

Role of Doppler Ultrasound Surveillance in Early Detection of Vascular Complications among Liver Transplant Recipients

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ABSTRACT

Living donor liver transplantation (LDLT) has been the last resort to treat endstage liver disease with improved success rates, provided the recent advances among the surgical technology, radiological appliances and new immune-suppressants. Vascular complications among liver transplant recipients are noted as a major threat to recipients' survival. Slender anastomotic vessels make recipients more prone to complications through the reconstruction process. Routine postoperative Doppler ultrasound surveillance is believed to play a major role in early diagnosis of complications through intra-operative and early post-operative assessment allowing timed accurate management and increasing chances of survival for the liver graft and recipients. This prospective work is done on 45 cases with end-stage liver disease for whom adult LDLT is performed. Forty-five liver transplant cases were included in our study. Routine Doppler ultrasound surveillance diagnosed twelve patients to have vascular complications. Further evaluation of these cases by triphasic CT study or by surgical exploration confirmed eleven out of the twelve cases to suffer true vascular complications and only one false positive case was found free from complication. Thirty-three cases were marked by Doppler ultrasound as free from complications and one false negative case was found. Routine DUS surveillance of liver graft recipients have 91.67% Sensitivity and 96.97% Specificity to detect vascular complications. Intra-operative assessment and early postoperative surveillance of adult living donor liver transplant recipients using Doppler ultrasound can detect or exclude vascular complications with high accuracy.



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1. INTRODUCTION

Candidate recipients/patients who suffer from end stage liver disease-exhibit versatile degrees of hepatic parenchymal dysfunction and spacious spectrum of hemodynamics dissimilarities [1]. Considering nature of

slender anastomotic vessels and their manipulation through the reconstruction process, vascular complications are not uncommon among post adult living donor liver transplantation [2]. The intra-operative and post-operative goals of Doppler ultrasound (DUS) inspection is to trace the anastomotic sites identifying the vascular complications as early as possible [2], [3]. Serial DUS surveillance allow the early diagnosis of vascular complications such as arterial or portal thrombosis/stenosis and venous thrombosis, they occur in approximately 1% to 10% of liver transplant recipients with the resulting increased risk of graft loss and post-transplant mortality. Further cross-sectional imaging is only performed in equivocal cases that show abnormal hepatic waveform where a more proximal abnormality is suspected [4].

This series primary aim is calculation of sensitivity and specificity of Doppler ultrasound routine surveillance in detecting vascular complications among liver transplant recipients.

2. Patients and Methods

The present Prospective diagnostic accuracy cross-sectional work is involving 45 consecutive cases with end-stage liver disease for whom adult LDLT is performed from October 2019 to December 2020 at our center to detect or rule out vascular complications among liver transplant recipients. Exclusion criteria were split liver transplantation and those with incomplete or missing relevant data. The research is obliged to ethical instructions of the 1975 Declaration of Helsinki, supervised by the responsible research ethical board of the transplant team and Ain Shams University ethical committee. Patient's consent to review their medical records and analysis were obtained ensuring patient data confidentiality through data collection. Assessment of recipients comprised routine surveillance by (DUS) carried out routinely by experienced radiologists of the transplant team, and further evaluation in equivocal cases by triphasic CT study or immediate surgical re-exploration in emergencies according to the team opinion. The surgery starts with total hepatectomy of the recipient liver followed by simultaneous implantation of the donor's liver. Anastomoses are performed between the donor liver and the recipient patient. Doppler Ultrasound (US) is mandatory to assess the graft's ultrasonographic texture, any possible focal masses, congestions or infarctions. Colored and Pulsed Doppler (triplex) are used to study the vascular anastomoses patency and flow pattern. A sample volume of the Doppler US system shall be placed in the midpart of the vessel. The angle correction is to be manually corrected during US evaluation. The lowest possible velocity scale and the least possible wall filter are simultaneously applied. The measurements were documented for consequent three times, the average of these measurements was calculated as regard each variable [5].

Vascular complications include acute complete or partial vascular occlusions (i.e., thrombosis or marked kinking), happening in the form of hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT), which are more common relative to hepatic venous or cavo-caval anastomoses [6]. The average hepatic artery of the graft is slender (2-5 mm in diameter) shows a rapid systolic upstroke waveform and continuous diastolic flow with Doppler assessment. The resistive index (RI) has to be in the range from 0.5 to 0.8 while the systolic acceleration time (SAT) has be below than 80 ms [7]. High resistance ($RI > 0.8$) might be encountered within 3 days postoperatively, returning to regular values afterwards. The Doppler ultrasound diagnostic criteria for HAT include the disappearance of arterial blood flow at the hepatic hilum (anastomotic site) or inside the graft on color Doppler flow imaging. If the HA isn't totally occluded, abnormal intrahepatic blood flow with a tardus-parvus spectrum ($RI < 0.5$ and $SAT > 80$ ms) can be detected [7].

The diagnosis of HAS on Doppler ultrasound is based on a focal increased blood flow velocity greater than 200 cm/s at the extrahepatic artery or the tardus- parvus waveform at the intra-hepatic arteries [8]. It is not difficult to diagnose PVT using gray-scale and Doppler ultrasound. The findings include partial or complete absence of flow or detection of a filling defect [4].

PVS is found mainly at the site of the anastomosis. During LDLT, vessel caliber mismatch is often encountered between the donor and recipient portal vein. Therefore, mild anastomotic stenosis is common but does not affect hemodynamics and liver function. When PVS is severe, symptoms of graft dysfunction and acute liver failure may occur, complicated with portal hypertension and ascites. Stenoses greater than 50% were considered hemodynamically significant [7].

Criteria for anastomotic site PVS include: regional anastomotic stenosis with a diameter < 2.5 mm, blood flow aliasing and acceleration at the stenotic site, blood flow velocity > 150 cm/s at the stenotic site, or velocity ratio $\geq 4:1$ between stenotic and pre-stenotic flow [4].

The diagnostic criteria for HVS using Doppler ultrasound remain controversial. The normal spectrum of the hepatic vein is a triphasic waveform reflecting the cardiac cycle, but in HVS cases the waveform is often biphasic even without any other signs or symptoms of outflow obstruction. HVS should be considered when a significant stenosis is revealed by the gray-scale ultrasound or a high-speed blood flow disorder appears at the stenosis. The ratio of stenotic to pre-stenotic blood flow velocity is greater than 3-4:1 with a flat hepatic venous wave and slow or even reversed blood flow at the distal-stenotic segment [7].

2.1 Intra-operative Doppler ultrasound

IODUS is conducted few minutes after the vascular anastomoses waiting for the early post-reperfusion hemodynamic changes to stabilize yet prior to biliary anastomosis. The ultrasound machine is placed to the recipient's right side with the non-sterilized left hand kept in contact with the machine. The abdominal cavity is better filled with warm saline and the operating table shall be tilted to the left.

Siemens multifrequency 7.5-10 MHz T-shaped transducers with color and pulsed Doppler is our choice.

a. Hepatic artery

Starting with HA evaluation which shall be unfolded unclamped allowing proper assessment of its patency detecting any possible thrombi, intraluminal flaps or strictures. We evaluate the hepatic artery at the pre-anastomotic, anastomotic and intra-graft sites. We obtain certain measures namely the peak systolic velocity (PSV), end diastolic velocity (EDV) and resistivity index (RI) which are documented ensuring correct technique as regard the PRF and angulation. The sample size is the least possible 2 mm, the wall filter is 100 Hz, and the pulse repetition frequency PRF is 3-4.5 kHz [6].

The pre and post anastomotic sites velocities are then divided to assess any possible hemodynamic significance. The intrahepatic optimal waveform of the artery implies a proper anastomosis and adequate arterial flow to the graft as well [8].

b. PV evaluation

It included initial inspection of the entire portal vein length most importantly in candidate recipients with portal vein thrombosis. The portal vein is assessed for the possible intraluminal thrombi, flaps, strictures or size mismatch between the donor and recipient site. Portal vein caliber and PSV are then assessed at the three different sites Pre anastomotic, anastomotic and intra-graft sites to identify any possible size mismatch or anastomotic strictures. Finally, evaluation of the intra-graft segments is done to ensure adequate intra-graft blood flow [9].

c. The hepatic veins

The hepatic veins anastomoses are identified (along with the hepatic veins or grafts for segments V and VIII). Starting with assessment of the hepatic venous caliber and velocity at the anastomotic and intra-graft sites calculating the ratio to detect any possible size mismatch. Ultrasonographic evaluation of the synthetic graft is technically unachievable, assessment of the intrahepatic flow implies its patency [10].

2.2 IV. Post-operative Doppler ultrasound

PO evaluation included Doppler ultrasound evaluation of the graft and the hepatic circulation. Doppler ultrasound (US) is carried out routinely every 24 hours in the first week. It is usually done using an ultrasound device (Siemens X 600 with Color Doppler equipment) employing a 3.75 MHz convex probe. The assessment is performed with the cases lying supine or semi-sitting and their arms raised above shoulder level. Vascular Scanning at the anterior axillary line using intercostal window. Assessment is done at the three usual levels namely pre-anastomotic, anastomotic site and intra-graft. In case a definite diagnosis of a vascular complication is reached and confirmed by Doppler ultrasound surveillance, interventional radiological treatment or open surgery is arranged for management. In equivocal diagnoses, further evaluation by MDCT angiography is arranged to reach a final diagnosis [4].

2.3 Statistical Analysis

Statistical analyses were performed by a statistician using the SPSS software, version 16.0 (SPSS, Chicago, IL, USA). Sensitivity and specificity were calculated for diagnostic CDUS, compared with the final clinical diagnosis intra-operatively or by CT triphasic study as the reference standard. Sensitivity was calculated as the proportion of patients with actual vascular complications who had an abnormal findings CDUS. Specificity was calculated as the proportion of patients with no actual vascular complications who had a normal anastomosis on CDUS. Accuracy was calculated as the proportion of patients whose vascular connections were correctly predicted using CDUS.

3. RESULTS

This prospective observational work was done on 45 end-stage liver disease cases who underwent adult LDLT.

		Subjects excluded by CT or clinically	Subjects confirmed by CT or clinically	
Negative vascular complications by Doppler	33 Cases	TN (True Negative) 32 free clinically	FN (False Negative) 1 Case Intra-graft distal HAT/damped proximally.	PN (Predicted Negative) FN + TN 33
Positive vascular complications by Doppler	12 cases 7 cases HAT 1 Case HAS. 2 case PVT. 1 case PVS. 1 Case HVS	FP (false positive) 1 case HAT Hemodynamic instability.	TP (true positive) 6 Cases HAT 1 case HAS. 2 case PVT. 1 case PVS. 1 case HVS.	PP (Predicted Positive) TP + FP 12
		ON (total Observed Negative) FP + TN 33	OP (total Observed Positive) TP + FN 12	Tot 45

Statistic	Value	95% CI
Sensitivity	91.67%	61.52% to 99.79%
Specificity	96.97%	84.24% to 99.92%
Positive Likelihood Ratio	30.25	4.36 to 210.00

Negative Likelihood Ratio	0.09	0.01 to 0.56
Disease prevalence (*)	26.67%	14.60% to 41.94%
Positive Predictive Value (*)	91.67%	61.31% to 98.71%
Negative Predictive Value (*)	96.97%	83.04% to 99.52%
Accuracy (*)	95.56%	84.85% to 99.46%

Forty-five liver transplant cases were included in our study. Routine Doppler ultrasound surveillance diagnosed twelve patients to have vascular complications. Further evaluation of these cases diagnosed eleven of them to have true vascular complications either clinically or by CT triphasic study and only one false positive case was found. By routine Doppler ultrasound surveillance 33 cases were marked as free from vascular complications of which 32 patients were confirmed later by clinical improvement and follow up. One missed patient who suffered undiagnosed true vascular complication was found. True vascular complications were twelve cases out of the forty-five cases. A sensitivity value of 91.67% and CI of 61.52% to 99.79%. with a specificity value of 96.97% and CI = 84.24% to 99.92%. with incidence rate of 26.67% and CI of 14.60% to 41.94%. Routine Doppler ultrasound surveillance carried 95.56% accuracy with CI= 84.85% to 99.46%.

The twelve Cases who were marked as vascular complication during the primary Doppler ultrasound surveillance were 7 cases of Hepatic artery thrombosis (HAT), 2 cases of portal vein thrombosis (PVT), one case of hepatic artery stenosis (HAS), one cases of Portal vein stenosis (PVS) and one cases of hepatic vein stenosis (HVS).

71 % of HAT cases (five out of seven) were diagnosed either by intra-operative Doppler or one day post-operatively that required immediate surgical exploration to confirm or exclude the diagnosis and redo the anastomosis, so no CT angiography was done. Two other cases exhibited no arterial flow by color Doppler duplex ultrasound during the first week post operatively, both underwent further evaluation by CT triphasic study prior to surgical exploration. One showed a slender yet patent HA all through its course in a pediatric recipient and so was interpreted as patent and included in our study as false positive case fig 1. Another one showed anastomotic site and intra-graft hepatic artery dissection who has been surgically explored on emergency basis and the HA was replaced by a synthetic graft. fig 2,3.

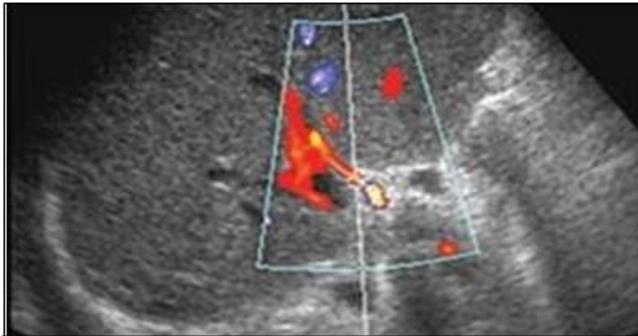


Fig 1. Color flow mapping of the hepatic artery Day 1 post-operatively showing the anastomotic and intra-graft HA course. Power Doppler shows

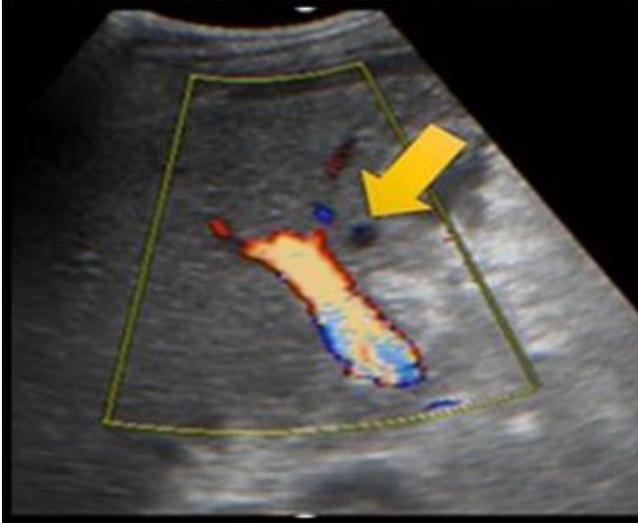


Fig 2. Color flow mapping of the hepatic artery Day 1 post-operatively showing the intra-graft HA with no detectable flow inside. further evaluation is required.

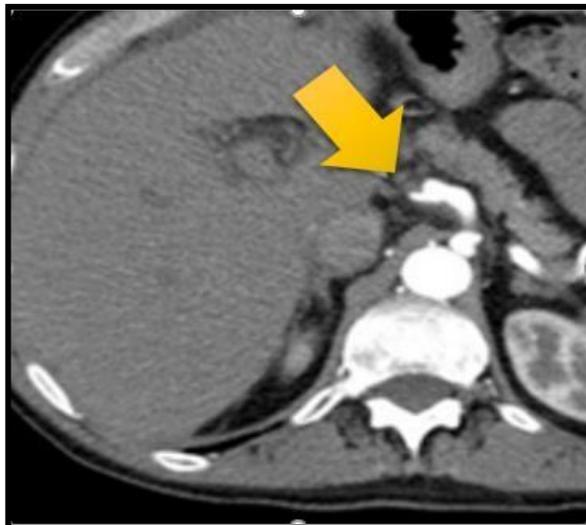


Fig 3. CT arteriography shows no hepatic arterial flow inside.

Two cases were diagnosed by color Doppler duplex ultrasound as PVT in two candidates who suffered pre-operative extensive thrombosis of the PV. One was diagnosed intra-operatively by echogenic intra-luminal partial thrombus with only peripheral flow inside who underwent surgical exploration and re-anastomosis was done successfully (Fig 4). Another patient developed PVT during the first week post-operative follow-up who underwent surgical exploration on emergency basis with unsuccessful reconstruction of the fenestrated loose vessels in the candidate recipient with long standing pre-operative portal vein thrombosis and the patient was lost few hours after surgery.

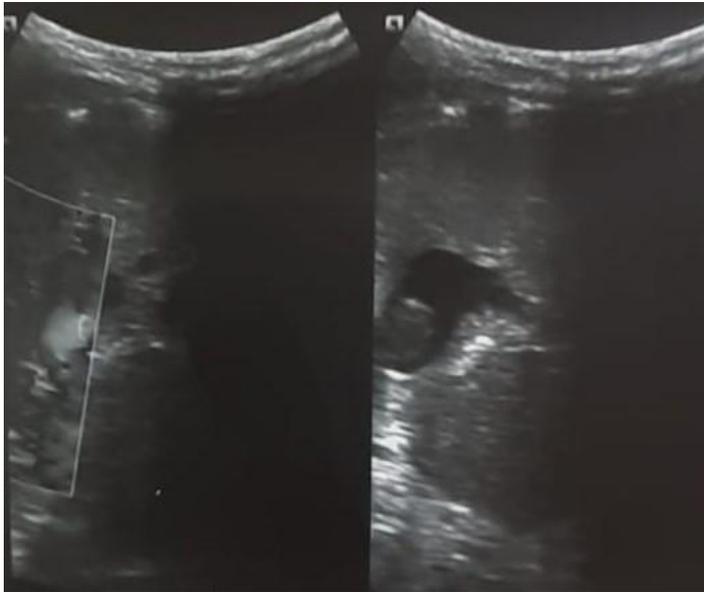


Fig 4. DUS surveillance showed day 3 post-operative intraluminal PV partial thrombosis at the anastomotic and intra-graft with preserved portal peripheral flow.

One candidate recipient who suffered hemodynamic instability post-operatively being a known cardiac patient showed a damped flow of the hepatic artery at the anastomotic and intra-graft sites by DUS. It was falsely related to the cardiac condition and no further evaluation was done. Two days later with worsening liver laboratory functions CT triphasic study showed anastomotic site and intra-graft arterial missed partial thrombosis and falsely negative result.

One case was diagnosed as HAS during the early postoperative DUS surveillance at the anastomotic site diagnosed by parvus-tardus wave and decreased RI below 0.4. MDT decision was conservative follow up as the patient lab was satisfactory. eventually the flow improved through collateral circulation few weeks later (out of our study scope time frame) Fig 5.



Fig 5. DUS shows damped intraluminal flow at the anastomotic site.

One case was diagnosed as PVS during the early postoperative DUS surveillance at the anastomotic site diagnosed by disproportionate calibers and markedly increased PSV pre-anastomotic > 3-fold of the flow at the anastomotic site with buffered Intra-graft flow with rapid ascitic fluid accumulation yet MDT decision was conservative follow up. Eventually Doppler showed normalized PVV with decrease of velocity across stricture and disappearance of ascites few weeks later (out of our study scope time frame).

One case was diagnosed as HVS during the early postoperative DUS surveillance at the anastomotic site diagnosed by disproportionate calibers and biphasic flow pattern at the anastomotic site. MDT decision was

conservative follow up as the patient didn't have the clinical features of graft outflow obstruction in the form of ascites formation and manifestations of portal hypertension.

4. DISCUSSION

Liver transplantation from a living donor for end stage liver disease patients has become the treatment of choice among adults and pediatric age groups. Provided the recent advances of surgery and in postoperative care, however, vascular complications are still a major cause of mortality and/or graft loss among liver transplant recipients. The clinical and laboratory diagnosis of graft vascular complications are usually nonspecific especially in mild and early graft affection, therefore radiologic diagnosis is essential. Early detection of vascular complications among liver transplant recipients, may allow the surgical team to reconstruct the anastomosis eventually reducing associated graft loss and patient's mortality [11]. Arterial complications are the most encountered and feared vascular complications among transplant recipients. The incidence of HAT varies from 5% to 26% and HAS from 5% to 11% reported in the literature [11- 17]. In our study, the incidence of HAT and HAS was as 13.3% and 2.2%, respectively. The significance of HAT or HAS is based upon the fact which states that intrahepatic biliary epithelium is only perfused through the hepatic artery. In complicated anastomosis with impaired hepatic artery flow might lead to graft ischemia, firstly affecting the bile ducts, and eventually leading to graft failure [12].

The clinical signs of HAT depend on its time of occurrence during the transplant surgery and early post-operative follow-up. Early thrombosis might cause fulminant necrosis with resulting recipient death unless a lifesaving re-transplantation is performed [22- 24]. However, some patients with HAT or HAS might be asymptomatic if chronic due to formation of rich collateral arterial supply [22], [23]. We observed collateral arterial vessels which were penetrating the liver parenchyma directly through the capsule in one patient with chronic arterial stenosis. The mortality rate from HAT varies from 22% to 58% in the literature [11- 14]. Despite considering biliary necrosis as incompatible with graft survival which requires subsequent emergency re-transplantation, the diagnosis and management of HAS or HAT before development of biliary necrosis might improve the overall patient outcome significantly [12], [16], [25], [26].

Thus, surgical intervention by open laparotomy to achieve thrombectomy and arterial re-anastomosis or interventional radiologic techniques may improve the overall patient's outcome and survival [22], [24], [27]. In our study, earlier detection of 4 patients with HAT allowed graft salvage upon which a surgical intervention of thrombectomy and arterial re-anastomosis was done. Early diagnosis and emergency re-exploration resulted in relatively low mortality rate among patients with Hepatic artery vascular complications.

Unlike HAT, HAS can be treated more easily and it is usually localized at the anastomotic site [22- 24].

In our study, one patient developed HAS yet keeping a satisfactory lab profile, the decision was conservative follow up and later one the patient showed arterial collateral formation. Although defining discriminatory threshold levels is problematic with our study design, our suggested thresholds were those reported for HAS or HAT by [16]. We analyzed our study group on the basis of derived thresholds of RI less than 0.45 and SAT greater than 0.08 s for identification of marked HAS or HAT. Requiring both RI and SAT to be abnormal to predict HAS or HAT, Doppler US resulted in a diagnostic sensitivity and a specificity of 91.67%% and 96.97%%, respectively. Our results are superior to [16] who reported a 73% sensitivity and specificity for the detection of marked hepatic arterial disease by using the same parameters, in another study that was consisted of 46 patients, [18] reported a sensitivity of 67% and a specificity of 96% for Doppler US in detecting HAS by using similar parameters.

Doppler ultrasound may yield false positive or false negative results. False positive results are mainly due to reduced hepatic arterial flow caused by hypotension, small hepatic artery caliber, early postoperative vasospasm, rejection reaction, improper adjustment of ultrasound machine or scanning. Reported false-positive rates are relatively high and reported the false-positive rate even reaching as high as 75%. False negative results arise mainly from collateral circulation, with a reported false-negative rate of 7%-29% [32].

Some studies described possible etiologies of false-positive and false-negative Doppler ultrasound studies in detecting hepatic artery disease. [16] reported two causes of false-positive findings for HAS such as studies performed either intra- operatively or in the early postoperative period could result in tardus et parvus waveforms without true HAS being present. Other studies mentioned presence of portal vein thrombosis or hepatic vein thrombosis as a possible cause for a false- positive classic tardus et parvus hepatic artery waveform [18- 30]. In our study, CT triphasic study- arterial phase- identified one case with false- positive spectral Doppler US findings suggestive for HAT. The DUS findings were non visualized hepatic artery at the anastomotic and Intragraft site yet with satisfactory liver laboratory profile. Its further evaluation by CT arteriography phase was showing a slender posteriorly and deeply located yet patent hepatic artery all through its course.

Causes of false-negative results of the Doppler US are clear to be more important than false-positive results in detecting hepatic artery disease. We observed one case of proven HAT who had damped waveform and borderline RIs and SATs referred at time of diagnosis to hemodynamic instability of the patient. In this patient, arteriograms demonstrated thrombosis of the distal parenchymal branches of the hepatic artery that can explain normally appearing Doppler US parameters within main hepatic artery and proximal parenchymal branches [20].

Thrombosis and/or stenosis of the portal vein and hepatic veins are reported to occur in 1-12.5% of liver recipients [12], [16], [20], [21], [27].

We observed portal vein complications in 6.66%, and hepatic vein complications in 2.22% of liver transplantations. The use of Doppler US in evaluating thrombosis particularly of the portal and hepatic vein has been widely applied, as it offers diagnostic criteria on Doppler US examinations. However, to our knowledge, study results that provide diagnostic criteria for using Doppler US in the evaluation of portal vein or hepatic vein stenosis are limited [20], [21].

For portal vein stenosis, we prospectively documented our study group on the basis of Doppler US criteria those previously reported by [20].

Our suggested thresholds for marked portal vein stenosis are consisted of a visualized portal vein diameter of 2.5 mm at the anastomotic site or less detected on ultrasound surveillance, and an accelerated flow at the stricture or a post- stenotic jet at least three times of the recordings in the proximal portal vein revealed by spectral Doppler US imaging. We diagnosed one instance of marked portal vein stenosis including both of the diagnostic parameters fore-mentioned and confirmed by CT portal venography [14].

CT triphasic study usage is limited for equivocal cases. Provided that end stage liver disease patient may associate with renal dysfunction and elevated serum creatinine, contrast hypersensitivity and difficult mobilization post-operatively. Combined use of sonography and spectral Doppler US parameters resulted in a diagnostic sensitivity and specificity of 100% for marked portal vein stenosis [8].

Hepatic vein stenosis has been described as one of the important vascular complications of living donor liver transplantation. In our study, the incidence of hepatic vein stenosis occurred in 2.22% of living donor liver recipients. Early detection of hepatic vein stenosis is important because when stenosis is located close to the anastomosis, balloon angioplasty with stent placement seems to be the treatment choice, and thereby improve the patient's chance for a successful outcome [31], [32].

In our study, one case of hepatic vein stenosis with otherwise unremarkable graft and satisfactory liver lab profile MDT decision was conservative follow up at the time of our study frame. In our study, the case of proven hepatic vein stenosis showed a persistent monophasic wave pattern on Doppler US examinations. Our data support [21] who reported that a monophasic waveform is considered a sensitive but not specific finding of hepatic vein stenosis, and correlation with clinical findings is required before an invasive procedure such as venography or an interventional procedure is considered. We recognize that our study has some limitations. Limitations of our study mainly relate to the limited time frame of follow-up period only one-week post-operative follow up besides the exclusiveness of living donor liver transplantation, no deceased donors are available.

In conclusion, we have presented the Doppler US findings for a series of liver transplant recipients who developed vascular complications after liver transplantation procedures. Diagnosis of vascular complications in liver transplant recipients requires real-time visualization of the entire length of the vascular structures, combined with spectral and color Doppler US investigations of the hepatic artery, portal vein, and hepatic veins. Failure to use these parameters results in a large number of false- negative findings and potentially increases the morbidity and mortality of affected patients. Although it is clear that Doppler US evaluation is an effective choice for diagnosing vascular complications after liver transplantation, we also identified the very important role of Doppler US examination in detecting vascular complications intraoperatively and improving the patient's chance for a successful outcome. Lastly, we believe that a normal Doppler examination performed by an experienced radiologist conclusively excludes the presence of clinically significant vascular complication.

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