Persisted post-operative color Doppler abnormalities is linked to reduced graft survival in pediatric patients after liver transplantation

Jochen Herrmann | Magdalini Tozakidou | Jasmin Busch | Uta Herden | Lutz Fischer | Michael Groth | Kay U. Petersen | Knut Helmke

1Department of Pediatric Radiology, Diagnostic and Interventional Radiology and Nuclear Medicine, University Clinic Hamburg-Eppendorf, Hamburg, Germany
2Department of Hepatobiliary Surgery, University Clinic Hamburg-Eppendorf, Hamburg, Germany
3Department of Psychiatry and Psychotherapy, University Hospital Tübingen, Tübingen, Germany

Correspondence
Jochen Herrmann, Abt. Pädiatrische Radiologie, Universitätsklinikum Hamburg-Eppendorf, Martinistraße 52, D-20246 Hamburg, Germany. Email: j.herrmann@uke.de

Abstract
Color Doppler US is a readily available imaging modality for the evaluation of liver transplants. The aim of our study was to evaluate the temporal course of color Doppler US findings in children after LTX and to investigate the effect of resolving and persisting abnormalities during follow-up on long-term outcome. All children who underwent LTX during January 2000 until December 2003 (155 LTX in 137 patients, 75 male and 62 female; mean age at LTX 4.1 ± 4.8 years; range, 0.1-16.3 years) were retrospectively evaluated. Following a predefined ultrasound protocol with prospective documentation, intraoperative, post-operative, and follow-up examinations were evaluated for color Doppler abnormalities. The time of occurrence and temporal course of the findings were recorded. Graft survival rates and graft survival times were compared. Abnormal color Doppler US examinations were noted in 98 of 155 grafts during the entire observational period (63.2%). In 57 of 98 grafts (58.2%), abnormalities were limited to the perioperative period (<30 days after LTX). Survival of grafts with transient perioperative abnormalities was similar to transplantations with regular color Doppler US examinations (graft survival rates, 80.7% vs 84.2%, P = .622; mean graft survival time, 2596.92 vs 2511.40 days, P = .67). Grafts with persisting color Doppler US abnormalities in the follow-up period (>30 days after LTX; 37/98 LTX, 37.8%) showed reduced survival compared with regular courses (graft survival rate 62.2% vs 80.7%, P = .047), indicating underlying organ-specific alterations. Standardized longitudinal evaluation during the perioperative and the follow-up period can enhance the prognostic capabilities of color Doppler US in children following LTX.

Keywords
children, Doppler, liver transplantation, prognosis, ultrasound

Abbreviations: LTX, liver transplantation; OLT, orthotopic liver transplantation; Red, reduced graft; RI, resistance index; Split, cadaveric split graft; Split-LR, living-related split graft; US, ultrasound.
1 | INTRODUCTION

Color Doppler US is the primary imaging modality for the evaluation of liver allografts after transplantation.\(^1\) The technique is easily available at the bedside and has good sensitivity for the detection of vascular and biliary complications, which are generally more frequent in pediatric transplantation. To aid in early diagnosis and therapy, most centers implemented post-transplantation color Doppler US monitoring programs applying close imaging intervals.\(^2\)

In the perioperative period after transplantation, multiple abnormalities may be seen on monitoring examinations.\(^3,4\) In addition to specific vascular and biliary complications occurring at the site of the anastomosis, the problems may be primarily intrahepatic and include reperfusion injury, acute rejection, toxic damage, hepatitis reactivation, or infection.\(^5\) Depending on the nature of the problems, color Doppler US findings may be specific and able to pinpoint a definite cause, or may yield unspecific results. Follow-up examinations are usually recommended to see whether abnormalities have resolved or persist. Transient color Doppler US findings with a tendency to normalize in short-term follow-up may be attributable to initial organ swelling or effective therapy. Persisting or increasing abnormalities point toward underlying structural deficits. Examples are problems with the anastomosis or irreversible parenchymal damage of whatever etiology.

The purpose of this study was to evaluate the temporal course of color Doppler US abnormalities in children after liver transplantation and the effect of resolving or persisting findings on long-term outcome.

2 | METHODS

2.1 | Patient population and observational period

All pediatric patients who were liver-transplanted for progressive liver failure at our institution during the period 01.01.2000 until 31.12.2003 were retrospectively evaluated. The observational period lasted until 01.06.2008. Of 182 consecutive LTX performed in 162 patients [mean age, 4.5 years; range, 0.1–18.4 years] in this period, 25 patients with a total of 27 LTX underwent US examinations conducted by multiple investigators and were primarily excluded. 137 pediatric patients with a total of 155 LTX were included in the study [75 male and 62 female; mean age at LTX 4.1 ± 4.8 years; range, 0.1–16.3 years]. Patients were identified from a review of a prospectively acquired liver transplant database. Data including patient demographics, perioperative findings, complications, and outcomes were extracted. The color Doppler US investigator results were prospectively documented. Ethics approval for this study was obtained from the local ethics committee with waived informed consent.

2.2 | US monitoring and classification

Protocol ultrasound investigations were performed by a single, experienced pediatric radiologist (KH) using a commercial scanner (HDI\(^®\) 5000 SonoCT\(^®\), Philips Medical Systems) with a L10-5 MHz linear array transducer and a C7-4 MHz curved array transducer. Intraoperative ultrasound was performed after reperfusion, before and after wound closure. Post-operative US was performed daily during the stay in the intensive care unit, for approximately 5 days. Thereafter, ultrasound investigations were done at least twice a week until hospital discharge. Follow-up visits in our clinic with routine US investigations were scheduled every 6 months for the first 2 years and then in yearly intervals.

The ultrasound examination included a real-time morphologic b-mode evaluation of the liver parenchyma and color Doppler US mapping of the hepatic artery, portal vein, hepatic veins, and inferior vena cava. Spectral analyses were obtained at the porta hepatitis and the site of the graft periphery about 1 cm below the liver surface. Morphological abnormalities included bile duct dilatation and inflammatory changes (abscess formation).

Color Doppler US abnormalities were diagnosed when one or more of the following criteria were present in at least two consecutive examinations: 1,2,6,12: hepatic artery—tardus-parvus pattern, RI < 0.5 or >0.8, peak systolic velocity <30 cm/sec or peak focal systolic velocity >200 cm/sec, change in systolic peak velocity of >30% in comparison with previous investigations, and absence of arterial flow at the porta hepatis or at intraparenchymal level; portal vein—peak velocity <20 cm/sec, disproportional peak velocity in the portal vein compared with the splenic vein (peak portal velocity < peak splenic velocity), undulating or retrograde portal venous flow, or change in peak portal velocity >30% in comparison with previous values; and hepatic veins—signs of hepatic outflow obstruction, loss of phasic waveform in follow-up, and peak venous velocity >120 cm/sec.

The perioperative period comprised the intraoperative and post-operative period until 30 days after transplantation. The follow-up period was defined as the time span after the post-operative period. Graft survival time was defined as the time span until re-transplantation, patient death, or end of the observational period.

- Courses without any abnormalities applying morphologic criteria color Doppler criteria during the perioperative and the follow-up period were defined as “normal US findings.”
- Courses without any color Doppler abnormalities were defined as “normal color Doppler findings.”
- Courses with transient perioperative color Doppler abnormalities limited to the period of 30 days after LTX were termed “perioperative color Doppler abnormalities.”
- Courses with persistent color Doppler abnormalities extending from the perioperative period into the follow-up period were termed “persistent color Doppler abnormalities.”
- Courses with unprecedented color Doppler abnormalities which newly developed during the follow-up period (>30 days after LTX) were termed “new color Doppler abnormalities at follow-up.”

2.3 | Statistical analysis

The frequency of different ultrasound abnormalities and courses was determined as the number of transplantations with these findings over the total number of transplantations performed. The re-LTX rate and
the graft survival rate in days were calculated for the whole group as well as for all subgroups. To test for differences between groups, Student’s t test was applied for metric variables and the chi-square test for non-metric variables. The mean age at LTX, weight at LTX, and cold and warm ischemic time between courses were compared by analysis of variance followed by post hoc tests for group-wise comparisons. The association between the US abnormalities and the re-LTX rate was determined using odds ratios, and P values were calculated by applying the Mantel-Haenszel test. A failure time analysis was performed to assess the relation between different courses and graft survival time. The Tarone-Ware test was used to compare graft survival functions in transplantations with different courses. SPSS software (11.51) was used for the calculation of the statistical analysis.

3 | RESULTS

3.1 | Courses with normal US findings

Courses with regular US examinations including a homogenous grayscale assessment of the liver parenchyma, non-dilated biliary tree, and a regular color Doppler evaluation of the hepatic vasculature were noted in 38 of 155 liver transplantations during the observational period (24.5%). Patients with normal US findings were characterized by higher graft survival rates and longer graft survival times compared with cases showing abnormalities (graft survival rate, 92.1% vs 72.6%, P = .015; graft survival time, 2833.1 ± 110.2 days vs 2380 ± 112.1 days, P = .016). The overall graft survival rate for the whole collective was 77.4% (120 of 155 transplantations; Figure 1).

3.2 | Courses with abnormal color Doppler US

Abnormal color Doppler findings of the graft vasculature were noted in 98 of 155 transplantations during the observational period (63.2%). In 57 of 98 transplantations with abnormalities (58.2%), the color Doppler abnormalities were resolving and limited to the perioperative period (<30 days after LTX). In 37 of 98 transplantations (37.8%), color Doppler abnormalities persisted from the perioperative into the follow-up period. In 4 transplantations, Doppler abnormalities were found for the first time during the follow-up period (4/98 cases, 4.1%; Table 1).

Graft survival was similar in transplantations with normal color Doppler findings (n = 57) and transplantations with abnormal color Doppler findings resolving within perioperative period (graft survival rates, 80.7% vs 84.2%, P value, .622; mean graft survival time, 2596.92 ± 143.5 vs 2511.40 ± 142.3 days, P value, .67; Table 2). Transplantations in which perioperative color Doppler abnormalities persisted into the follow-up period demonstrated reduced graft survival when compared with transplantations without color Doppler abnormalities in the post-operative period (graft survival rate, 62.2% vs 80.7%, P value, .047; graft survival time, 2008.37 days vs 2511.4 days, P value, .34; Figure 2, Table 2).

3.3 | Specific Doppler US findings

Among the specific Doppler US findings, hepatic artery thrombosis was most closely associated with later re-transplantation (Table 3). Hepatic artery thrombosis was surgically confirmed and revised in 13 transplantations. Immediate re-transplantation was necessary in 5 cases. Of the 8 longer-term survivors (>150 days), outcome was significantly better when follow-up examinations were normal (3/8 transplantations vs 5/8 transplantations, graft survival rates, 100% vs 0%, P = .005).

Color Doppler US abnormalities noted during follow-up after hepatic artery thrombosis in the longer-term survivors were a reduced maximum systolic flow velocity, increased resistive indices, and transcapsular arterial neovascularization. Hepatic artery stenosis was not associated with reduced graft survival. Portal vein thrombosis and hepatic vein stenosis occurred rarely (Table 3).
Organ monitoring of the transplant periphery showed a retrograde portal venous flow in 19 liver transplants. The finding was observed either transiently in the perioperative period (n = 8) or occurred later in the follow-up period (n = 11). Perioperative intraparenchymatous retrograde portal venous flow was attributed at the time to post-operative organ swelling and was not associated with a significantly reduced organ survival rate but reduced survival times (62.5%, vs 78.2%; OR, 2.16; *P* value, .31; graft survival time, 986.75 ± 673.0 vs 1550.8 ± 721.1 days, *P* value, .032). The development of retrograde portal venous flow during follow-up was linked to reduced graft survival rates and times (graft survival rate, 27.3%, vs 81.1%; OR, 11.56; *P* value, .001; 872.6 ± 688.7 days vs 1571.3 ± 708.5 days, *P* value, .002). Eight of 11 patients with retrograde portal venous flow detected during follow-up demanded later re-transplantation. Histopathology showed irreversible parenchymal damage in all explanted livers with high-grade fibrotic changes in 7 of 8 organs (87.5%), and extensive parenchymal necrosis in one case demanding subacute re-transplantation.

### TABLE 1
Recipient characteristics in patients with different postoperative courses as categorized by color Doppler US

| Parameters                                      | Normal (n = 57) | Perioperative abnormalities (n = 57) | Persisting abnormalities (n = 37) | P value |
|-------------------------------------------------|-----------------|--------------------------------------|-----------------------------------|---------|
| Age at LTX (y)                                  | 4.79 ± 5.07     | 4.26 ± 5.09                          | 2.66 ± 3.5                        | .043    |
| No. of male/female                              | 29/28           | 28/29                                | 24/13                             | .284    |
| Weight at LTX (kg)                              | 17.98 ± 15.4    | 16.18 ± 15.53                        | 10.9 ± 7.3                        | .005    |
| Preoperative patient status<sup>a</sup>          | 10/47           | 12/45                                | 7/30                              | .892    |

#### Type of transplantation<sup>b</sup>
(OLT/Red./Split/Split-LR)

| Type of transplantation                         | 15/4/26/12      | 8/6/22/21                            | 5/8/13/11                         | .113    |

#### Cold ischemic time (min)

| Cold ischemic time (min)                         | 530.95 ± 169.11 | 423.88 ± 190.51                      | 447.84 ± 177.79                   | .006    |

#### Warm ischemic time (min)

| Warm ischemic time (min)                         | 36.19 ± 12.7    | 34.57 ± 13.4                         | 39.2 ± 13.0                       | .266    |

Note: Significant differences between groups of ultrasound courses were noted. Group-wise comparisons showed significant differences between regular/persisting abnormalities regarding age at LTX (Tamhane test, *P* value .053) and weight at LTX (*P* value .011). Cold ischemic time was significantly longer in regular/perioperative abnormalities (Scheffé test, *P* value .008).

<sup>a</sup>Preoperative patient status was defined according to Eurotransplant liver allocation system, differentiating high-urgency listing from chronic disease (elective).

<sup>b</sup>Type of transplantation gives the No. of patients with full graft OLT, Red., Split, and Split-LR. Significant findings (*p* < .05) are marked in bold.

### TABLE 2
Results of longitudinal color Doppler evaluation after liver transplantations and association with graft survival

| Parameters                                      | N    | Graft survival rate | Odds ratio | P value |
|-------------------------------------------------|------|---------------------|------------|---------|
| Color Doppler abnormal                          | 98   | 75.5%               | 1.41       | .406    |
| Limited to perioperative period                 | 57   | 84.2%               | 0.52       | .127    |
| Persisting into follow-up period                | 37   | 62.2%               | 2.81       | .013    |
| Appearing in follow-up period                  | 4    | 75.0%               | 1.15       | .907    |
| Color Doppler normal                            | 57   | 80.1%               |            |         |
| All transplantations                            | 155  | 77.4%               |            |         |

Note: Perioperative color Doppler abnormalities: intra- and post-operative changes limited to the period <30 d after LTX; follow-up color Doppler abnormalities: changes appearing in the period >30 d after LTX; persisting color Doppler abnormalities: changes persisting from the perioperative period into the follow-up period. Significant findings (*p* < .05) are marked in bold.
This study showed that longitudinal evaluation of standardized US examinations performed intraoperatively, post-operatively, and during follow-up carries prognostic information regarding transplant viability and long-term outcome.

During the perioperative period (intraoperatively until 30 days after LTX), abnormal Doppler results were a frequent finding and
noted in 60.6% of all transplantations in children (94/155 LTX). Abnormal findings included specific vascular complications and distinct intrahepatic conspicuities. Among the vascular complications, hepatic artery thrombosis and hepatic artery stenosis were the most common and occurred in 8.4% (13/155 transplantations) and 5.8% (9/155 transplantations), respectively, which is in accordance with the numbers reported in the literature.1,2,13-17

The largest share of post-operative Doppler findings was accounted for by distinct intrahepatic anomalies including arterial flow disturbances and hepatofugal portal venous flow. The cause of these intrahepatic abnormalities affecting one or more tributaries may be multifactorial. In principle, parenchymal damage induced by preservation-reperfusion injury, early rejection, increased intra-abdominal pressure by disproportionate size of the graft in relation to the abdominal cavity, and altered post-operative hemodynamics can be responsible.18 In practice, conspicuous intrahepatic anomalies prompted short-term follow-up examinations to assess the clinical significance of these findings. Our study showed that Doppler abnormalities limited to the perioperative period (<30 days after LTX) were not associated with adverse outcome irrespective of their type or quality. The transient nature of the findings indicates that the underlying causes have resolved (eg, post-operative reperfusion injury) or have not translated into definite structural deficits. The case can be illustrated in long-term survivors of hepatic artery thrombosis. When Doppler examinations after surgical revascularization were within normal limits, the graft survival rate was significantly higher compared with transplantations that showed continuing abnormalities.

In contrast, grafts with persisting Doppler abnormalities, which were detectable in the perioperative and repeatedly during the follow-up period, were characterized by reduced graft survival indicative for underlying structural problems. The case can be illustrated by reversed intrahepatic portal venous flow. The finding was only relevant for prognostication when noted during the follow-up period and was always linked with previously complicated post-operative courses. Studies on adult patients demonstrated that hepatofugal flow of the intrahepatic portal vein branches is associated with cirrhosis, poorer prognosis, and more severe manifestations of liver disease.19-21 Our study of pediatric patients fully supports this finding. Children with reversed intrahepatic portal venous flow during follow-up were characterized by very high re-LTX rates. Histopathology confirmed irreversible parenchymal damage with high-grade fibrotic or necrotic changes in the explanted organs. Reversed intrahepatic portal venous flow in the acute post-operative situation was always self-limiting. The finding may be explained by disturbed equilibrium and organ swelling.

It is important to note that prolonged Doppler abnormalities were noted significantly more often in the smaller recipients. Although speculative, the reason may be attributed to disproportionate size of the donor and recipient vessels and the generally more difficult procedure in small children resulting in a larger proportion of transplantations with difficulties in the younger age-group.

This study has the following limitations: (a) The study design was retrospective, depending on medical documentation and prone to selection bias. All the Doppler US results were prospectively documented. (b) It was single-center, single investigator study. Doppler US results are known to be operator-dependent and require a high level of skill. To avoid interoperator variability and ensure the sufficient quality of the results, transplantations examined by multiple sonographers were primarily excluded from the analysis. Reproducibility of the results by other investigators has not been shown. (c) In order to only compare data acquired with the same US machine, we analyzed follow-up examination only until June 2008. Later follow-up examinations were not included due to technical/equipment changes in our department at that time point. Since care of transplanted patients and, thus, transplant survival has improved in the last decade, survival data in our cohort might have been different in later cases. However, the primary aim of our study was not to present survival data, but to present the prognostic value of standardized follow-up US examinations (d) Doppler US findings with high clinical impact, for example, hepatic artery thrombosis, usually prompted immediate surgical revision or intervention. Unspecific findings or findings with suspected low clinical impact were followed-up. Histopathological correlation was usually not available.

In conclusion, standardized longitudinal evaluation of color Doppler US results in children with LTX enhances the methods of prognostic capability regarding long-term outcome. The findings of this study support the rationale to perform close intra- and post-operative organ monitoring as perioperative Doppler abnormalities can be found in a large proportion of transplantations. In these patients, timely follow-up visits are indicated to see whether persisting deficits can be found which are linked with adverse outcome. Transplants with inconspicuous perioperative courses rarely present with abnormalities during follow-up and are characterized by high graft survival rates. In these patients, wider intervals between follow-up visits may be appropriate.

AUTHOR CONTRIBUTIONS
J. Herrmann: designed study, acquired the data, analyzed the data, and prepared the manuscript. M. Tozakidou: prepared the manuscript. J. Busch and M. Groth: prepared the manuscript and acquired the data. U. Herden and L. Fischer: critically revised the article. KU Petersen: involved in data analysis/statistical evaluation. K. Helmke: designed the study and acquired the data.

ORCID
Magdalini Tozakidou https://orcid.org/0000-0002-4831-8312

REFERENCES
1. Crossin JD, Muradali D, Wilson SR. US of liver transplants: normal and abnormal. Radiographics. 2003;23(5):1093-1114.
2. Broering DC, Kim JS, Mueller T, et al. One hundred thirty-two consecutive pediatric liver transplants without hospital
mortality: lessons learned and outlook for the future. Ann Surg. 2004;240(6):1002-1012; discussion 1012.
3. Singh AK, Nachiappan AC, Verma HA, et al. Postoperative imaging in liver transplantation: what radiologists should know. RadioGraphics. 2010;30(2):339-351.
4. Gu L, Fang H, Zhang S, Chi J, Li F, Xia Q. Intra-operative portal hemodynamics in pediatric LDLT: doppler ultrasound surveillance. Pediatr Transplant. 2018;22(5):e13200.
5. Rawal N, Yazigi N. Pediatric liver transplantation. Pediatr Clin North Am. 2017;64(3):677-684.
6. Berrocal T, Parron M, Alvarez-Luque A, Prieto C, Santamaria ML. Pediatric liver transplantation: a pictorial essay of early and late complications. Radiographics. 2006;26(4):1187-1209.
7. De Gaetano AM, Cotroneo AR, Maresca G, et al. Color Doppler sonography in the diagnosis and monitoring of arterial complications after liver transplantation. J Clin Ultrasound. 2000;28(8):373-380.
8. Ganschow R, Nolkemper D, Helmke K, et al. Intensive care management after pediatric liver transplantation: a single-center experience. Pediatr Transplant. 2000;4(4):273-279.
9. Garcia-Criado A, Gilabert R, Nicolau C, et al. Early detection of hepatic artery thrombosis after liver transplantation by Doppler ultrasonography: prognostic implications. J Ultrasound Med. 2001;20(1):51-58.
10. Suzuki L, de Oliveira IR, Widman A, et al. Real-time and Doppler US after pediatric segmental liver transplantation: II. Hepatic vein stenosis. Pediatr Radiol. 2008;38(4):409-414.
11. Suzuki L, de Oliveira IR, Widman A, et al. Real-time and Doppler US after pediatric segmental liver transplantation: I. Portal vein stenosis. Pediatr Radiol. 2008;38(4):403-408.
12. Wozney P, Zajko AB, Bron KM, Point S, Starzl TE. Vascular complications after liver transplantation: a 5-year experience. AJR Am J Roentgenol. 1986;147(4):657-663.
13. Dodd GD 3rd, Memel DS, Zajko AB, Baron RL, Santaguida LA. Hepatic artery stenosis and thrombosis in transplant recipients: doppler diagnosis with resistive index and systolic acceleration time. Radiology. 1994;192(3):657-661.
14. Legmann P, Costes V, Tudoret L, et al. Hepatic artery thrombosis after liver transplantation: diagnosis with spiral CT. AJR Am J Roentgenol. 1995;164(1):97-101.
15. Yazigi NA. Adherence and the pediatric transplant patient. Semin Pediatr Surg. 2017;26(4):267-271.
16. Cuenca AG, Kim HB, Vakili K. Pediatric liver transplantation. Semin Pediatr Surg. 2017;26(4):217-223.
17. Neil DA, Hubscher SG. Are parenchymal changes in early post-transplant biopsies related to preservation-reperfusion injury or rejection? Transplantation. 2001;71(11):1566-1572.
18. Hoevels J, Lunderquist A, Tylen U. Spontaneous intermittent reversal of blood flow in intrahepatic portal vein branches in cirrhosis of the liver. Cardiovasc Radiol. 1979;2(4):267-273.
19. von Herbay A, Frieling T, Haussinger D. Color Doppler sonographic evaluation of spontaneous portosystemic shunts and inversion of portal venous flow in patients with cirrhosis. J Clin Ultrasound. 2000;28(7):332-339.
20. Wachsberg RH, Bahramipour P, Sofocleous CT, Barone A. Hepatofugal flow in the portal venous system: pathophysiology, imaging findings, and diagnostic pitfalls. Radiographics. 2002;22(1):123-140.
21. Hackl C, Schmidt KM, Susal C, Dohler B, Zidek M, Schlitt HJ. Split liver transplantation: current developments. World J Gastroenterol. 2018;24(47):5312-5321.
22. Eurotransplant-Foundation. ET Liver Allocation System (ELAS). Eurotransplant Manual - version 5.5. 2016: Chapter 5.

How to cite this article: Herrmann J, Tozakidou M, Busch J, et al. Persistence of post-operative color Doppler abnormalities is linked to reduced graft survival in pediatric patients after liver transplantation. Pediatr Transplant. 2019;23:e13593. https://doi.org/10.1111/petr.13593