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Routine Liver Elastography Could Predict Actuarial Survival after Liver Transplantation

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ABSTRACT

Background & Aims: Transient elastography (TE) has routinely been implemented in the diagnosis and assessment of chronic liver disease. Little data are available in the post liver transplant (LTx) setting.
Methods: Three months after LTx, we performed TE in 137 liver transplant recipients and investigated its predictive value upon further clinical outcome. The mean follow-up time for clinical outcome was 24 months.
Results: Mean TE value was 10.6 kPa (± 6.3 kPa; range 2.8 – 29.9 kPa). There was a significant correlation between TE and aspartate aminotransferase (AST) (p=0.004), gamma-glutamyl transferase (GGT) (p=0.031) and bilirubin (p<0.001) serum levels. In Cox univariate analysis, TE served as a predictor of actuarial survival free of liver transplantation (OR=1.111, 95%CI: 1.051–1.174; p<0.001). In multivariate analysis, TE remained an independent risk factor associated with reduced actuarial survival free of liver transplantation (OR=1.080, 95%CI: 1.001–1.166; p=0.047), along with thrombocytes (OR=0.992, 95%CI: 0.986–0.999; p=0.020) and metabolic co-disease (OR = 0.250, 95%CI: 0.070–0.895; p=0.033).
Conclusion: Transient elastography measurement at three months after LTx seems a robust predictor of survival in liver transplant recipients.

Key words: transient elastography – liver transplantation – actuarial survival free of liver transplantation – predictor of survival.

Abbreviations: APRI: AST-to-platelet radio index; LTx: liver transplantation; NAFLD: nonalcoholic fatty liver disease TE: transient elastography.

INTRODUCTION

As recurrent liver fibrosis development represents a serious threat to the transplant recipient, the management of patients after liver transplantation (LTx) involves a broad variety of laboratory markers and non-invasive as well as invasive diagnostic procedures to identify graft damage. Liver biopsy still has a central role in this process mainly to grade fibrosis or to exclude liver graft rejection [1]. However, sample error, potentially severe complications and patient reluctance to undergo an invasive procedure are important shortcomings of the technique [2]. Thus, non-invasive diagnostic tools have been introduced into the liver transplant setting for the detection of graft fibrosis [3]. Liver stiffness measurement using transient elastography (TE) is a noninvasive test that accurately estimates the presence of advanced fibrosis and cirrhosis in patients with chronic liver disease [4]. Prospective cohort studies showed that liver stiffness measurement may predict development of decompensated cirrhosis [5] and hepatocellular carcinoma [6], and estimates mortality in patients with cholestatic liver diseases [7]. In the highly specific setting of liver transplantation, recurrent liver fibrosis indicates impaired graft survival and the need for re-transplantation, thus impacting overall survival [8]. In particular, nonalcoholic fatty liver disease (NAFLD) affects more than 20% of liver transplant recipients, which can be attributed to the high rate of metabolic syndrome triggered by weight gain or immunosuppressive medications following LTx [9].

In liver transplant recipients, TE has been shown to correlate with METAVIR biopsy fibrosis grading [10]. However, in the post-transplant setting, studies investigating TE were either not obtained at standardized times following liver transplantation or performed in the diagnosis of liver graft rejection [11-13]. In the present study, we performed TE

routinely three months after LTx and investigated its predictive value upon further clinical outcome.

METHODS

Study design

This is a retrospective analysis of a study cohort, prospectively enrolled at Eurotransplant from October 2012 and until October 2018. All medical data from the time of enrolment were recorded for each patient. Informed consent was obtained from the patients. The study was approved by the Ethical Committee of the University of Heidelberg and carried out in accordance with the Declaration of Helsinki in its present form. Following Ltx, patients were discharged from our hospital and routinely scheduled for an outpatient visit at our clinic three months after LTx. At this time, laboratory markers were evaluated and TE was performed. Patients with complicated postoperative course, who could not be discharged after three months, were excluded from our study. Patients with severe cholestasis were not included into the study cohort.

Endpoint definition and scoring calculation

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

APRI-SCORE (AST-to-platelet radio index) was calculated using the formula [14]: APRI = 100 x AST/(upper limit of normal for AST) / platelet count (10^9/L).

FIB-4 Score (Fibrosis 4 – Score) was calculated using the following formula [15]: FIB-4 = Age (years)×AST (U/L)/ [PLT(10^9/L)×$ALT^{1/2}$(U/L)].

Hepatic decompensation 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 [16].

Transient elastography

For the TE measurement of liver stiffness, a FibroScan (Echosens, Paris, France) was used. This device creates a low-frequency acoustic wave to an ultrasonic transducer. Its speed is measured with an ultrasound imaging, and using the measured speed, the tissue stiffness is computed where the acoustic wave penetrates the tissue [17]. The results are expressed in kilo-Pascal (kPa). In order to measure liver stiffness, patients laid on their backs with the right arms raised above their heads. The probe was placed vertically on the intercostal skin of the right lobe of the liver. The lung area and intercostal areas were avoided when using FibroScan's ultrasonic TM mode (time-motion) and A-mode (amplitude mode) images. The liver parenchyma stiffness was measured between 2.5 to 6.5 cm under skin by pressing the probe's oscillator button. The measurements were ended when 10 successful values had been obtained for each patient. Stiffness was determined as the average value, 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. The presence of ascites was determined with an abdomen ultrasound scan on the day of the FibroScan. In the presence of ascites, FibroScan was no longer performed and patients were excluded from further analysis. The median value generated by the ultrasound software was used to establish the elastography grade as follows: < 4.6 kPa = F0; 4.6-5.6 kPa = F1; 5.7-7.0 kPa = F2; 7.1-12.0 kPa = F3 ; > 12 kPa = F4 [18].

Statistical analysis

Preliminary testing for normality was conducted by using the Shapiro-Wilk test. If the preliminary test for normality was not significant, the *t* test was used; if the preliminary test rejected the null hypothesis of normality, a nonparametric test (Mann-Whitney's U test) was applied in the main analysis [19]. Spearman's rho was used as the nonparametric measure of statistical dependence between two variables. The rate of actuarial survival free of liver transplantation was estimated using the Kaplan-Meier method. Differences between the actuarial estimates were analyzed using the log-rank test. The following variables were selected for univariate analysis based on the results of previous studies: age, gender, body mass index, presence of metabolic co-diseases (diabetes, hypertriglyceridemia, hypercholesterolism), TE, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phopsphatase (AP), bilirubin, albumin, creatinine, international normalized ratio (INR) and 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

Liver transplantation cohort

Of the 137 patients that had received liver transplantation, 40 were female (29.2%) and 97 were male (70.8%). The underlying hepatic disorders contributing to liver transplantation were: alcoholic liver disease (ALD, n=27), chronic hepatitis B (HBV, n=13), chronic hepatitis C (HCV, n=31), primary sclerosing cholangitis (PSC, n=19), non-alcoholic steatohepatitis (NASH, n=10), and other hepatic disorders (n=37, each subgroup n<10). Mean follow-up time was 24.4 months ± 15.6 (range: 1.3 – 70.3). Of these 137 patients, 10 patients received recurrent liver transplantation (Re-LTx) while 9 patients died after LTx. Serological markers, APRI and FIB-4-scores and clinical data 3 months after liver transplantation are shown in Table I.

Transient elastography values after LTx

Mean TE value at three months after liver transplantation was 10.6 kPa (± 6.3 kPa; range 2.8–29.9 kPa). Fifteen patients (10.9%) were characterized as F0, 11 patients (11%) as F1, 20 patients (14.6%) as F2, 48 patients (35.0%) as F3 and 43 patients (31.4%) as F4.

Correlation of TE values and liver enzyme levels after LTx

There was a statistically significant positive correlation between TE and serum AST (p=0.004, Pearson correlation coefficient: 0.244), GGT (p=0.031, Pearson correlation coefficient: 0.184) and bilirubin (p<0.001, Pearson correlation

Table I. Patient characteristics 3 months after liver transplantation

Liver elastography (kPA), mean, SD	10.6 ± 6.3
AST (U/l), mean, SD	40.4 ± 47.6
ALT (U/l), mean, SD	56.5 ± 75.2
GGT (U/l), mean, SD	176.1 ± 281.4
AP (U/l), mean, SD	156.5 ± 144.8
Bilirubin (mg/dl), mean, SD	1.00 ± 1.3
Thrombocytes (/nl), mean, SD	181.6 ± 107.9
INR mean, SD	1.06 ± .2
Albumin (g/dl), mean, SD	3.9 ± .6
Creatinine (mg/dl), mean, SD	1.0 ± .6
Metabolic co-disease n, (%)	76/137 (55.5%)
Age at LTx (years), mean, SD	48.5 ± 12.9
Gender	40 females, 97 males
BMI mean, SD	26.4 ± 5.2
APRI-Score mean, SD	0.64 ± 1.05
FIB-4 Score mean, SD	2.10 ± 2.02
Immunosuppressive agent	Ciclosporin: n=76 (55.5%); Tacrolimus n = 61 (44.5%)

coefficient: 0.355). This correlation was not observed for ALT (p=0.158), AP (p=0.087), INR (p=0.265), albumin (p=0.265), creatinine (p=0.625) and thrombocytes (p=0.059).

Transient elastography values and histological Desmet score

In 27 patients, liver biopsy was performed on the same day with TE measurement. Three patients were classified as F0, 4 patients as F1, 11 patients as F2, 7 patients as F3 and 2 patients as F4. When comparing the histological Desmet Score [20] with the scoring system used to grade TE, we observed a highly significant correlation (p<0.001, Spearmans correlation coefficient: 0.674). We also found that liver fibrosis score obtained by liver biopsy was significantly lower (mean: 2.04 ± 1.26) compared to the fibrosis score obtained by TE measurement (mean: 2.85 ± 1.09, p<0.001).

Transient elastography values and clinical complications after LTx

At three months after LTx, TE values did not correlate with development of acute liver rejection (38 events, OR=1.013, 95%CI: 0.957–1.073; p=0.650) or bile duct stenosis (61 events, OR=1.019, 95%CI: 0.971–1.069; p=0.448) during further follow-up. However, TE did correlate with development of hepatic artery stenosis requiring intervention (OR=1.202, 95%CI: 1.085–1.333; p<0.001; no hepatic artery stenosis: TE 10.2±6.04 kPa vs hepatic artery stenosis: TE 16.1±8.6 kPa, p=0.007). Hepatic artery stenosis occurred at 8.1±17.1 months after TE measurement.

For comparing time until hepatic decompensation, the patients were grouped according to fibrosis score F0/1, F2/3 and F4. We observed a significantly reduced time until the development of ascites in patients with higher fibrosis scores (F0/1: 78.7±4.4 months; 95%CI: 70.0 – 87.4; events: n=2 (7.7%); F2/3: 51.9 ± 3.1 months; 95%CI: 45.8 – 58.0; events: n=7 (10.3%); F4: 30.5±5.8 months; 95%CI: 18.9 – 42.0; events: n=20 (23,4%), p<0.001, Fig. 1A). Furthermore, time until the development of the hepatorenal syndrome (HRS) (F0/1: 0 events: n=0 (0.0%); F2/3: events: n=2 (2.9%); F4: events: n=6 (14.0%), p = 0.013, Fig. 1B) and time until the development of overt hepatic encephalopathy was significantly reduced (F0/1: 0 events: n=0; F2/3: events: n=3 (4.4%); F4: events: n=13 (30.2%), p<0.001, Fig. 1C). No statistical data of survival estimates or CIs are given for the time until development of HRS and hepatic encephalopathy due to the low number of events in the subgroups.

To evaluate the differences in the study population between patients with high TE scores vs. patients with low TE-scores, we grouped patients into low-TE score (T0/1/2) and high-TE score (T3/4). Although there was a trend towards elevated liver enzymes and cholestasis markers between the two groups, this was not statistically significant (Table II). There were no significant differences regarding the underlying hepatic

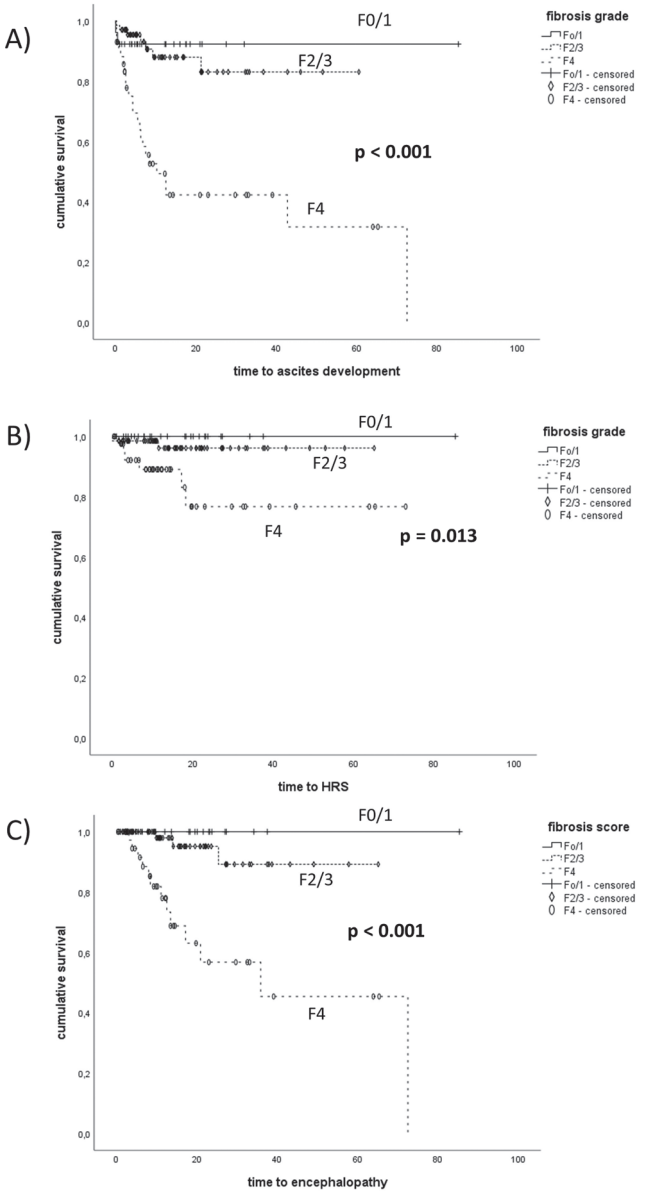

Fig. 1. Kaplan–Meier analysis of time until hepatic decompensation based on elastography grade (F0/1 vs F2/3 vs F4) obtained by TE 3 months after LTx. A) Time until development of persistent ascites. B) Time until development of hepatorenal syndrome. C) Time until development of overt hepatic encephalopathy.

disorders (p =0.611) or HCV-recurrence (p =0.140) between the two groups.

TE-based fibrosis scoring is associated with actuarial survival free of liver transplantation

In patients with F0 and F1 TE-based fibrosis score there were no deaths/recurrent liver transplantations observed during the time of follow-up. In the F2 group, 3 of the 20 patients (15%) died or needed liver transplantation. In the F3 group, 1 of the 48 patients (2%) died or needed liver transplantation while 15 patients (34.8%) of the 43 patients in the F4 group died or needed liver transplantation (Log Rank Mantel-Cox: p<0.001).

When comparing patients with fibrosis score F0/1 to patients with F2/3 and F4, actuarial survival was significantly reduced with pronounced fibrosis (Fig. 2; p<0.001).

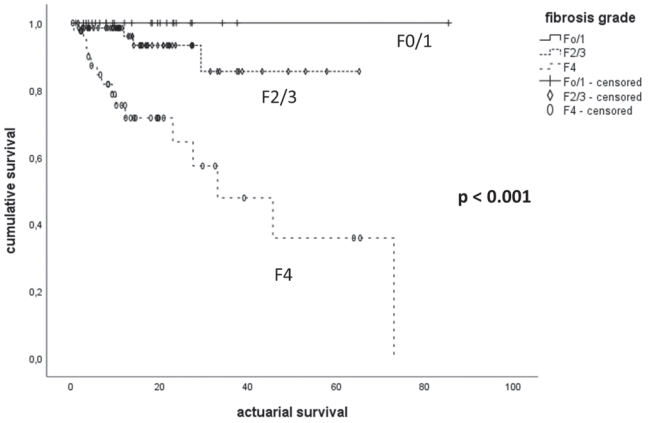

Fig. 2. Kaplan–Meier analysis of actuarial survival free of liver transplant recipients based on elastography grade (F0/1 vs F2/3 vs F4) obtained by TE 3 months after LTx.

Transient liver elastography might predict actuarial survival after LTx

Age at time of enrolment at Eurotransplant, gender, BMI, metabolic co-disease, TE, serum AST, serum ALT, serum GGT, serum AP, serum bilirubin, serum albumin, INR, thrombocytes were subjected to Cox univariate analysis (Table III). Transient elastography, AST, ALT, GGT, AP, serum bilirubin thrombocytes and metabolic co-diseases were below the set p-value of 0.1 and therefore subjected to further multivariate analysis. In multivariate analysis, TE remained an independent risk factor associated with the reduced actuarial survival free of Ltx (OR=1.080, 95%CI: 1.001–1.166; p=0.047), along with thrombocytes (OR=0.992, 95%CI: 0.986–0.999; p=0.020) and metabolic co-disease (OR=0.250, 95%CI: 0.070–0.895; p=0.033; Table III).

Using ROC-analysis, the optimal cut-off value to predict actuarial survival in our study cohort would be a TE-value of 10.6. This cut-off value would lead to a sensitivity of 0.789 and a specificity of 0.720 (ROC: 0.786, Supplemental Fig. 1).

Transient liver elastography might predict actuarial survival independent of established APRI or FIB-4 Score

Transient elastography 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 liver transplantation

Table II. Patient characteristics with low TE fibrosis score vs high TE fibrosis score.

	Low fibrosis score	High fibrosis score	p-value
Liver elastography (kPA), mean, SD	5.14 ± 1.2	13.4 ± 6.1	< 0.001
ALT (U/l), mean, SD	40.7 ± 59.6	64.5 ± 81.1	0.081
GGT (U/l), mean, SD	112.3 ± 133.4	208.3 ± 328.1	0.059
AP (U/l), mean, SD	145.5 ± 116.2	162.1 ± 157.6	0.526
Bilirubin (mg/dl), mean, SD	0.7 ± 0.6	1.1 ± 1.6	0.077
Thrombocytes (/nl), mean, SD	161.5 ± 125.3	132.3 ± 90.3	0.196
INR mean, SD	1.05 ± 0.1	1.06 ± 0.2	0.720
Albumin (g/dl), mean, SD	3.7 ± 6.0	3.9 ± 6.1	0.066
Creatinine (mg/dl), mean, SD	1.0 ± 0.5	1.0 ± 0.6	0.985
Metabolic co-disease* n, (%)	18/46 (39.1%)	43/91 (47.2%)	0.366
Age at LTx (years), mean, SD	49.6 ± 12.2	47.9 ± 13.2	0.468
Gender	13 female, 33 male	27 female, 64 male	0.864
BMI mean, SD	26.2 ± 5.1	26.6 ± 5.2	0.709
APRI-Score mean, SD	0.35 ± 0.35	.79 ± 1.24	0.021
FIB-4 Score mean, SD	1.5 ± 0.9	2.4 ± 2.3	0.015
Underlying hepatic disorder n/total (%)	ALD: 12/46 (26.1%) viral: 13/46 (28.3%) PSC: 7/46 (15.2%) NASH: 2/46 (4.3%) others: 12/46 (26.1%)	ALD: 15/91 (15.5%) viral: 31/91 (34.1%) PSC: 12/91 (13.2%) NASH: 8/91 (8.8%) others: 25/91 (27.5%)	0.611
HCV-recurrence n/total (%)	2/10 (20.0%)	10/21 (47.6%)	0.140

ALD: alcoholic liver disease; PSC: primary sclerosing cholangitis; NASH: non-alcoholic steatohepatitis;
* defined as diabetes mellitus type I and II, hypercholesterolemia, hypertriglyceridemia.

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

	Cox univariate analysis OR [95% CI]	p - value	Cox multivariate analysis OR [95% CI]	p - value
Transient elastography (kPA)	1.111 [1.051–1.174]	**< 0.001**	1.08 [1.001–1.166]	**0.047**
AST (U/l)	1.007 [1.001–1.014]	**0.028**	1.011 [0.992–1.030]	0.254
ALT (U/l)	1.003 [0.998–1.008]	**0.08**	0.990 [0.976–1.005]	0.197
GGT (U/l)	1.001 [1.000–1.002]	**0.028**	1.001 [0.999–1.004]	0.365
AP (U/l)	1.003 [1.001–1.005]	**0.008**	1.002 [0.998–1.007]	0.304
Bilirubin (mg/dl)	1.242 [1.067–1.446]	**0.005**	1.120 [0.922–1.587]	0.169
Metabolic co-disease*	0.333 [1.26–0.877]	**0.026**	0.250 [0.070–0.895]	**0.033**
INR	0.658 [0.061–7.112]	0.730	n.a.	n.a.
Albumin (g/dl)	0.983 [0.913–1.058]	0.648	n.a.	n.a.
Creatinine (mg/dl)	1.126 [0.558–2.273]	0.741	n.a.	n.a.
Age at Ltx (years)	1.011 [0.976–1.046]	0.542	n.a.	n.a.
Gender	1.105 [0.393-3.107]	0.849	n.a.	n.a.
BMI	1.029 [0.941-1.124]	0.530	n.a.	n.a.
Thrombocytes (/nl)	0.992 [0.985-1.000]	**p = 0.042**	n.a.	n.a.
Immunosuppression	0.510 [0.180-1.445]	p = 0.205	n.a.	n.a.

* defined as diabetes mellitus type I and II, hypercholesterolemia, hypertriglyceridemia; n.a.: not applicable

(OR=1.278, 95%CI: 0.981–1.664; p=0.069). When subjected to multivariate analysis, TE remained an independent predictor of survival (OR=1.109, 95%CI: 1.044–1.177; p=0.001) while APRI-Score did not (OR=1.028, 95%CI: 0.750–1.408; p=0.865).

Transient elastography vs. FIB-4 Score: in univariate analysis, the FIB-4 score met the specified threshold of significance of <0.1 for actuarial survival free of liver transplantation (OR=1.190, 95%CI: 1.024–1.381; p=0.023).

At multivariate analysis, TE remained an independent predictor of survival (OR=1.100, 95%CI: 1.034–1.169; p=0.002) while FIB-4 did not (OR=1.073, 95% CI: 0.903–1.275; p=0.426).

DISCUSSION

While liver stiffness measurement has been routinely implemented in the diagnosis and management of patients with chronic liver disease, little data is available to what degree it provides meaningful data in the specific setting after LTx, particularly in the context of a predictive marker of patient survival. There are pre-existing data showing that non-invasive fibrosis measurement correlates with histological fibrosis after LTx. However, these data were either obtained during the diagnosis of acute cellular rejection [13] or were not obtained at standardized times following LTx [10].

In our prospectively enrolled study cohort, we measured TE routinely at three months after LTx, with a mean follow-up time of clinical outcome of 24 months. It is interesting, that 81% of the overall study population had a fibrosis score ≥ 2 three months after LTx. Indeed, elevated TE-scores have been reported in the post-transplant setting [21]. However, drawbacks of TE measurement such as hepatitis-associated necroinflammatory activity, cholestasis and vascular congestion [22], steatosis [23], and extrahepatic obstructive cholestasis [24, 25] need to be taken into account. In 27 patients we performed liver biopsies on the same day TE was performed. Although the study population is small, it is interesting to see that grading based on histology was significantly lower than fibrosis grading based with TE ($p < 0.001$). Sampling error and intraobserver variation in liver biopsy in patients with chronic liver diseases are a common source of discrepant fibrosis staging [26]. Particularly, in high grade fibrosis stages, present in 31% of our study population, differences in TE and liver biopsy grading have been reported with an AUROC for the prediction of F4 of only 0.89 [27]. A current study validating TE in autoimmune hepatitis suggested liver inflammation, a common histopathological feature in the post-transplant setting, as a severe confounder of liver stiffness measurement [28]. Transient elastography measurement at three months after LTx did not only correlate with liver enzyme levels, but correctly predicted hepatic decompensation and actuarial survival free of Ltx, independent of liver function markers or established scoring-systems such as APRI or FIB-4. For a non-invasive diagnostic tool that can easily be performed in liver transplant recipients, these data appear to be very promising to identify LTx patients at risk. It is interesting that patients developing hepatic artery stenosis in the further clinical course had higher TE measurements three months after Ltx. This might be attributed to microperfusion problems already creating liver fibrosis prior to the actual event.

There are several limitations of this study. Although this is a prospectively enrolled study cohort, the data analysis was performed retrospectively. Furthermore, TE measurement was routinely performed only at three months after LTx and not repeated at standardized times. Therefore, we cannot report whether changes in contrast to baseline TE measurements would even further increase the predictive value. Moreover, data of the organ donors would have been required, particularly age and pre-existing illnesses.

CONCLUSION

In the present study, we were able to show that TE measurement at three months after LTx could be a predictor of actuarial survival free of liver transplantation. Therefore, TE measurement can be implemented in the post LTx workup.

Conflicts of interest: The authors declare that they do not have anything to disclose regarding funding from industries or conflict of interest with respect to this manuscript.

Authors contributions: K.F., K.H.W., M.M., J.P., A.M. conceived the study and drafted the paper. K.F., K.H.W., J.P. were responsible for data collection, statistical analysis of results, writing, editing and submitting the manuscript. K.F., D.H., P.H., C.W., B.v.H., V.L., K.H.W., J.P. revised the manuscript.

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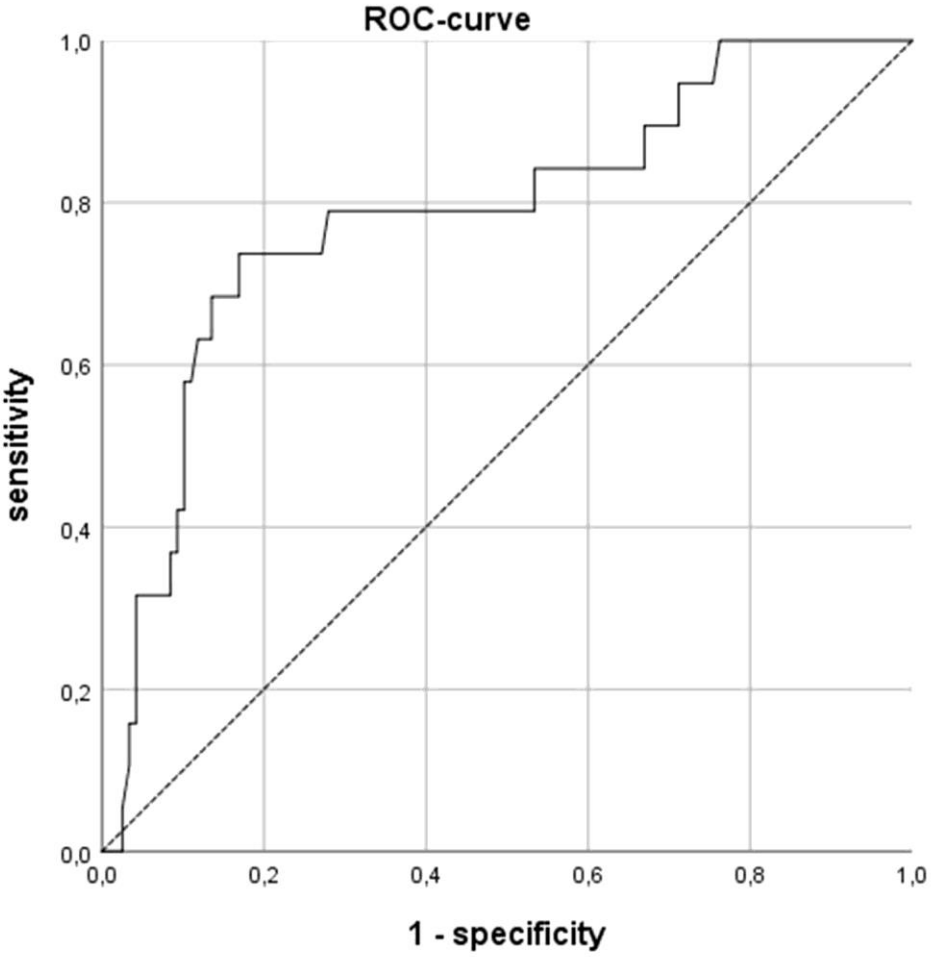

Supplementary Fig. 1. ROC analysis of TE measurement and actuarial survival.