Peak Systolic Velocity at Arterial Doppler Ultrasound in Pediatric Liver Transplantation: as Predictor of Acute Severe Complications.

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Research Article

Keywords: Pediatric, Liver transplantation, Doppler Ultrasound, Arterial complications

Posted Date: August 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-774076/v1>

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Abstract

The objective of this study is to determine whether hepatic artery Doppler ultrasound parameters can predict arterial complications in the immediate period after a liver transplantation in children.

A retrospective review of the pediatric liver database at our tertiary-care pediatric hospital was performed. The study included 57 pediatric patients who underwent liver transplantation from 2016 to 2020. Clinical, laboratory and Doppler findings were recorded daily the first 5 days after transplantation. Especial attention was focused on extrahepatic post-anastomotic Peak Systolic Velocity (PSV) and intrahepatic Resistive Index (RI).

Forty-nine liver transplant recipients were analyzed. Patients with acute hepatic artery complications, including acute thrombosis and stenosis, had lower PSV values at 3 and 4 days after surgery compared to the group with non-complications, with a statistical significance ($p=.015$). Receiver operating characteristic (ROC) curve analysis determined an optimal cut-off value of PSV less than 30 cm/s to discriminate children with and without acute hepatic arterial complications, which is lower than that proposed in adults. It correlates with acute arterial stenosis and thrombosis in children even before RI, clinical symptoms or laboratory anomalies appear.

Introduction

Acute hepatic artery complications are an emergency in the postoperative period after liver transplantation in children and adults. Hepatic arterial stenosis and hepatic arterial thrombosis are the most common causes of morbidity and mortality in the immediate period, especially the firsts days after surgery [1, 2]. They compromise the blood flow of the liver graft leading to hypoperfusion of the intrahepatic biliary epithelium [3–6]; and without prompt management; they progress to acute bile duct necrosis leading to biliary sepsis and graft failure [1, 2, 5, 7–11]. Timely detection of these complications is crucial to reduce liver damage [3]. Unfortunately, the clinical manifestations are often non-specific [12, 13]. Therefore, early and accurate radiological graft evaluation plays a major role to guide prompt management. Doppler ultrasound (US) is the established initial imaging modality to detect vascular complications after liver transplantation [14–16]. Treatment with thrombectomy, angioplasty or hepatic artery reconstruction during the postoperative period has been related to successfully graft salvage, reduced morbidity and a reduced probability of retransplantation [6, 9, 14, 15].

The incidence of acute arterial complications is higher in children compared to adults. Acute hepatic artery thrombosis and stenosis have an incidence up to 13% in adults and up to 26% in children [3]. Pediatric liver transplantation differs from adults in several aspects, being at greater risk for vascular complications. Technical difficulties and the small size of vessels seem the most likely explanation of this difference. Transplantation surgical techniques using special vascular anastomosis, such as reduced-size or split-liver transplantation are more commonly performed in children [3, 18–22]. In addition, disease etiologies requiring liver transplantation in children show a trend to specific vascular

complications. Moreover, children have their own particular characteristics with the hemostatic system still developing [16, 17] and hemodynamics varying highly with age, being hyperdynamic in young children.

Therefore, normal ranges for Doppler parameters after liver transplantation in children are likely to differ from adults. Peak systolic velocities (PSV) and resistive index (RI) are Doppler US parameters that have been proven to be effective for vascular graft evaluation [8]. Parvus tardus wave morphology of the intrahepatic artery and low RI correlate with stenosis at the arterial anastomosis in adults and children [4]. RI values of 0.5–0.7 are considered normal in adults. Higher values of up to 0.95 are considered to be normal in children, especially in infants [3, 4, 18]. PSV correlates with the risk of thrombosis and hypoperfusion of the liver graft and several studies detected that the hepatic artery has to be carefully evaluated when velocities are less than 50cm/s [3, 5, 18]. However, to our knowledge, there is no consensus defining normal ranges and an optimal cut-off value of the peak flow arterial velocity in children.

The aim of this study is to evaluate the utility of the PSV at Doppler US the first days after pediatric liver transplantation and determine an optimal cut-off value which may urge further imaging investigations to detect acute arterial complications in children. A Doppler US protocol during the first days after a pediatric liver transplantation is also proposed.

Methods

Patient selection

We performed a retrospective case-control study of the liver transplantation database at our tertiary-care pediatric hospital. Informed consent from a parent or legal guardian of each patient was obtained for study participation. The research ethics board of our hospital approved the study (Ethic Committee of Clinical Investigation of Vall d'Hebrón Hospital (CEIC)). A total of 57 consecutive children, from birth to 16 years old, underwent liver transplantation between June 2016 and October 2020. Patients were enrolled in the study on the basis of the following criteria: surgical transplantation performance at our hospital and availability of US and clinical data records every day during the first 5 days after liver transplantation. US, clinical and laboratory analyses daily the first 5 days after surgery were established as a routine postoperative protocol by our multidisciplinary team in pediatric liver transplantation. Forty-nine patients met the inclusion criteria. Eight patients were excluded because there were no available US data every day during the first 5 days after transplantation. For patients who met the inclusion criteria the following information was retrieved: age, gender, main liver underlying disease, type of transplant and surgical technique, complications, and US Doppler parameters.

Imaging acquisition and interpretation

All methods were carried out in accordance with relevant guidelines and regulations. Ultrasound was performed portable to the bedside patient in the pediatric Intensive Care Unit every 24 hours during the first 5 days after liver transplantation. All portable pediatric US were performed with a Toshiba Medical Systems Aplio 300 US machine. As the study was retrospective and data were collected over the course of 5 years, different radiologists performed the studies. However, all radiologists followed our pediatric protocol of routine US liver graft evaluation, which included grey-scale and Doppler longitudinal and transverse images with curvilinear 2–6 MHz transducers. Patients were placed in supine position with the right arm abducted that allowed an oblique intercostal access. Vascular imaging included hepatic artery evaluation (color-flow assessment, spectral waveform, and measurement of velocities) within at least 3 cardiac cycles traced. PSV was measured extrahepatic distal to the site of anastomosis, at the hepatic hilum, whereas arterial wave morphology and RI was analyzed in the intrahepatic branches, as peripherally as possible. All angles were corrected to be between 30° and 60° for assessing velocities.

US data were obtained from the Hospital PACS System. PVS and RI recorded on US images were annotated. The mean value obtained from multiple sampling was recorded. Two radiologists reviewed the images; one with 4 years of experience in liver graft US evaluation and the other with 10 years experience in pediatric liver graft US. The readers first evaluated the images independently and then discussed the discrepancies to reach consensus. PVS measurements that were not extrahepatic distal to the anastomotic site and wave morphology or RI measurements that were not clearly defined nor located intrahepatic were excluded. The mean measurement between the two readers was calculated. Both reviewers were blinded to clinical outcomes until the end of the imaging analysis.

Clinical data after transplantation were reviewed in the hospital electronic health system until January 2021. Acute arterial complications were defined in the clinical course of the patients or in radiological CT or angiography reports. All acute arterial complications were confirmed and evaluated by CT or angiography, used as reference standard. Both radiologists also reviewed CT and angiography. No discrepancies were detected.

Statistical analysis

Extrahepatic PSV distal to the arterial anastomosis and intrahepatic RI measurements in children with and without acute arterial graft complications were compared. Statistical analysis as logistic regression analysis was implemented. Univariate analysis was performed using Chi-square to assess qualitative variables such as age, liver disease or surgical technique and ANOVA to assess quantitative variables. Furthermore, Receiver Operator Curves (ROC) was generated for VPS to compare diagnostic accuracy and determine an ideal cut-off value to predict graft arterial complications in the immediate postoperative period. Statistical analyses were performed using SPSS software version 23 (SPSS, Inc., Chicago, IL, USA). RI value between 0.5–0.9 were considered normal values. P values less than .05 were considered to be statistically significant.

Results

A total of 49 pediatric liver transplantations performed in 49 patients (55.1% male and 44.9% female) fulfilled the inclusion criteria. The mean age at transplantation was 5.93 ± 4.89 years (median 5 years; IQR interquartile range 17 months to 10 years). Most of the patients received a cadaveric total liver graft corresponding to 38.8% (19/49); 32.7% (16/49) had a split-liver graft from a cadaveric donor and 28.6% (14/49) received living related partial-liver graft. The most common indication for liver transplantation was cholestatic liver disease corresponding to 42.9% of the total (21/49). Biliary atresia accounted for the 34.7% (17/49). Other underlying liver diseases were 20.4% (10/49) metabolic disorders and 14.3% (7/49) malignancies. Patients with underlying cholestatic and metabolic diseases were significantly younger from a statistical point of view ($p = .035$) (mean age 4.5 and 4.8 years respectively) compared to the rest (mean age of 7.2 years).

Eleven acute arterial complications were identified in the 49 liver grafts (22.4%), including 8 anastomotic stenosis and 3 anastomotic thrombosis. Seven patients with mild arterial stenosis at CT (reduction less than 50% of the arterial caliber) received no treatment. One patient with severe arterial stenosis at CT (reduction of more than 50% of the arterial caliber and filiform visualization of the postanastomotic and intrahepatic arterial branches) was treated with immediate angioplasty. Only one patient with arterial thrombosis was treated medically as a partial thrombosis was seen on CT. The other two patients with acute arterial thrombosis were treated with thrombolysis, one requiring splenic embolization because an arterial steal syndrome was identified during the process, and the other requiring surgical reconstruction after rethrombosis. Only the patient with rethrombosis and surgical repair of the main artery had signs of biliary ischemia of the liver graft, which were reported on US, MRI and clinical data. None of the 7 patients with non-treated stenosis, neither the 3 patients with immediate angioplasty or thrombolysis had any other complication, with all of them followed up more than 1 year except two patients, one with a follow-up of 9 months and the other with a follow-up of 6 months. The 7 patients with non-treated stenosis had progressive improvement of the US findings getting normal values over the second week after surgery. The 3 patients with immediate angioplasty or thrombolysis had normal values within the first 2 days after treatment.

RI measured in the intrahepatic branches of the hepatic artery depicted no significant variations over the first days after surgery. Patients with acute post-surgical hepatic artery stenosis tended to have lower RI in the monitoring US control after surgery compared to the other groups, without significance from a statistical point of view ($p > .05$) (Fig. 1).

Extrahepatic PSV was the highest in the immediate post-transplant period. A downward trend of the PSV at 3 days after transplantation was identified in all patients (Fig. 2).

Patients with acute hepatic artery complications, including acute thrombosis and stenosis had lower PSV values at 3 and 4 days after transplantation compared to the group with non-complications, with a statistical significance ($p = .015$). Median PSV at 3 days after surgery was 26 cm/s (IQR 25 to 29 cm/s) for the 8 children with acute arterial stenosis and 19 cm/s (IQR 18 to 19 cm/s) for the 3 children with acute arterial thrombosis, whereas 46 cm/s (IQR 33 to 46 cm/s) was seen in the 38 children without

arterial complications. Variation between the three groups was statistically significant ($p = .022$). Median PSV at 4 days after surgery was 31 cm/s (IQR 25 to 36 cm/s) for the 8 children with acute arterial stenosis and 13 cm/s (IQR 11 to 20 cm/s) for the 3 children with acute arterial thrombosis, whereas PVS of 53 cm/s (IQR 40 to 65 cm/s) was seen in the 38 children without arterial complications. Variation between the three groups was statistically significant ($p = .025$). Patients with acute hepatic artery thrombosis had lower PSV values compared to the group with arterial stenosis at 2 days after surgery, with a statistical significance variance ($p = .036$). Patients with acute hepatic artery complications, including acute thrombosis and stenosis, had lower PSV values at 3 and 4 days after surgery compared to the group with non-complications, with a statistical significance ($p < .040$). (Tables 1 and 2).

Table 1
Post transplantation Hepatic Artery PSV the first 5 days after surgery stratified by category of vascular complication.

Vascular Complications	Hepatic Artery Peak Systolic Velocity									
	1st day		2nd day		3rd day		4th day		5th day	
	Mdn	IQR	Mdn	IQR	Mdn	IQR	Mdn	IQR	Mdn	IQR
Hepatic artery thrombosis (n = 3)	56	36–61	23*	21–25	19**	18–19	13***	11–20	31	26–37
Hepatic artery stenosis (n = 8)	44	39–51	45	25–53	26**	25–29	31***	25–36	29****	24–40
No acute vascular complication (n = 38)	61	53–66	55	52–54	46	33–46	53	40–65	56	41–54
Total (n = 49)	56	43–71	49	36–60	41	31–50	45	32–58	42	36–58
Mdn = median, IQR = Interquartile Range										
* Statistical significance ($p = .036$) comparing PSV in thrombosis compared to hepatic artery stenosis and uncomplicated patients.										
** Statistical significance ($p = .022$) comparing PSV in complications (thrombosis and acute stenosis) compared to no complications.										
*** Statistical significance ($p = .025$) comparing PSV in complications (thrombosis and acute stenosis) compared to no complications.										
**** Statistical significance ($p = .031$) comparing PSV in acute stenosis compared to uncomplicated subgroup.										

Table 2
Early Post transplantation Hepatic Artery Peak Systolic Velocity the first 5 days after surgery by category of complication.

All complications	Hepatic Artery Peak Systolic Velocity					
	3rd day		4th day		5th day	
	Median	P value	Median	P value	Median	P value
Acute vascular complication (n = 11)	22.5	0.022	22	0.025	30	0.025
No acute vascular complication (n = 38)	46		53		56	

No correlation was observed between acute arterial complications and underlying hepatic disease or age. No significant relation was proved between hepatic artery flow dynamics and oral feeding or diminished sedation. No statistical differences between split-liver grafts and whole liver grafts were found in median values of PSV during the first 5 days.

Receiver operating characteristic (ROC) curve analysis for optimal PVS cut-off discriminated children with and without hepatic arterial acute complications determining an optimal cut-off value of PSV less than 30 cm/sec at 3 days after transplantation (Fig. 3). We calculated the diagnostic values for the cut-off value of less than 30 cm/s to predict acute arterial complications in pediatric liver grafts at 3, 4 and 5 days after transplantation (Table 3). We also calculated the diagnostic values for the cut-off value of less than 50 cm/s to predict acute arterial complications in pediatric liver grafts at 3, 4 and 5 days after transplantation (Table 4).

Table 3
Diagnostic value of cut-off PSV < 30 cm/s for diagnosis of acute arterial complications.

	AUC	S (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)	False-positive rate (%)
3rd day	0.968	81.8	86.8	64.3	94.3	85.7	13.2
4th day	0.877	63.6	89.5	63.6	89.5	83.7	10.5
5th day	0.836	54.5	92.1	66.7	87.5	83.7	7.9
AUC = area under the curve, S = Sensibility, SP = Specificity, PPV = Positive Predictive Value, NPV = Negative predictive value.							

Table 4
Diagnostic value of cut-off PSV < 50 cm/s for diagnosis of acute arterial complications.

	AUC	S (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)	False-positive rate (%)
3rd day	0.968	100	34.2	30.6	100	46.9	65.8
4th day	0.877	90.1	39.5	30.3	93.8	51	60.5
5th day	0.836	81.8	44.7	30	89.5	57.1	55.3
AUC = area under the curve, S = Sensibility, SP = Specificity, PPV = Positive Predictive Value, NPV = Negative predictive value.							

Discussion

Imaging is essential to provide the diagnosis of clinically unsuspected acute arterial complications during the postoperative period of liver transplantation. Routine Doppler US is the established imaging method of choice to monitor the liver graft during the first days after transplantation in children and adults [23, 24]. Arterial PSV and RI have been proven to be effective detecting arterial complications [3].

Hemodynamic differences between children and adults are reflected by the Doppler parameters. However, the majority of findings and reference values of Doppler US in liver transplantation are based on US parameters established for adults. Most acute arterial complications occur at the anastomosis.

Nevertheless, the evaluation of velocities at the anastomotic site or proximal to the anastomosis during the postoperative period is technically difficult to achieve because of their deep location, small caliber, discontinuous flow and presence of anatomical reconstruction variants, especially in children. Post anastomotic Doppler parameters are indirect indicators of anastomosis [4, 5] and easier to depict. Some studies evaluated RI and systolic acceleration parameters at the anastomosis [25–27], while others did it on the post anastomotic main artery or the intrahepatic arteries [23, 28, 29]. Several studies detected that critical stenosis and imminent thrombosis have to be carefully evaluated when hepatic artery velocities are less than 50cm/s in both children and adults [3, 5, 18]. However, there are a limited number of investigations performed only in children regarding reference values of arterial Doppler US parameters during the acute postoperative period. Moreover, there are some controversies about the abnormal values of PSV measured at or distal to the anastomosis ranging from 30 to 50 cm/s. [30–32].

As the assessment of the Doppler parameters at the anastomotic site is especially difficult in children and infants, we evaluated arterial Doppler parameters distal to the anastomosis, near the hepatic hilum. The hepatic hilum is almost always clearly depicted on pediatric US, and measurements at this location become easily reproducible. Therefore, in order to diagnose acute arterial complications as easy and early as possible, we aimed for evaluate the utility of RI and PSV of the hepatic artery distal to the anastomosis and determine a cut-off value for PSV that may urge further imaging investigations in children. We noticed that the arterial PSV less than 50cm/s at hepatic hilum distal to the anastomosis at 3 and 4 days after transplantation correlated with normal findings at CT, suggesting that false-positive rate tended to occur. We found that the median velocity at 3 days after surgery was 46 cm/s among the non-

complications group, whereas it was 26cm/s in patients with acute arterial stenosis and 19cm/s in patients with thrombosis. At 4 days after surgery, the median velocity among the non-complications group was 53 cm/s; and in patients with acute arterial complications was 31cm/s in stenosis and 13cm/s in thrombosis. Variation between the three groups was statistically significant ($p < .025$). At ROC analysis, we found that the optimal PSV threshold value to discriminate pediatric acute hepatic arterial complications was less than 30 cm/s. These velocities are congruent with the study of Someda et al in children [33] and slightly lower than those detected by Park et al. in 374 adults where 48cm/s was the optimal cut-off value [5]. None of the patients with acute arterial thrombosis or stenosis had abnormal liver function, so we succeeded in detecting them before hypoperfusion had any clinical manifestation. In our pediatric cohort, normal RI values and normal wave morphology showed statistically significant association with normal graft status. However, unlike other studies such as Ahmad et al [3], RI nor parvus tardus pattern did not attempt to predict acute arterial complications during the first 5 days of the postoperative period. Our study did not confirm that RI less than 0.5 was statistically associated with acute arterial complications during the first days after surgery. However, our Doppler analysis showed that low PSV distal to the anastomosis the first 5 days after liver transplantation, preceded a parvus tardus waveform in some cases. This is congruent with the study by Choi et al [12] where Systolic Acceleration Time (SAT) and parvus-tardus wave morphology were reliable predictors of hepatic artery stenosis whereas RI was not and with the study of Dodd et al [4] where the combination of SAT, peak velocity, RI and no flow had a 97% sensitivity and 64% specificity for the diagnosis of arterial complications. An optimal cut-off PSV of less than 30 cm/s at 3 days after surgery had 81.6% sensitivity and 86.8% specificity for detecting acute arterial complications, with a false positive rate of 13.2%. Similar values were detected at 4 and 5 days after surgery. Moreover, from these preliminary results, we observed that PSV less than 50cm/s in children could also be found during the first days after transplantation in normal grafts. A cut-off PSV of less than 50 cm/sec at 3 days after surgery had 100% sensitivity and 34.2% specificity for assessing acute arterial complications, with a false positive rate of 65.8%. Specificity tended to increase progressively at 4 and 5 days after surgery obtaining a slightly lower false positive rate. Therefore, in order to avoid unnecessary radiation exposure and invasive examinations, further imaging with CT or angiography is recommended in children with PSV values between 30-50cm/s only along with constellation of other US, laboratory or clinical findings. In order to detect maintained lower velocities, which may indicate hypoperfusion, or progressively reduced velocities indicating progressive thrombosis, we propose a strict Doppler US evaluation each 12 hours for PSV values ranging from 30-50cm/s with no other associated anomalies. In addition, and specially in patients in whom may urge an invasive procedure, it is important to point out that clinical assessment of transplant patients must be include into the decision-making process during the whole postoperative period.

Two main limitations associated with our study deserve further explanation, the retrospective design and the small sample size. During the 5 years that US data were recorded, different radiologists performed the US studies. Doppler US tends to be dependent of the operator's experience and skills. However, all parameters were collected using a strict protocol that was already established and included

measurements of the PSV and RI distal to the anastomosis. The other limitation resides in the sample size. Although the number of pediatric patients with liver transplantation is considered substantial, the analysis of differences in age, disease prevalence and liver graft types are limited from a statistical point of view. In addition, several confounders may determine graft status as a complex multifactorial condition and several factors may explain low velocities. Although we did not find any statistical relation, enteral feeding, severe allograft edema, portal venous hyperperfusion in reduced-size grafts, dehydration and intravascular volume depletion have been described as possible contributing factors [10]. However, the diversity of the study population can be defended as strength of the study measuring velocities rather than a limitation, and the described values are of clinical utility in guiding the complete radiological interpretation.

To our knowledge, there is no prior consensus defining an optimal cut-off value of the PSV, neither a monitoring protocol during the postoperative period in pediatric liver transplantation. Our results argue in favor of close monitoring the hepatic artery with routine Doppler US daily at least the first 5 days after surgery. Other authors also suggested serial Doppler US for the detection of clinically unsuspected vascular complications, with different time intervals [9, 23, 34, 35]. Further studies would help clarify the long-term outcome of pediatric liver recipients with PSV less than 50cm/s without evidence of arterial complications.

Conclusion

In conclusion, the diagnosis of acute arterial complications in children after liver transplantation urges prompt diagnosis and treatment. A cut-off value of PSV less than 30cm/s at arterial Doppler US distal to the anastomosis correlates with acute arterial stenosis and thrombosis in children even before RI, clinical symptoms or laboratory anomalies appear. This cut-off value is slightly lower than that proposed in adults (50cm/s). Therefore the detection of PSV less than 30cm/s at arterial Doppler US distal to the anastomosis in the postoperative period of pediatric liver transplantation must be further investigated with CT or angiography. Daily routine Doppler US evaluation at least the first 5 days after hepatic transplantation in the pediatric population is recommended to predict potentially life-threatening acute arterial complications as early as possible.

Declarations

No funding was received to assist with the preparation of this manuscript.

None of the authors declares any conflict of interest

All data and material are available.

The research ethics board of our hospital approved the study and individual patient consent was obtained.

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Figures

Figure 1

Resistive Index Variation (y-axis) during the first 5 days after surgery (x-axis) categorized by the uncomplicated group, patients with arterial hepatic stenosis and patients with hepatic arterial thrombosis.

Figure 2

Box and whiskers plot shows median PSVs in the 49 pediatric liver transplant recipients. Horizontal line inside each box represents median, and lower and upper boundaries of boxes represent 25th percentile and 75th percentile quartiles respectively. Vertical lines extend from minimal to maximal value, excluding outside and far out values, which are displayed as separate points: o = outside values: larger than upper quartile plus 1.5 times interquartile range (inner fence). *= far out values: larger than upper quartile plus three times the interquartile range (outer fence).

Figure 3

Receiver operating characteristic curve for optimal cut-off PSV used to discriminate patients with and those without hepatic arterial acute complications determining an optimal cut-off PSV less than 30 cm/sec at 3 days after surgery, with 86,8% sensitivity and 95,2% specificity (area under the curve, 0.968; 95% CI: 0.917, 1.000)