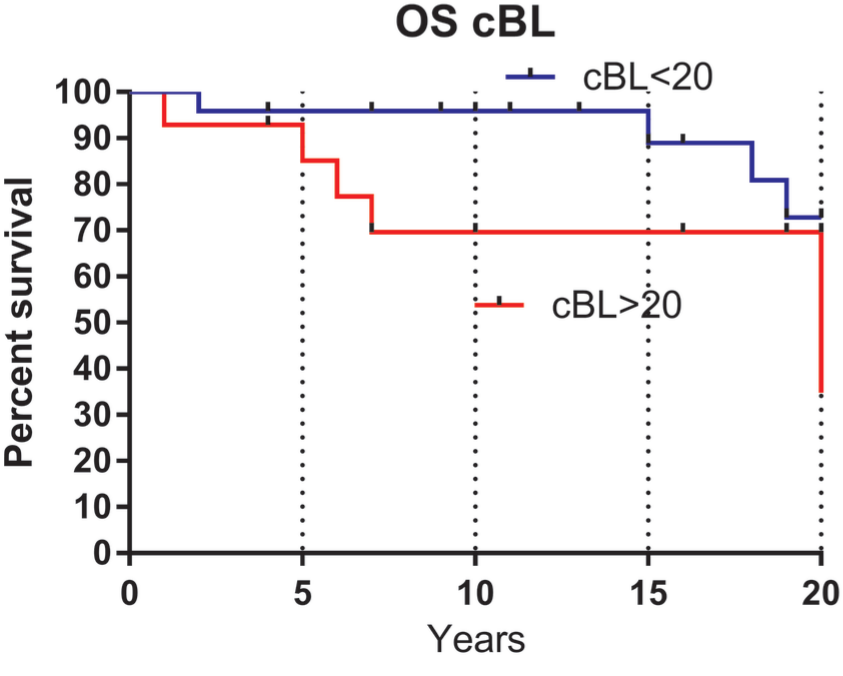
OS cBL
cBL<20
cBL>20
Percent survival
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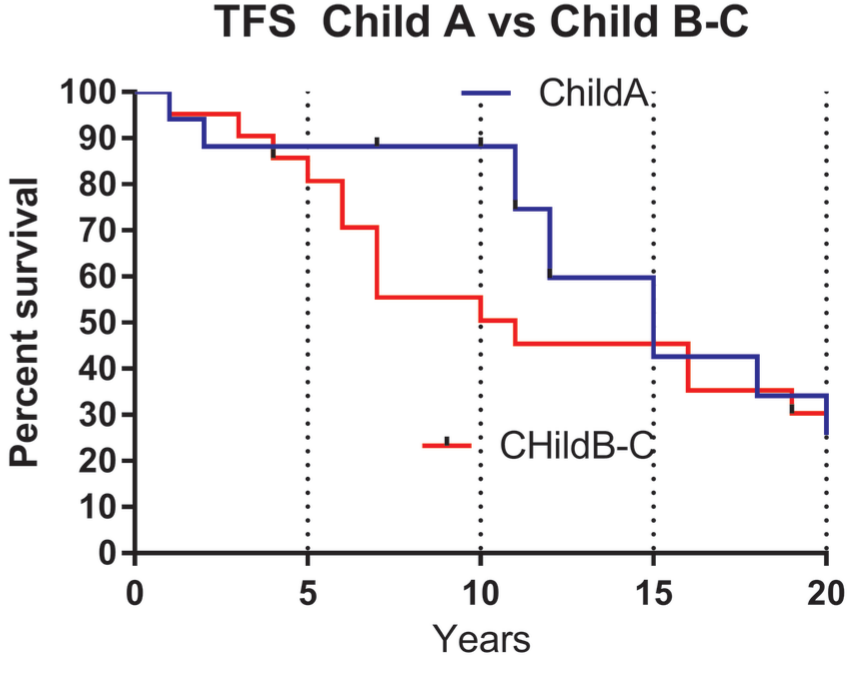
TFS Child A vs Child B-C
ChildA
CHildB-C
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
Years

TABLES

Platelets (G/l)	81 [10-273]
Prothrombin Time (%)	78[47-100]
Factor V (%)	71[31-100]
cBL (umol/l)	13[5-85]
Child-Pugh Score:	7[5-10]
A	17
B	19
C	2

Table.1: Biology and Child-Pugh score of the patients at the time of SPS after a Kasai procedure.

	<1984 n=27	>=1984 n=11	P
Age at SPS	**5[2-10]**	**6,5[2-13]**	**0.246**
cBrb	**28[10-50]**	**12[5-85]**	**0.099**
Pugh Score	**7 [5-10]**	**7[5-10]**	**0.824**
PT	**78[61-100]**	**84[47-100]**	**0.4610**

Table2 : comparison of patients characteristics betfore(<1984) and after (>1984) the era of transplantation

Indication	Number of transplanted patients
Recurrence of jaundice and liver failure	5
Hepatic encephalopathy	5
Hepatopulmonary shunts	3
Recurrence of Portal hypertension	2
Unknown	9

Table3: Indication for liver transplantation among patients with SPS after a Kasai procedure.

	OS			TFS		
Years	**5 Years**	**10 Years**	**15 years**	**5 Years**	**10 Years**	**15 years**
Cohort n=38	91%(35)	87%(27)	82%(22)	84%(32)	70%(25)	45%(15)
cBrb<20 n=24	**96%(23)**	**96%(19)**		83%(21)	79%(18)	
cBrb>20 n=14	**85%(12)**	**70%(8)**		85%(12)	54%(7)	
P Survival curve	**0.031**			0.171		
>1984 n=27	96%(26)	92%(19)		85%(24)	70%(17)	
<1984 n=11	82%(10)	73%(8)		82%(10)	72%(8)	
P Survival curve	0.121			0.846		
Splenorenal n=18	89%(17)	83%(13)		83%(16)	77%(13)	
Others n=20	95%(19)	89(14)		85%(18)	63%(12)	
P Survival curves	0.619			0.383		
Child-PughA n=17	94%(16)	94%(14)		**88%(16)**	**88%(14)**	
Child-PughB-C n=21	90%(19)	80%(13)		**80%(17)**	**55%(11)**	
P Survival curve	0.253			**0.049**		
Complication n=23	95%(23)	87%(17)				
No Compl. n=15	87%(11)	87%(10)				
P Survival curve	0.832					

tBL<20 n=14	92%(13)	92%(12)	78%(12)	78%(11)
tBL>20 . n=24	95%(22)	82%(17)	91%(21)	65%(16)
P Survival curve	0.729		0.834	

Table4: showing OS and TFS at 5 and 10 years for each analyzed parameter, P reflects the Logrank test for each curve. (In parenthesis is the number of subject at risk in each group).

	EL	SS	P
PT	72[6-100]	78[47-100]	0.016
tBL	28[5-79]	26[8-90]	0.384

Table 5: Comparison of Prothrombin time (PT) and total bilirubin (tBL) of patients in Endoscopic ligation group and surgical shunt group.

Procedure	OS% (nb at risk)		P	TFS%(nb at risk)		P
	5years	10 years		5 years	10years	
SPS	91%(34)	86%(27)		84%(32)	70%(25)	
Endoscopy	96%(38)	91%(19)	0.361	63%(28)	49%(10)	0.060
TIPS	0%(0)	0%(0)	<0.001	0%(0)	0%(0)	<0.001

Table 6: comparisons of overall (OS) and transplant free (TFS) survival between surgical portosystemic shunts (SPS), endoscopic treatment of varices and transjugular intrahepatic portosystemic shunts (TIPS) as treatment of severe portal hypertension after a Kasai.