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Impact of Doppler Ultrasound on Diagnosis and Therapy Control of Lienalis Steal Syndrome After Liver Transplantation

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Lienalis steal syndrome is a rare complication after orthotopic liver transplantation leading to severe complications. Routine duplex sonography allows early and safe detection of lienalis steal syndrome and secondarily helps to monitor the outcome by evaluating the hemodynamics.

Material/Methods: This analysis included eight patients who after orthotopic liver transplantation needed splenic artery embolization due to lienalis steal syndrome. Lienalis steal syndrome was assumed in case of elevated transaminases, bilirubinemia or persistent ascites, and the absence of further pathologies. Diagnosis was supported by ultrasound, confirmed by digital subtraction angiography, and followed by splenic artery embolization for treatment. We analyzed blood levels and ultrasound findings before and after splenic artery embolization as well as during follow-up and evaluated for incidence of severe biliary complications and survival.

Results: Arterial resistive index (RI) significantly regularized after splenic artery embolization while the maximum arterial velocity increased. The portal venous flow volume and maximum velocity decrease. Laboratory parameters normalized. Two of eight patients developed ischemic-type biliary disease. Survival rate was 88% over a median follow-up of 33 months.

Conclusions: Beside unspecific clinical findings, bedside ultrasound examination enabled a quick verification of the diagnosis and allowed direct treatment to minimize further complications. Furthermore, ultrasound can immediately monitor the therapeutic effect of splenic artery embolization.

MeSH Keywords: Hypertension, Portal • Liver Transplantation • Splenic Artery • Ultrasonography, Doppler

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Background

Lienalis steal syndrome was first described in 1991 and is a rare post-transplant phenomenon affecting arterial liver perfusion [1]. In contrast to liver parenchyma, the biliary tree develops an exclusive arterial perfusion causing vulnerability. Besides parenchymal damage with associated graft dysfunction, untreated lienalis steal syndrome can cause severe biliary complications (e.g., non-anastomotic strictures and biliary abscess formation) leading to graft loss and the need for retransplantation [2]. The incidence of lienalis steal syndrome varies from 3% to 10% in liver transplants [3–5].

Advanced liver disease is often accompanied by splenomegaly, and after orthotopic liver transplantation, the increased blood perfusion volume can compete against the arterial circulation of the liver. This stealing phenomenon has been described as lienalis steal syndrome and leads to a reduced arterial perfusion of the liver attended by portal hyperperfusion [3,4,6]. An alternative pathophysiological model is the splenic artery syndrome: high venous blood flow from the spleen towards the portal vein activates the hepatic artery buffer response and therefore lowers the hepatic arterial supply [7–10]. It has been postulated that the hepatic artery buffer response maintains an adequate hepatic blood flow by an auto-regulating system using the adenosine pathway as a strong vasodilator [10,11]. High portal blood flow provokes arterial vasoconstriction by low concentration of adenosine due to an increased washout [10,11]. Finally, the reason for portal hyperperfusion, and whether one or both mechanisms are responsible for the reduced arterial supply, remains unclear [10]. Important risk factors for lienalis steal syndrome include a preoperative spleen volume exceeding 830 mL, in addition to an increased spleen diameter and diameter ratio between the common hepatic artery and the splenic artery [12,13].

Lienalis steal syndrome should be considered in patients with abnormal laboratory and clinical findings after liver transplantation especially in the absence of cellular rejection, infections, and toxicity [10]. Patients may present with solitary increased levels of bilirubin or transaminases, persisting thrombocytopenia, or refractory ascites [5]. Ultrasound is a fast, inexpensive and easy method to diagnose lienalis steal syndrome by the evaluation of the flow volume, waveform and resistant index (RI) of hepatic artery [14]. The gold standard for the diagnosis of a lienalis steal syndrome remains the digital subtraction angiography of the abdominal aorta above the celiac trunk with an early and predominant enhancement of the splenic artery and parenchyma compared to the common hepatic artery and liver. This invasive imaging method also allows for immediate treatment of the lienalis steal syndrome via proximal splenic artery embolization.

The difficulty is to identify patients with lienalis steal syndrome correctly to enable early treatment on the one hand, but also to avoid unnecessary CT scanning or even invasive angiography on the other hand. Bedside ultrasound is a safe method to gain functional information about flow volumes and velocities and has already been employed for this indication [5]. However, ultrasound can also directly evaluate the therapeutic success of splenic artery embolization by bedside monitoring of the liver perfusion and might help to prevent further complications. To verify successful treatment, we investigated biliary complications, e.g., non-anastomotic biliary strictures, laboratory results, and liver function during the follow-up period.

This retrospective study investigates the performance of bedside ultrasound in patients after orthotopic liver transplantation to monitor the treatment of lienalis steal syndrome.

Material and Methods

A total of eight consecutive adult patients (five male and three female) with an average age of 56.9±10.8 years, who had undergone orthotopic full size liver transplantation at our center from October 2010 to January 2015 and who were treated by splenic artery embolization for lienalis steal syndrome afterwards, were included in this investigation.

Lienalis steal syndrome was assumed in cases of elevated transaminases and bilirubin or persistent ascites, and the absence of acute cellular rejection, infection, or toxicity. The diagnosis was supported by pathological ultrasound findings. Ultrasound showed a raised arterial RI beyond 0.75 with an elevated maximum arterial velocity over 100 cm/sec, a low or diminished diastolic flow and an all-in-all reduced flow volume [14]. In addition, the portal flow presented with a pathological hyperperfusion with increased volumes over 900 mL/minute and maximum velocity over 80 cm/second [5,9,10,14]. Finally, lienalis steal syndrome was confirmed by digital subtraction angiography and an angiographic predominant enhancement of the splenic artery and parenchyma compared to the common hepatic artery and liver [12].

All patients received a pre-transplant CT scan to evaluate the vascular liver anatomy and determine presence of splenomegaly. Generally, routine ultrasound was performed in all patients from the day of operation until the 7th day after transplantation and in cases of any clinical abnormalities. According to clinic standards, blood was taken daily within the first postoperative period (14 days) and then twice a week (during the first three months), as well as in cases of any pathologies. Severe biliary complications and survival data were collected from follow-up at our outpatient department. This retrospective study was approved by the institutional review board. Demographic data is given in Table 1.

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Table 1. Demographic display of cohort (n=8), from October 2014 till October 2014.

Number of patients (n=8)	3 female (37.5%) 5 male (62.5%)
Indication for liver transplantation	
Alcohol induced cirrhosis	5 (62.5%)
Hepatitis C cirrhosis	1 (12.5%)
Acute liver failure	1 (12.5%)
Non-alcoholic steatohepatitis	1 (12.5%)
Age at liver transplantation	56.4±10.9 years
Spleen size pre-transplantation [cm]	14.4±1.7
Time to embolization after liver transplantation [days]	10.5±6.5
Complications	
Ischemic type biliary disease	2 (25.0%)
Death after cerebral bleeding	1 (12.5%)

Data is given in absolute numbers, percentage and in case of age at liver transplantation, spleen size and time to embolization by mean with standard deviation.

The serum levels of bilirubin, GGT, alanine amino transferase (ALT), aspartate amino transferase (AST), thrombocytes and thromboplastin time (Quick) were collected two days before (d-2), one day before (d-1), on the day of splenic artery embolization (d0), on day after (d1), two days after (d2) and from the latest available value during the further follow-up (dx). Follow-up at time of analysis was 30 months (median) ranging from six to 58 months. All patients received an extended ultrasound examination before and after the treatment for lienalis steal syndrome.

Ultrasound examination technique

The extended ultrasound examination was not routinely done but triggered through elevated bilirubin or transaminases without further explanation (n=5), abnormal findings on routine daily duplex sonography during the first week after the transplantation (n=3), or on a recall visit because of raising bilirubin and the absence of other causes (n=1). All extended ultrasound examinations were performed by one of three experienced examiners with a Philips CX50 (Philips Healthcare, Best, The Netherlands) ultrasound machine and a curved array abdominal imaging probe (5 to 1 Mhz) and digitally archived. The ultrasound examination encompassed hepatic artery RI, maximum arterial maximum flow velocity, portal vein blood flow volume and portal vein maximum flow velocity. The same examiner repeated all measurements within two days after lienalis steal syndrome treatment (POD1).

Treatment of lienalis steal syndrome

Eight patients underwent invasive angiography to confirm lienalis steal syndrome by the typical flow pattern and interventional splenic artery embolization in the same session by applying a vascular plug (Amplatzer Plug II, St. Jude Medical, St. Paul, MI, USA) [15].

Data analysis

Statistical comparison was done for blood values before and after the lienalis steal syndrome intervention, for the ultrasound parameters before and after the intervention and for spleen volume and the extent of change of the ultrasound flow parameters. Statistical analysis was performed by EXCEL (Version 15.21.1 2016, Microsoft, Redmond, WA, USA) with the add-in XLSTAT (Version 2016.02.27941, Addinsoft, New York, NY, USA). Non normally distributed values were tested by Mann-Whitney U test or if variables were related by the Wilcoxon signed-rank test. A *p*-value less than 0.05 was accepted as significant.

Results

We found valid data from eight patients who received splenic artery embolization after orthotopic liver transplantation at our institution due to lienalis steal syndrome and included them for further analysis.

Indications for liver transplantation were alcohol induced liver cirrhosis (n=5), hepatitis C cirrhosis (n=1), acute liver failure (n=1) and non-alcoholic steatohepatitis (n=1) (Table 1). Lienalis steal syndrome was diagnosed at an average of 10.5±11.7 days after orthotopic liver transplantation (Table 1).The spleen size due to the preoperative CT scan was at an average of 14.4±8 cm (Table 1). Two patients developed an ischemic type biliary disease during the further follow-up (25.0%) and one patient died by an intracerebral bleeding (12.5%).

Lienalis steal syndrome was sonographically diagnosed and treated with an interventional splenic artery plug embolization in all patients (Table 1). Ultrasound was performed directly before and one day after the intervention. We found a significant lower arterial RI after splenic artery embolization (post 0.60±0.21 versus prae 0.70±0.24, $p<0.016$) (Figure 1). Furthermore, there was a non-significant increase of the maximum arterial velocity (post 57.7±17.2 cm/sec versus prae 47.1±11.4 cm/sec, $p<0.052$) and a decrease of the maximum portal velocity (post 41.4±11.0 cm/sec versus. prae 63.3±23.2 cm/sec, $p<0.092$) as well as the portal flow (post 1.29±0.94 L/minute versus prae 1.81±0.76, $p<0.281$) after splenic artery embolization (Figure 2).

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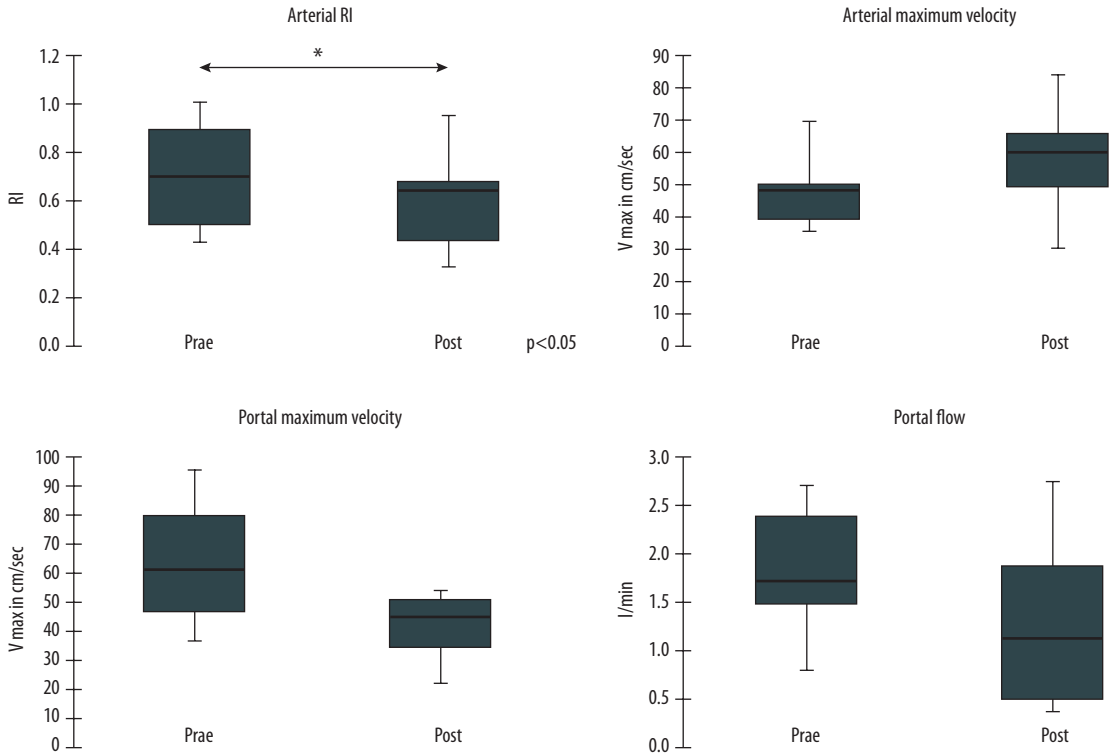

Figure 1. Doppler sonographic findings. Measurement of the hepatic artery resistance index (RI), maximum arterial flow velocity in cm/sec, maximum portal vein flow velocity in cm/sec and portal flow volumetry in L/min before and after splenic artery embolization. A significant reduction of the arterial RI and maximum arterial flow velocity could be shown ($p<0.05$) and a decrease of the maximum arterial velocity. Portal vein changes were not significant but maximum velocity as well as blood flow volume were distinctly decreased after the intervention. (n=8).

On the day of diagnosis of lienalis steal syndrome, laboratory parameters showed elevated values in seven patients for bilirubin as well as ALT (87.5%), in six patients for GGT (75.0%), and in five patients for AST (62.5%) (Figure 2). Seven patients showed a depressed Quick and thrombocytopenia (87.5%) (Figure 2). During the follow-up, there was a decrease of the elevated GGT and AST and a significant decrease of bilirubin and ALT on dx, compared to the day of the intervention (d0) (Figure 2). The low Quick value increased until the dx and there was a significant increase of thrombocytes compared d0 to dx with only three patients retaining a thrombocytopenia but with an overall higher count for thrombocytes (Figure 2).

Discussion

Orthotopic liver transplantation is the only cure to end stage liver disease. Survival rates of graft and patient depend on a variety of different factors and especially vascular complications remain a relevant threat to the organ and finally to the recipient. Although many parameters cannot be modified (e.g., donor age, cold ischemia time), others can be successfully controlled by immediate medical intervention during the perioperative course.

Lienalis steal syndrome is one of the known vascular complications after liver transplantation declining the perfusion of the graft. Even if the reason for portal hyperperfusion and decreased arterial blood flow is not entirely clear, undetected and untreated lienalis steal syndrome can cause severe biliary complications leading to graft loss [8,13]. Clinical symptoms remain unspecific and include ascites and abnormal laboratory findings like hyperbilirubinemia and thrombocytopenia [5].

In this study, ultrasound provided diagnosis and monitoring of lienalis steal syndrome and its adequate therapy in eight patients after orthotopic liver transplantation. Considering laboratory parameters, we found an unspecific elevated bilirubin, GGT, and transaminases as well as a depressed quick and thrombocytopenia (Figure 2). Further post-transplantation pathologies like initial graft failure and acute cellular or antibody-mediated rejection have been investigated and excluded. Previous data described unspecific sonographic signs for lienalis steal syndrome, like RI values over 0.8 and maximum

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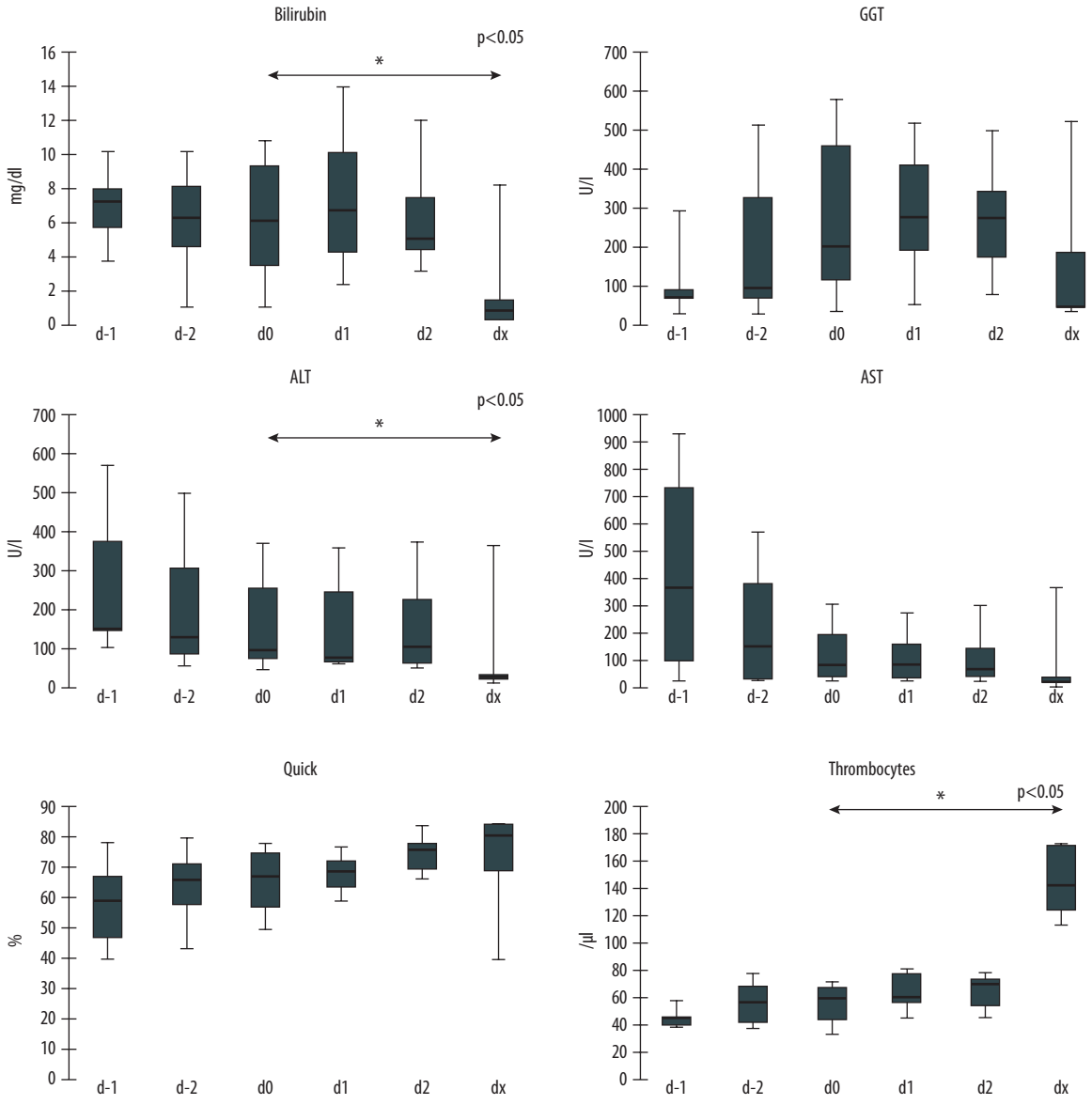

Figure 2. Changes in laboratory parameters. Laboratory parameters with standard deviation. Grey arrows mark significant changes with * $p<0.05$. Angiography and splenic artery embolization was performed on d0. Values were collected before (d-2, d-1), on the day of embolization (d0) and after (d1, d2), as well as the latest available value during the further follow up (dx). There were significant changes of bilirubin, ALT and thrombocytes compared dx to d0 (n=8).

arterial flow velocity <35 cm/second for lienalis steal syndrome as well as raised portal maximum flow velocity and unspecific portal hyperperfusion [15,16]. Ultrasound evaluation of our case series was suspicious in all patients with elevated arterial RI values of 0.70±0.24 and partly pathological arterial RI values up to 1, reduced arterial maximum flow velocity of 47.1±11.4 cm/second, raised portal maximum velocity 63.3±23.2 cm/second and a pathological portal vein hyperperfusion with a flow volumetry of 1.81±0.76 L/minute (physiological standard value: 900 mL/minute) (Figure 1). These ultrasound findings correlated with the blood results and the absence of further post-transplantation pathologies, aroused suspicion for lienalis steal syndrome. Therefore, all patients were immediately transferred to angiography where the diagnosis of lienalis steal syndrome was confirmed and a rapid splenic artery embolization was performed for treatment.

After successful splenic artery embolization, ultrasound examination directly allowed a real-time monitoring of the therapeutic effects on liver perfusion, particularly as the laboratory

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parameters did not change immediately. Literature described a significant reduce of the hepatic artery RI and portal venous maximum flow velocity after splenic artery embolization in case of lienalis steal syndrome [16]. In our patients, the post-interventional ultrasound examination showed an improved liver perfusion with already significant normalization of the hepatic artery RI (post 0.60±0.21 versus prae 0.70±0.24, $p<0.016$), increased arterial maximum flow velocity of 57.7±17.2 cm/second, a decreased portal vein maximum velocity to 41.4±11.0 cm/second and volumetry 1.29±0.94 L/minute (Figure 1). During the follow-up, there was a decrease of the elevated GGT and AST and a significant decrease of bilirubin and ALT as well as an increasing Quick value and a significantly raising amount of thrombocytes (Figure 2). Only two patients developed severe biliary complications requiring further endoscopic therapy two and 12 months after orthotopic liver transplantation (one patient with need for balloon dilatation, one patient with need for stenting). Corresponding to actual literature, ultrasound examination and sonographic perfusion measurements allow a good and easy prediction about the success of splenic artery embolization before regression of the pathologic laboratory parameters [17]. Thus, ultrasound is an easy tool for monitoring the treatment procedure.

Conclusions

All patients presented unspecific clinical hyperbilirubinemia and thrombocytopenia as well as suspicious ultrasound findings corresponding to a lienalis steal syndrome as supported by literature [2,5,10,15,16]. The bedside ultrasound examination enabled a quick verification of the diagnosis and enabled direct treatment, thus minimizing complications during further follow-up. Furthermore, ultrasound allowed for monitoring of the therapeutic effect after splenic artery embolization before blood results had been normalized.

A limitation of our study was that it was retrospective and had a small number of patients. In particular, the standard deviations were high because of the small sample size. Further investigations are necessary, especially as the identification of patients who might develop lienalis steal syndrome after orthotopic liver transplantation still remains challenging and few risk factors (e.g., splenomegaly) are known. Ultrasound might diagnose lienalis steal syndrome after orthotopic liver transplantation, but it would also be of assistant to know whether a patient will actually develop lienalis steal syndrome or not before the transplantation.

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Conflicts of interest

None.

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