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ORIGINAL ARTICLE

Clinical utility of microbubble contrast-enhanced ultrasound in the diagnosis of hepatic artery occlusion after liver transplantation

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Summary

To evaluate the frequency of use and the diagnostic accuracy of real-time contrast-enhanced ultrasound (CEUS) in the diagnosis of hepatic artery occlusion after liver transplantation. One hundred and fifty-two liver transplantations in 142 adult subjects, comprising 80 male patients and 62 female patients, were studied. After surgery, liver circulation was routinely assessed by conventional Doppler ultrasound (US). Wherever the examiners were not confident about the state of the circulation, CEUS was performed with one or more doses of a sulfur hexafluoride (SF-6)-containing second-generation contrast agent intravenously. Clinical follow up including repeat Doppler US, computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) of the liver vasculature were used as reference standards. During the first month after transplantation, Doppler US was inconclusive with regard to patency of the hepatic artery (HA) circulation in 20 (13 %) of 152 transplantations. CEUS was performed in these patients, and detected six cases of HA thrombosis (HAT) in five transplants. CEUS correctly ruled out HA occlusion in 15 transplants. All HA occlusions occurred during the first 14 days after transplantation. In the subset of transplantations examined with CEUS, the sensitivity, specificity and accuracy of CEUS were 100%. In approximately 13% of cases, conventional Doppler US did not provide sufficient visualization of the HA after liver transplantation. In these cases, correct diagnosis was achieved by supplementary CEUS.

Introduction

Liver transplantation is a well-accepted therapeutic option for both acute and chronic liver failure. However, postoperative complications may limit the long-term success. Among the clinically most significant complications are: arterial and venous thrombosis and stenosis, biliary disorders, infections, graft rejection, fluid collections and neoplasm [1]. Hepatic artery thrombosis (HAT) occurs in 3–8% of the transplant recipients. It may occur within the first 24 h, and is an important cause of retransplantation [2–8]. Early diagnosis is of utmost importance as revascularization may prevent damage to the transplanted organ, especially the bile ducts.

Usually, conventional Doppler ultrasonography (US) is the initial imaging technique for identification of vascular complications [2,3,7,9,10]. It is also used for long-term follow up because it is mobile, does not involve ionizing radiation or iodinated contrast material, is noninvasive, and inexpensive. Contrast-enhanced US (CEUS) improves flow visualization in both the hepatic artery (HA) and portal vein (PV) and correctly differentiates between

thrombosis and a patent artery in patients without HA flow at conventional Doppler US [4,6,7,11–13]. However, the clinical value of a two-step approach, first conventional ultrasound Doppler, and second, in case of uncertainty, CEUS of liver transplant vasculature with a second-generation contrast agent has not been determined.

Having used CEUS for this indication during the last several years, we retrospectively determined the frequency of use and diagnostic accuracy of CEUS with regard to HA occlusion after liver transplantation.

Patients and methods

The study was approved by our institutional review board. The investigation included only routine clinical follow-up data of liver transplanted patients and informed consent was not required. All consecutive liver transplant recipients above 18 years of age who had undergone transplant procedure in our institution during the period between September 2004 and October 2007 were eligible for inclusion in our study. During the above period, 153 liver transplantations had been performed in 143 recipients (our institution is the sole transplantation center in Norway), all from deceased donors, except three patients in whom *ex vivo* resection of otherwise unresectable hepatobiliary malignancies and autotransplantation were performed. One retransplantation was not included, because the patient died peroperatively. Hence, the study included 152 liver transplantations, including 10 retransplantations in 142 patients (median 50 years, range from 19 to 73 years, 80 men, Table 1). Radiologic information was retrospectively retrieved from RIS/PACS. The electronic journal files of patients were also reviewed.

Table 1. Diagnosis and number of transplantations included.

Diagnosis	Number of transplantations
Primary sclerosing cholangitis	32
Fulminant liver failure	15
Hepatitis C	13
Primary bilary cirrhosis	12
Alcoholic liver disease	12
Hepatocellular carcinoma	11
Retransplantations*	10
Liver metastases	12
Autoimmune hepatitis/cirrhosis	6
Nonalcoholic steatohepatitis	5
Cryptogenic cirrhosis	5
Cystic liver disease	4
Cholangiocarcinoma	3
Hepatitis B	2
Oxalosis	2
Budd-Chiari syndrome	2
Other†	6
Total	152

*Reasons for retransplantation during study period were: Primary graft failure (n = 3), hepatic artery thrombosis (n = 2), portal vein thrombosis (n = 2), infection including multiple abscesses (n = 1), complications of bile leakage (n = 1) and recurrence of primary sclerosing cholangitis (n = 1).

†Malignant hemangioendothelioma, gall bladder cancer, liver fibrosis of unknown etiology, recurrence of systemic lupus erythematosus, portal vein occlusion and secondary biliary cirrhosis because of biliary atresia, one case each.

Ultrasound

Intra-operative US examinations were not included. All patients were routinely examined according to our post surgical protocol with Doppler US on the first postoperative day. Later, they were examined at 1, 6, and 12 months, and yearly thereafter. Clinical indications for additional ultrasonographic examinations were increased levels of liver enzymes, fever or drop in serum hemoglobin indicating bleeding. Several radiologists performed the examinations with routine gray-scale, color and spectral Doppler US using a Siemens Acuson Sequoia 512 (Siemens Acuson, Mountain View, CA, USA) with a 4C1 or 4V1 transducer. During off-duty hours, the examination was performed by the radiologists on call, all of whom had more than 2 years of experience with abdominal ultrasound. The radiologists had all been trained to examine liver-transplanted patients with respect to size of the liver and echogenicity of parenchyma, state (open or not) of the HA both intra- and extra-hepatically including measurement of resistive index (RI, normal 0.5–0.7). The normal hepatic artery Doppler waveform should have a rapid systolic upstroke and continuous diastolic flow [9]. Patency and flow direction of portal vein (PV), retrohepatic vena cava and hepatic veins were also evaluated.

In cases where the examiner could not find an open HA with a normal arterial spectral curve, the Doppler US was repeated by another, more experienced radiologist during the same session. If still in doubt about the patency of the artery, the more experienced radiologist performed CEUS with the same scanner using one or more 2.4 ml doses of a sulfur hexafluoride-containing second-generation contrast agent (SonoVue, Bracco, Milan, Italy) given intravenously in an antecubital vein with a 5-ml 0.9% saline flush. A radiologist with 7 years of experience with CEUS at the start of the study performed the majority (90%) of the CEUS examinations with regard to the patency of HA. Three other, experienced radiologists performed the remaining 10% of CEUS examinations.

The Cadence contrast program with low mechanical index imaging and pulse inversion technique was used.

The operator could choose to display the contrast information in different ways; either as an image exclusively based on contrast echoes or as an overlay on a low mechanical B-mode image (mixed mode). A dual screen display with the contrast images and low mechanical gray-scale image side-by-side was instructive and often used. The images were saved as still images and/or video clips. Patients were under medical supervision during and for at least 30 min following the administration of the contrast agent.

Reference standards

Data of clinical follow-up examinations including further Doppler US examinations, CT or MR angiography of the liver vasculature in selected cases, laboratory analyses of liver enzymes, liver function tests, clinical examination and surgery were used as reference standard.

Computed tomographic angiography (CTA) was obtained with a 64-detector row CT scanner (Light speed VCT; GE Medical Systems, Milwaukee, WI, USA). Contrast-enhanced CT scanning was performed after intravenous injection of 150 ml of iodixanol (iodine 320 mg/ml; GE Healthcare, Oslo, Norway) and 50-ml saline flush through a catheter inserted into an antecubital vein by using a power injector at a flow rate of 5 ml/s. Arterial phase imaging was initiated with a bolus-tracking technique (Smart Prep; GE Medical Systems).

Three-dimensional (3D) gadolinium-enhanced MR angiography of the abdomen including hepatic vessels was performed using a 1.5-T whole-body unit (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) equipped with a body phased array coil. A fast 3D spoiled gradient-echo sequence was acquired in a coronal plane during breath-hold in expiration before and after contrast medium injection of 0.2 mmol/kg body weight gadopentate dimeglumine (Magnevist, Schering, Berlin, Germany) followed by 20-ml saline, both injected at a rate of 2.5 ml/s using an automated injector pump. Imaging was performed in the arterial phase and in two venous phases. To guarantee proper timing, a test bolus technique was applied.

Statistical analysis

The sensitivity, specificity, and accuracy for determination of HA occlusion (both extra- and intra-hepatically) in the subset of patients examined with CEUS were calculated. Sensitivity was defined as the probability of a positive test in a transplant with an occluded artery. Specificity was the probability of a negative test in a transplant with an open artery.

Results

The first examination was performed within 4 days in all but three transplantations, median 1 day (range 0–12 days). Totally, 600 Doppler US examinations (median 4 per patient, range 1–12) were performed during the first month postoperatively (including the exam at the end of month 1). During the entire study period, a total of 1118 Doppler US examinations were performed (median 7 per transplantation, range 1–32). The median time of follow up was 1 year (366 days, range 1 to 1125 days). Major findings are included in Fig. 1.

Of the 600 Doppler ultrasonographic examinations performed during the first month after transplantation, the examiners were confident about the state of the HA in 572 Doppler US examinations after 132 (87%) transplantations. No case of HA thrombosis was detected during the follow up in this group. However, eight cases of main HA stenoses or suspected stenoses and one case of left HA stenosis were detected with Doppler US. They were detected because of abnormal spectral curves and RIs and confirmed by CTA, MRA and conventional angiography. Of these, three patients were treated with

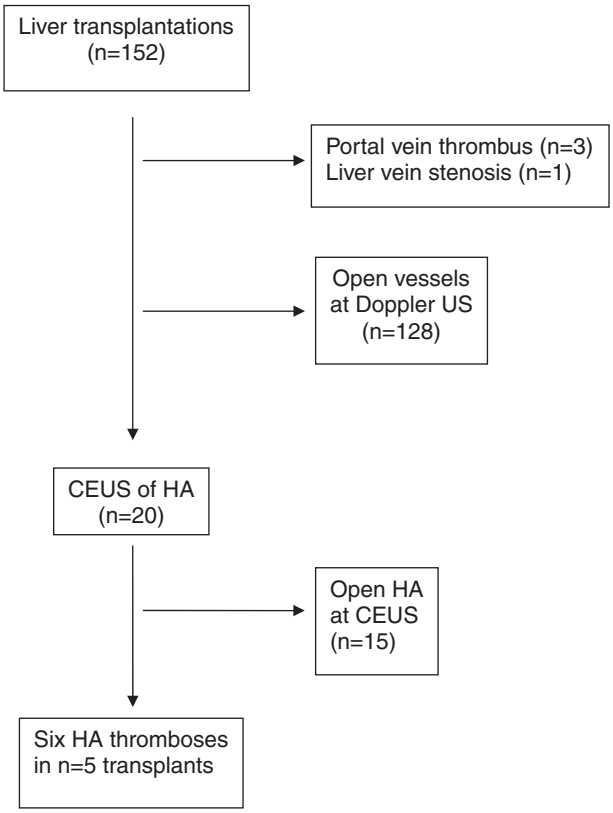

Figure 1 Flow-chart of included patients (*n* = number of transplantations). HA, Hepatic artery; CEUS, contrast-enhanced ultrasound.

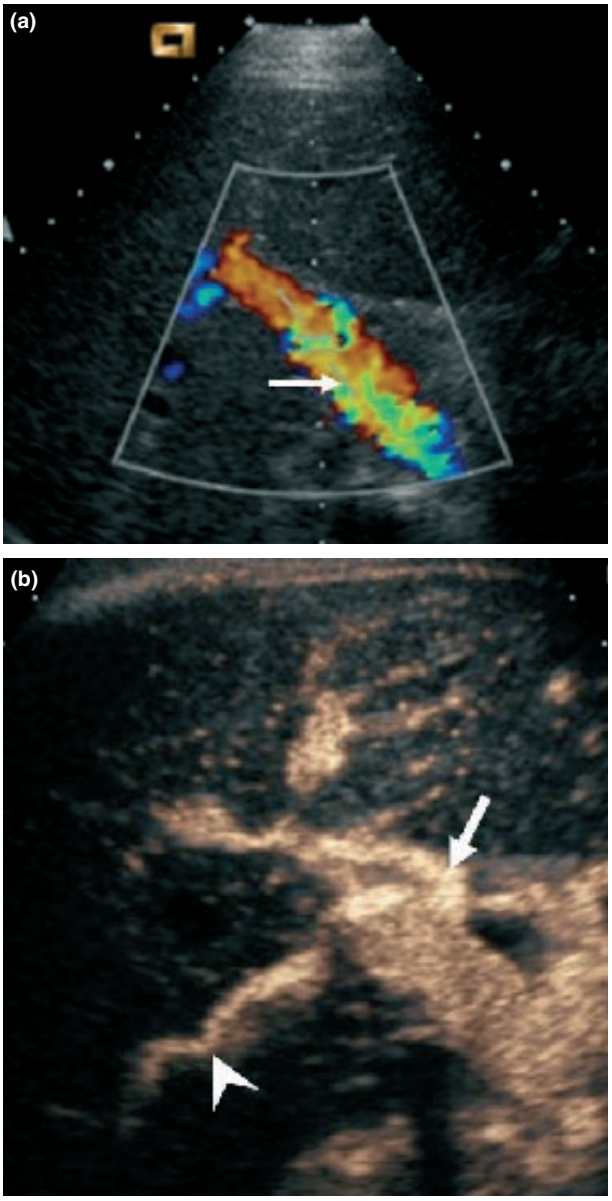

Figure 2 Forty-one-year-old male patient, 1 day after liver transplantation. (a) Transversal color Doppler ultrasound (US) image through the liver hilum. The portal vein (arrow) is clearly depicted, but the hepatic artery can not be seen with confidence. Corresponding axial image (b) after contrast-enhancement (CE) clearly shows an open hepatic artery in the hilum (arrow) as well as a right intra-hepatic branch (arrowhead) of the intra-hepatic artery in right liver lobe.

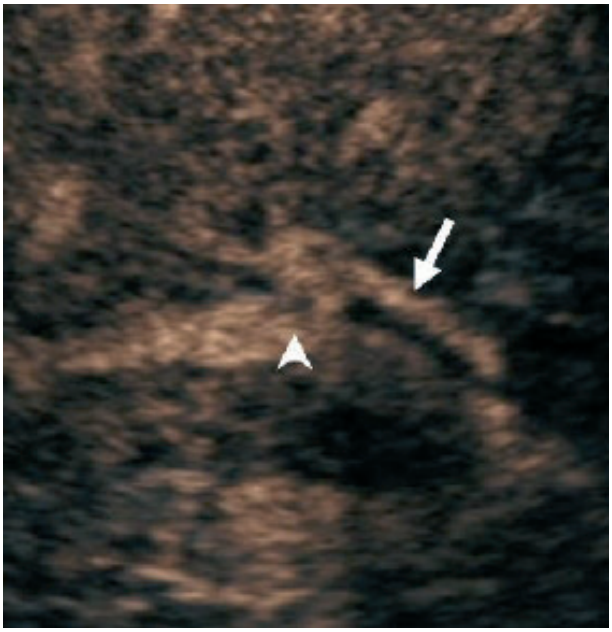

Figure 3 Sixty-three-year-old male patient, first postoperative day after transplantation. An open, but small hepatic artery (arrow) is seen parallel to the portal vein (arrowhead) in the liver hilum at contrast-enhanced ultrasound (CEUS). The artery could not be seen with color Doppler US. Early contrast-enhancement of the small hepatic artery made spectral analysis possible.

stenting and one patient with balloon angioplasty during the follow-up period.

On the other hand, Doppler US was inconclusive in 23 cases after 20 out of 152 (13%) transplantations with regard to HA patency. These examinations were supplemented with CEUS during the same session which detected six cases of HA thrombosis in five of these transplants (Figs 2a,b, 3, and 4a,b). Five HA occlusions were confirmed the same day at surgery; the last one by CT angiography 7 days later. One HA thrombosis was falsely diagnosed as open with Doppler US at primary reading, but an experienced radiologist who read the examination the morning after considered the HA spectral curve abnormal and recommended reexamination. This Doppler US examination was therefore considered inconclusive and CEUS was performed during the same session and documented an occluded artery. The patients was transferred to surgery where a HA occlusion was confirmed. In the remaining 17 examinations of 15 transplants an open HA was found by CEUS and documented by clinical follow up, including renewed Doppler US examinations. Of these cases, CT angiography documented an open artery in 10 and MRA in two cases.

HA occlusions were detected by CEUS at day 0, 1, 1, 2, 5 and 14 after transplantation respectively. US was the first imaging modality to detect an occluded artery in all cases. Five of the six cases were confirmed by surgery. Reoperation was not considered an option in the last case, and an occluded artery was confirmed by CT angiography 7 days after CEUS. Sensitivity, specificity and accuracy of CEUS for detection of HA occlusion were all 100% on a per examination basis (Table 2).

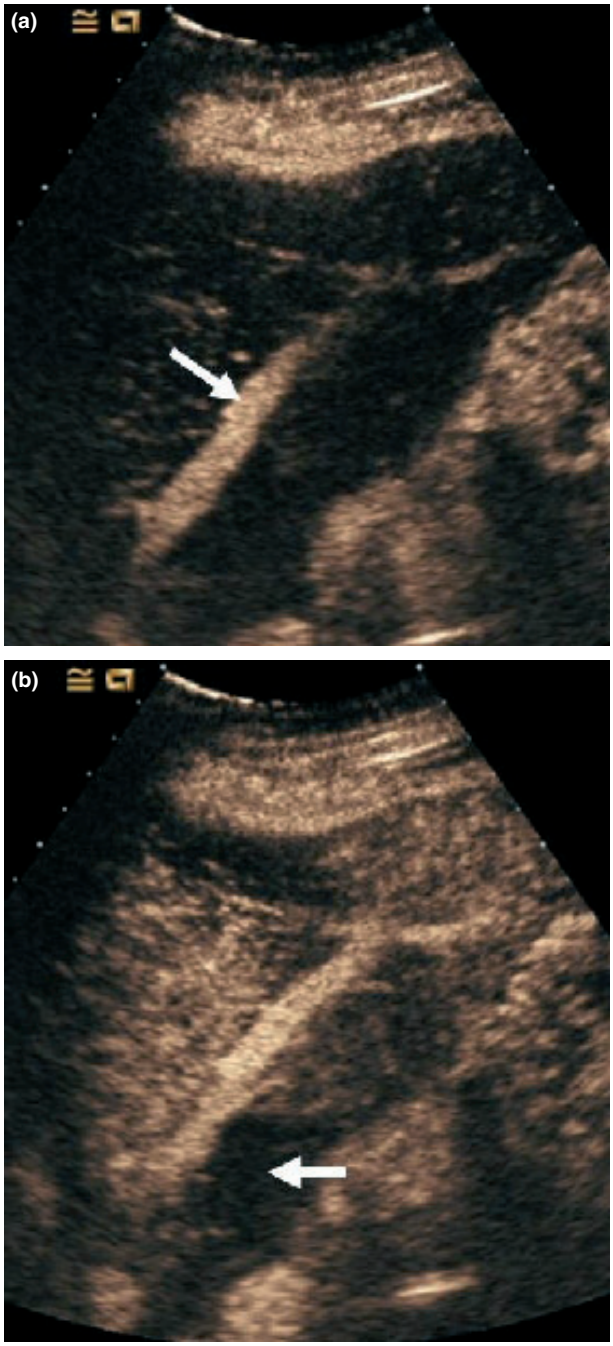

Figure 4 Forty-four-year-old auto-liver-transplanted female patient. Contrast-enhanced ultrasound (CEUS) showed an occluded hepatic artery 2 days after transplantation, confirmed surgically. The artery was reopened, but at day 6, CEUS again showed no arterial signal. (a) Transversal scan of the left lobe shows filling of portal veins only. (b) 19 s after contrast-medium injection, large nonenhancing regions of the liver parenchyma (arrow) indicate avascular zones.

Of 23 CEUS examinations, the Doppler ultrasonographic signal of HA had been considered insufficient in 16 (no intra-, but signal extra-hepatically). Of these, the HA was open in 15 and occluded in one. Of the seven examinations without any Doppler signal at all in HA, the artery was occluded in five and open in two. One of these patients had an uneventful follow up; the other was examined with CEUS perioperatively. CEUS revealed an open, but small HA with weak contrast enhancement and the HA flow was regarded as insufficient. The arterial anastomosis was revised, and thereafter, a strong HA Doppler signal was found with conventional US. No HA occlusion occurred subsequent to 14 days post-transplantation.

Table 2. Data for calculation of sensitivity and specificity (both 100%) of hepatic artery occlusion in 23 contrast-enhanced ultrasound (CEUS) examinations after 20 transplantations.

	Hepatic artery occlusion (reference standard)	
CEUS	Present	Absent
Occluded	6	0
Open	0	17

Discussion

In this study, a two-step approach for assessment of liver vessel patency was performed, first conventional Doppler US, and then, in case of uncertainty, real-time CEUS with a second-generation contrast agent intravenously. By this approach, all six HA occlusions that had occurred in five out of 152 liver transplantations were disclosed. A prevalence of HA occlusion of 4% is in agreement with previous studies [2,4–6,8]. In these patients, this serious complication could be corrected surgically without undue delay because of bed-side documentation of an occluded HA with CEUS. There was no false positive diagnosis of HA occlusion, and in 17 doubtful cases (according to Doppler US), an open artery could be visualized by CEUS, thus avoiding laparotomy or other more expensive imaging procedures.

In most cases, conventional Doppler ultrasound was sufficient to document an open HA after liver transplantation. Supplementary CEUS provided correct information in the remaining 13% of transplantations. In accordance with previous studies, CEUS improved flow visualization of the HA and PV and correctly differentiated between thrombosis and a patent artery in patients without HA flow at conventional Doppler US [4,6,11–13]. However, we are not aware of any previous study of the second-generation microbubble contrast agent SonoVue for this indication. Previous studies have used conventional angiography as a reference standard, whereas we used clinical follow up including renewed Doppler US and, in selected cases, CT and MR angiography. Microbubble

contrast was only given to the patients in whom the HA was not visualized with certainty. Doppler US including evaluation of flow curves has previously been shown to diagnose HA occlusion with high sensitivity [3,4,6,7,14]. We are therefore confident that clinical follow up including routine Doppler US and was able to exclude HA occlusion in the transplants that escaped CEUS examination during the study period. The most important time point for CEUS may be the immediate postoperative period (<24 h). Three of the six occlusions in our study occurred during this time period after transplantation, and all cases of HA occlusion occurred before day 14 after transplantation. Most occlusions (5 of 6) occurred in cases where the primary examiner had found no HA Doppler signal at all. This shows that if there is Doppler signal in the HA outside the liver, there is very little chance of an intra-hepatic thrombus.

Previously, the arrival times of microbubble contrast media in HA and PV have been reported to be approximately 12 and 16 s in normal livers and 14 and 21 s, respectively, in liver transplants [4,15]. In our experience, the interval between contrast media filling of HA and PV is shorter in the first days after transplantations leaving less time for the exclusive examination of the HA. This observation could reflect circulatory changes including a high resistance to HA flow that may shorten the arrival time in the PV, and should be explored in future studies.

Contrast-enhanced ultrasonographic examinations may have to be performed in the operating theater or in the intensive care unit where conditions are far from ideal. The opportunity to switch back and forth from contrast mode to spectral analysis should ideally be available as the Doppler waveform may provide crucial, additional information concerning the status of the HA. The fact that the artery is open does not always mean that the arterial supply to the transplant is sufficient as was the case in one of our patients. According to our findings, conventional Doppler is adequate in most cases. In case of doubt, CTA/MRA may be considered, but may be more cumbersome and time-consuming to perform postoperatively than CEUS. CEUS improved visualization of both extra- and intra-hepatic parts of the HA. This quality of CEUS is particularly valuable in the early postoperative phase when the often weak Doppler signals from intra-hepatic arteries are sometimes obscured by portal venous flow. Doppler US and CEUS should therefore be considered as complementary rather than competitive methods.

We did not detect any case of occlusion later than 2 weeks after transplantation, but eight patients required further examinations because of suspected stenosis of the HA at Doppler US. Collateral transformation of the hepatic artery after liver transplantation may occur [4,8,16]. However, we did not find any case of arterial collateral formation, but conventional angiography was used only for intervention and we cannot exclude the possibility that this could occur unnoticed by our follow-up regimen which did not include diagnostic conventional angiography of the liver vasculature.

One shortcoming of the study is the fact that all information was retrieved retrospectively. We consider it unlikely that incidences of HA thromboses other than those considered in this study may have been lost or gone unnoticed, because all liver transplantations in Norway are performed at our hospital, and all patients are followed closely for at least 10 years post-transplant. Our stored image material is therefore extensive and quite complete. Because of the retrospective design, we were not able to record how often the 'on-call radiologist' received a supporting hand by an 'expert radiologist' with regard to the conventional Doppler US. In contrast, all drug administrations were registered, and CEUS was only given in cases where both examiners could not confidently identify an open vessel.

In conclusion, conventional Doppler US proved sufficient to document open vessels after liver transplantation in most cases. Supplementary CEUS provided correct information in the remaining patients.

Authorship

AEB: designed and performed research/study, collected data, analyzed data, wrote paper. KB: performed research/study, collected data, analyzed data, wrote paper. AF: collected data, analyzed data, wrote paper.

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