Original Article

Spleen transient elastography predicts actuarial survival after liver transplantation

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Background: Splenic transient elastography (TE) correlates with increased portal pressure. Little data are available in the post liver transplantation (LTx) setting.

Methods: Three months after LTx, we performed splenic TE in 125 LTx recipients.

Results: Mean splenic TE values were 29.4 (±6.3; range, 21.6–49.2) kPa. Splenic TE correlated with reduced time to development until persistent ascites (30 events, OR =1.082, 95% CI: 1.034–1.133; P=0.001), hepatorenal syndrome (8 events, OR =1.109, 95% CI: 1.015–1.211; P=0.022) and hepatic encephalopathy (16 events, OR =1.136, 95% CI: 1.066–1.211; P=0.000). In Cox univariate analysis, splenic TE served as a predictor of actuarial survival free of liver (OR =1.114, 95% CI: 1.050–1.182; P<0.001) and remained an independent risk factor associated with reduced actuarial survival free of LTx in multivariate analysis (OR =1.103, 95% CI: 1.026–1.186; P=0.008).

Conclusions: Splenic TE measurement at 3 months after LTx serves as a robust predictor of survival in LTx recipients.

Keywords: Spleen; liver transplantation (LTx); transient elastography (TE); survival

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Introduction

Transient elastography (TE) is a widely available method that was initially designed to assess hepatic stiffness (1-3). Liver TE measurement accurately estimates the presence of advanced fibrosis and cirrhosis in patients with chronic liver disease (4). However, recent studies further showed that spleen stiffness, measured by transient elastography correlates with hepatic venous pressure gradient (5-8). Therefore, splenic elastography was shown to identify clinically significant portal hypertension (9-12). Increased spleen stiffness in patients with liver cirrhosis has been attributed to splenic tissue hyperplasia and splenic lymphoid activation (13,14). However, increased portal pressure and the associated hyperdynamic circulation have been suggested as predominant factors for spleen stiffness (15). In the post liver transplantation (LTx) setting, portal hypertension constitutes a significant and severe complication, resulting in a highly increased mortality (16). The etiology of increased portal pressure after LTx ranges from portal vein thrombosis/anastomotic stenosis to graft rejection and recurrent liver fibrosis and cirrhosis of the transplanted graft (17-19). At present, there are only few descriptive studies investigating spleen elastography after

LTx (12). These descriptive studies showed that spleen elastography is elevated before LTx and declines after LTx. At present, there are no information available as to what extend spleen elastography predicts complications or survival following LTx. In this present study, we performed splenic TE routinely 3 months after LTx and investigated its predictive value upon further clinical outcome.

Methods

Study design

This is a retrospective analysis of a prospective study cohort. The prospective study cohort started in October 2012. All medical data from the time of enrolment at Eurotransplant were recorded for each patient. Informed consent to participate in the study was obtained from each patient. The study was approved by the Ethical Committee of the University of Heidelberg (No. S-270/2015) and carried out in accordance with the Declaration of Helsinki (as revised in 2013). Clinical data presented in this study were retrospectively analyzed during the time from October 2012 until October 2018. Following LTx, patients were discharged from our hospital and routinely scheduled for an outpatient visit at our clinic 3 months after LTx. At this time, laboratory markers were evaluated and splenic TE was performed. Patients with complicated postoperative course, who couldn't be discharged after 3 months were excluded from our study. Patients with splenectomy, portal thrombosis, liver thrombosis or coiling of the splenic artery before or after LTx were not included to the study.

Endpoint definition and scoring calculation

Actuarial survival free of LTx was defined as either death or recurrent LTx (Re-LTx) as endpoints.

APRI-score (AST-to-platelet radio index) was calculated using the formula (20):

$$\text{APRI} = 100 \times \text{AST}/(\text{upper limit of normal for AST} \times \text{platelets}, \times 10^9/\text{L}) \quad [1]$$

FIB-4 score (fibrosis-4 score) was calculated using the following formula (21):

$$\text{FIB-4} = \text{age (years)} \times \text{AST (U/L)}/[\text{platelets } (10^9/\text{L}) \times 1/2\text{ALT (U/L)}] \quad [2]$$

Hepatic decompensation of patients on the LTx list was assessed by documenting the occurrence of hydropic decompensation requiring paracentesis or forced diuretic treatment, hepatic encephalopathy ≥ grade II, according to West Haven Criteria, and hepatorenal syndrome, according to EASL guidelines (22).

Transient elastography

For the TE measurement of spleen stiffness, a FibroScan (Echosens, Paris, France) was used. This device creates a low-frequency acoustic wave to an ultrasonic transducer. We measure its speed first with an ultrasound imaging, and using the measured speed, the tissue's stiffness is computed where the acoustic wave penetrates (23). The result was expressed in kilopascal (kPa) and all examinations were performed using the standard probe (M probe). In order to measure splenic stiffness, patients were lying on their backs with their left arms raised to their heads. The probe was placed vertically on the intercostal skin of the spleen. The lung area and intercostal areas were avoided when using FibroScan's ultrasonic TM mode (time-motion) and A-mode (amplitude mode) images. The measurements were ended when 10 successful values had been obtained for each patient. Stiffness was determined as the average value of the 10 measurements, after excluding the highest and the lowest values. The success rate was defined as the number of successful results divided by the total number of examinations.

Statistical analysis

Preliminary testing for normality was conducted by using the Shapiro-Wilk test. If the preliminary test for normality is not significant, the *t*-test is used; if the preliminary test rejects the null hypothesis of normality, a nonparametric test (Mann-Whitney's U test) is applied in the main analysis (24). Spearman's rho was used as the nonparametric measure of statistical dependence between two variables. The actuarial survival free of LTx rate was estimated using Cox univariate/multivariate analysis. Differences between the actuarial estimates were analyzed using the log-rank test. The following variables were selected for univariate analysis based on results of previous studies: age, gender, body mass index, presence of metabolic co-diseases (diabetes, hypertriglyceridemia, hypercholesterolemia), splenic TE, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), bilirubin, albumin, creatinine, international normalized ratio (INR) and

Table 1 Patient characteristics 3 months after LTx

Characteristics	Value
Spleen elastography (kPA), mean ± SD	29.9±6.3
AST (U/L), mean ± SD	41.1±48.9
ALT (U/L), mean ± SD	56.9±75.5
GGT (U/L), mean ± SD	168.3±243.7
AP (U/L), mean ± SD	157.0±141.7
Bilirubin (mg/dL), mean ± SD	1.00±1.4
Thrombocytes (/nL), mean ± SD	177.8±92.1
INR mean, SD	1.06±0.2
Albumin (g/dL), mean ± SD	3.8±0.6
Creatinine (mg/dL), mean ± SD	1.0±0.6
Metabolic co-disease, n (%)	67/125 (53.6)
Age at LTx (years), mean ± SD	48.3±13.2
Gender	38 females, 87 males
BMI (kg/m^2), mean ± SD	26.5±5.3
APRI-score, mean ± SD	0.66±1.09
FIB-4 score, mean ± SD	2.13±2.03
Immunosuppressive agent	Ciclosporin: n=70 (56.0%); tacrolimus n =55 (44.0%)

LTx, liver transplantation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; AP, alkaline phosphatase; INR, international normalized ratio; APRI-score, AST-to-platelet radio index; FIB-4 score, fibrosis-4 score.

thrombocytes. A P value of <0.1 in univariate analysis was defined for variables to be included in a Cox's proportional hazards model, using a stepwise procedure with a threshold of α=0.05. Statistical analysis was performed using SPSS version 25.0 software (SPSS Inc., Chicago, USA), and significance was accepted for values of P<0.05.

Results

LTx cohort

Of the 125 liver transplanted patients, 38 were female (30.4%) and 87 were male (69.6%). The underlying hepatic disorders contributing to LTx were: alcoholic liver disease (ALD, n=24), chronic hepatitis B (HBV, n=10), chronic hepatitis C (HCV, n=30), primary sclerosing cholangitis (PSC, n=19), non-alcoholic steatohepatitis (NASH, n=8), and other hepatic disorders (n=34, each subgroup n<10). Mean follow-up time was 18.3±16.0 (range, 0.35–85.3) months. Nine patients received Re-LTx while 9 patients died in the course after LTx. Serological markers, APRI/FIB-4-scores and clinical data 3 months after LTx are shown in *Table 1*.

Distribution of splenic TE 3 months after LTx

Mean transient splenic elastography values 3 months after LTx was 29.4 (±6.3; range, 21.6–49.2) kPa.

Splenic TE reflects liver enzymes 3 months after LTx

There was a statistically significant positive correlation between TE and AST (P=0.028, Pearson correlation coefficient: 0.197), GGT (P=0.028, Pearson correlation coefficient: 0.197), bilirubin (P>0.000, Pearson correlation coefficient: 0.362). This correlation was not observed for ALT (P=0.084), AP (P=0.362), INR (P=0.292), albumin (P=0.701), creatinine (P=0.595) and thrombocytes (P=0.059).

Clinical complications after LTx

The cause of death for the 9 deceased patients were all hepatic and/or transplant related (recurrent liver disease in 4 patients, non-anastomotic biliary strictures in 2 patients, chronic rejection in 1 patient, recurrence of hepatocellular carcinoma in 2 patients). Hepatic decompensation occurred in 26 patients over the course of follow-up. Mean time until development of hepatic decompensation was 11.4±13.7 months after the time of splenic TE measurement.

TE and clinical complications after LTx

At 3 months post LTx, TE values did not correlate with development of acute liver rejection (34 events, OR =1.013, 95% CI: 0.953–1.077; P=0.682) or development of biliary stenosis (57 events, OR =1.043, 95% CI: 0.991–1.098; P=0.109) during further follow-up.

However, we observed a highly significant correlation for splenic TE and reduced time to development of persistent ascites (30 events, OR =1.082, 95% CI: 1.034–1.133; P=0.001), hepatorenal syndrome (8 events, OR =1.109, 95% CI: 1.015–1.211; P=0.022) and hepatic encephalopathy (16 events, OR =1.136, 95% CI: 1.066–1.211; P=0.000).

Table 2 Features associated with death/recurrent LTx in patients 3 months after LTx according to Cox's proportional hazards model

Features	Cox univariate analysis		Cox multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Splenic TE (kPA)	1.114 (1.050–1.182)	0.001	1.103 (1.026–1.186)	0.008
AST (U/L)	1.007 (1.001–1.014)	0.032	1.000 (0.992–1.007)	0.933
Bilirubin (mg/dL)	1.241 (1.064–1.448)	0.006	1.120 (0.922–1.587)	0.169
Metabolic co-disease	0.389 (0.146–1.039)	0.060	0.377 (0.126–1.130)	0.082
Thrombocytes (/nL)	0.993 (0.986–1.000)	0.057	0.993 (0.986–1.000)	0.053
INR	0.647 (0.059–7.040)	0.721	NA	NA
albumin (g/dL)	0.974 (0.905–1.048)	0.475	NA	NA
Creatinine (mg/dL)	1.172 (0.594–2.313)	0.647	NA	NA
Age at LTx (years)	1.016 (0.979–1.054)	0.402	NA	NA
Gender	1.021 (0.359–2.902)	0.968	NA	NA
BMI (kg/m^2)	1.024 (0.937–1.119)	0.598	NA	NA

LTx, liver transplantation; TE, transient elastography; AST, aspartate aminotransferase; INR, international normalized ratio.

Transient liver elastography predicts actuarial survival after LTx

Age at LTx, gender, BMI, metabolic co-disease, splenic TE, serum AST, serum bilirubin, serum creatinine, serum albumin, INR, thrombocytes were subjected to Cox univariate analysis (*Table 2*). Metabolic co-disease (OR =0.389, 95% CI: 0.146–1.039; P=0.060), TE (OR =1.114, 95% CI: 1.050–1.182; P<0.001), serum AST (OR =1.007, 95% CI: 1.001–1.014; P=0.032), serum bilirubin (OR =1.241, 95% CI: 1.064–1.448; P=0.006) and thrombocytes (OR =0.993, 95% CI: 0.986–1.000; P=0.057) were below the set P value of 0.1 and therefore subjected to further multivariate analysis. In multivariate analyses, splenic TE remained an independent risk factor associated with reduced actuarial survival free of LTx (OR =1.103, 95% CI: 1.026–1.186; P=0.008; *Table 2*).

Using ROC-analysis, the optimal cut-off value to predict actuarial survival in our study cohort would be a splenic TE value of 32.4. This cut-off value would lead to a sensitivity of 0.789 and a specificity of 0.722 (ROC: 0.781, *Figure 1*).

Transient liver elastography predicts actuarial survival independent of established liver fibrosis scores (APRI or FIB-4 score)

Splenic TE *vs.* APRI-score: in univariate analysis, APRI-score was below the set cut-off value of P<0.1 to predict actuarial survival free of LTx (OR =1.267, 95% CI: 0.961–1.670; P=0.093). When subjected to multivariate analysis along with splenic TE remained as an independent predictor of survival (OR =1.113, 95% CI: 1.044–1.186; P=0.001) while APRI-score did not (OR =1.012, 95% CI: 0.727–1.408; P=0.943).

Splenic TE *vs.* FIB-4 score: in univariable analysis, the FIB-4 score met the prespecified threshold of significance of <0.1 for actuarial survival free of LTx (OR =1.188, 95% CI: 1.019–1.384; P=0.028).

After multivariable analysis, splenic TE remained an independent predictor of survival (OR =1.103, 95% CI: 1.033–1.178; P=0.004) while FIB-4 did not (OR =1.063, 95% CI: 0.888–1.272; P=0.505).

Discussion

While TE of the liver is widely incorporated in screening protocols of liver disease patients (4,25,26), splenic TE has been shown to correlate with increased portal pressure (5,6) and recently been implemented in variceal screening protocols in patients with compensated liver cirrhosis (27). However, no data are available to what degree splenic TE measurement provides meaningful data in the specific setting after LTx, particularly in the context of a predictive marker of patient survival. In this prospective study cohort, we measured splenic TE routinely 3 months after LTx, with

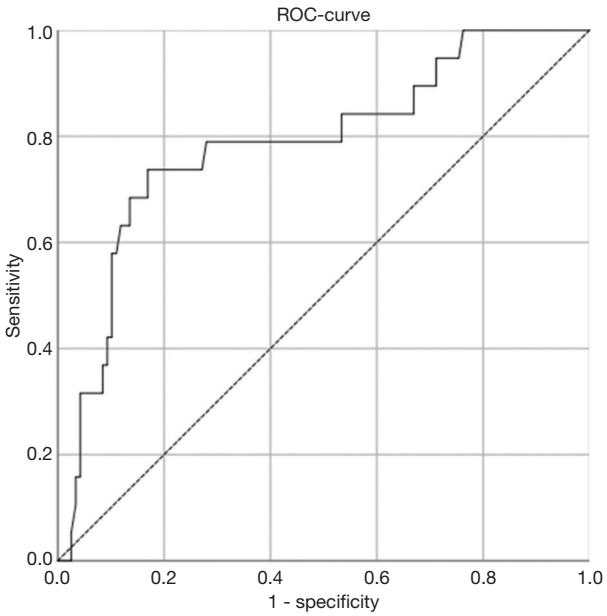

Figure 1 ROC analysis of splenic TE measurement and actuarial survival. ROC, receiver operating characteristic; TE, transient elastography.

a mean follow-up time of 18 months.

Chin *et al.* reported that after LTx the density of the spleen reduced to 41.9 kPa in the second week and to 32.9 kPa in the fourth to eighth week (12), therefore showing comparable results with our splenic TE measurements 3 months after LTx (29.4±6.3 kPa). At 3 months following LTx, splenic TE correlated with serological markers of liver function (AST, GGT and bilirubin). As splenic TE identifies portal hypertension (9), it is interesting that splenic TE measurement after LTx significantly correlated with time to development until development of persistent ascites, hepatorenal syndrome and overt hepatic encephalopathy. Furthermore, splenic TE correlated with actuarial survival free of LTx and, in direct comparison surpassed liver fibrosis scores such as FIB-4 or APRI regarding the predictive value of actuarial survival free of LTx.

Following LTx, diagnosis of portal hypertension identifies patients of high-risk requiring particular medical attention. However, diagnosis of portal hypertension after LTx is challenging, particularly due to vascular changes prior to LTx. The definitive diagnosis of portal hypertension can only be established by invasive direct portal pressure measurement, which is therefore not routinely performed and inept as a predictive tool. In our present study, we propose splenic TE to function as an easily performable, non-invasive test in liver transplanted patients, that can significantly identify patients at high risk for reduced actuarial survival. There several limitations to this study. Although this is a prospective study cohort, the data analysis was performed retrospectively. Furthermore, splenic TE measurement was routinely only performed 3 months after LTx and not repeatedly at standardized times. Therefore, no data is available how changes in contrast to baseline splenic TE would mean for the transplanted patient.

In the present study, we were able to show that splenic TE measurement at 3 months after LTx, adequately serves as a predictor of actuarial survival free of LTx. Therefore, TE measurement should be implemented in the post LTx workup to identify transplanted patients at risk that need further medical attention.

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Footnote

Data Sharing Statement: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-19-343/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-19-343/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All medical data from the time of enrolment at Eurotransplant were recorded for each patient. Informed consent to participate in the study was obtained from each patient. The study was approved by the Ethical Committee of the University of Heidelberg (No. S-270/2015) and carried out in accordance with the Declaration of Helsinki (as revised in 2013).

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