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ORIGINAL ARTICLE

Comparison of liver stiffness, fibrotest and liver biopsy for assessment of liver fibrosis in kidney-transplant patients with chronic viral hepatitis

Laurent Alric,[1,2] Nassim Kamar,[3,4] Delphine Bonnet,[1] Marie Danjoux,[5] Florence Abravanel,[6,7] Valérie Lauwers-Cances[8] and Lionel Rostaing[3,7]

1 Service de Médecine Interne, Fédération Digestive, CHU Purpan, Toulouse, France
2 Laboratoire UPRES EA2405, Université Paul Sabatier, Toulouse III, France
3 Service de Néphrologie et Unité de transplantation d'organe, CHU Rangueil, Toulouse, France
4 INSERM U858, IFR 31, CHU Rangueil, Toulouse, France
5 Laboratoire d'Anatomopathologie, CHU Purpan, Toulouse, France
6 Laboratoire de Virologie, CHU Purpan, Toulouse, France
7 INSERM U563, IFR 30, CHU Purpan, Toulouse, France
8 Département d'épidémiologie et de statistiques, CHU Purpan, Toulouse, France

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Correspondence
Laurent Alric, Service de Medecine Interne, Federation Digestive, CHU Purpan, 31059 Toulouse, France. Tel.: 33 5 61 77 95 51; fax: 33 5 61 77 22 30; e-mail: alric.l@chu-toulouse.fr

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Summary

To assess the accuracy of the noninvasive tools, fibrotest (FT) and liver stiffness measurement (LSM) for assessing liver fibrosis in kidney-transplant patients with chronic hepatitis virus B (HBV) or C (HCV) infection. Thirty-eight consecutive kidney-transplant patients with HCV ($n = 26$) or HBV ($n = 12$) underwent liver biopsies followed by a FT and LSM. Liver biopsies gave the following fibrosis-grade distribution using METAVIR scores: F0/F1, $n = 10$ (26.9%); F2, $n = 14$ (36.8%), F3, $n = 7$ (18.42%); F4, $n = 7$ (18.4%). The area under the receiver-operating characteristic curve for mild fibrosis stage <F2 was 0.69 (0.47–0.91) for the FT and 0.68 (0.45–0.90) for LSM; for severe fibrosis stage F3–F4, they were 0.55 (0.35–0.76) for the FT and 0.69 (0.50–0.87) for LSM. Eighty to 90% of patients with no significant liver fibrosis (<F2) were well-classified, with a cut-off value <0.5 for the FT and <7.1 kPa for LSM. Diagnosis of patients with severe liver fibrosis (F3/F4) by FT and LSM differed by 38.4% from the liver biopsy data. The FT and LSM are acceptably accurate for diagnosing mild liver fibrosis in kidney-transplant patients with chronic HCV or HBV infections, but their diagnostic value for predicting severe liver disease needs to be confirmed.

Introduction

The prevalence of hepatitis C (HCV) or hepatitis B (HBV) virus infection in patients with end-stage kidney disease is very high, and 20–30% of candidates for kidney transplantation have HCV or HBV [1] infection. HBV infection is frequently observed following kidney transplantation, mainly in the absence of anti-HBV prophylactic therapy. [2]. With respect to HCV infection, although patient and graft survival seem to be lower in HCV-positive than in HCV-negative recipients, the natural history of progression of liver infection remains controversial. Increased patient mortality after kidney transplantation in the HCV population has been reported to be related to liver disease and sepsis [3]. Recently, HCV infection has been reported to be an independent risk factor for tuberculosis after kidney transplantation [4]. We have previously reported on 36 HCV-positive kidney-transplant patients who underwent two consecutive liver biopsies after transplantation: liver fibrosis progressed in <50% of

patients at more than 10 years after kidney transplantation [5,6]. Liver biopsy is the gold standard for assessing fibrosis, but is a costly procedure and, in the population of kidney-transplant patients, is an invasive method associated with life-threatening complications [7]. Thus, assessing liver fibrosis using noninvasive procedures is a novel and exciting challenge. Several serum-marker scores have been reported to be accurate for predicting liver fibrosis in many liver diseases without renal failure [8,9]. One of these, the fibrotest (FT), has been extensively validated in patients with chronic HCV [7,10] and HBV [11] infections. Recently, transient elastography has been demonstrated to be another noninvasive tool for assessing liver fibrosis in patients with chronic HCV or HCB infection [8,12,13]. Liver stiffness measurement (LSM) by Fibroscan (EchoSens, Paris, France) could also be a promising simple tool to assess liver fibrosis in chronic liver diseases [8]. However, the accuracy of FT or LSM for evaluating liver fibrosis in kidney-transplant patients remains to be demonstrated. Our target groups were METAVIR F0/F1 versus METAVIR F3/F4 because kidney-transplant patients with mild fibrosis are not at risk of liver complications, whereas patients with severe fibrosis or cirrhosis must be screened for portal hypertension and hepatocellular carcinoma.

The aim of the study was to assess the diagnostic performance of FT and LSM for evaluating liver fibrosis in kidney-transplant recipients with chronic HCV or HBV infection.

Patients and methods

Patients

A total of 38 consecutive kidney-transplant recipients with chronic HCV or HBV infection were prospectively included in this study. As the natural history of progression of the liver infection remains controversial in HCV positive and/or HBV positive kidney-transplants, liver biopsies are routinely performed in this population in our department. The HBV and HCV infections were diagnosed by serological detection of HBV surface antigens or HCV antibodies (Elisa III; Orthodiagnostics systems, Roissy, France), respectively. All HCV-infected patients had HCV RNA in their serum. All other causes of chronic liver disease, such as HIV co-infection, autoimmune liver disease, or excess alcohol intake defined as >20 g/day, were excluded.

None of the 26 HCV-infected kidney-transplant recipients had antiviral therapy with interferon and/or ribavirin after transplantation. All 12 HBV-infected patients had been given lamivudine and/or adefovir therapy, all of them had responded, and their serum was negative for HBV DNA. Their immunosuppression regimen after renal transplantation was based on a combination of cyclosporine and/or azathioprine and corticosteroids. The duration of viral infection was determined from archived frozen sera. It has been the policy of our center, for over 20 years, to obtain a serum sample every 6 months from each dialysis- and kidney-transplant recipient.

All 38 patients underwent a liver biopsy via the percutaneous route. Each patient had FT, a surrogate of serum markers of liver fibrosis, and LSM, by Fibroscan, on the same day, within 3 months after the liver biopsy.

Methods

Histologic evaluation

All 38 consecutive kidney-transplant patients underwent a liver biopsy after transplantation (mean time 132.79 ± 48 months). All liver biopsy samples had at least eight portal spaces and were more than 15 mm long. The same pathologist (M.D.), with a specialist interest in liver histology, examined the liver-biopsy specimens blinded to whether FT or LSM had been used. The stage of fibrosis was assessed according the METAVIR score [14], as follows: A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity; F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis.

Serum surrogate fibrosis markers

The following parameters were determined in the same laboratory on blood samples within 3 months after the liver biopsy: alanine transaminase (ALT) level, γ-glutamyl transpeptitase level, total bilirubin level, α2-macroglobulin level, apolipiprotein A1 level, and haptoglobin level. The FT score (Biopredictive, Paris, France) is calculated using a mathematical combination of values for the six biochemical markers [10], as provided by the web site: http://www.biopredictive.com.

Liver stiffness measurement

Liver stiffness measurement was performed by a single experienced physician (L.A.) on the same day as the FT, using a new medical device based on elastometry, Fibroscan [12,13]. The results were expressed in kilopascals (kPa) and the median value was considered representative of the elastic modulus of the liver. As required by EchoSens, only procedures with 10 validated measurements and a success rate of at least 60% were considered reliable [12,13] .

Statistical analyses

The diagnostic performance of FT and LSM were assessed using receiver-operating characteristic (ROC) curves.

Connected with any cut-off value is the probability either a true positive (sensitivity) or the probability of a true negative (specificity). The ROC curve is a plot of sensitivity versus specificity for all possible cut-off values. The most commonly used index of accuracy is the area under the ROC curve (AUROC), with a value close to 1 indicating high diagnostic accuracy. Quantitative variables were expressed as mean ± SE or a median with its 95% confidence interval.

Results

Characteristics of patients

Patient characteristics are shown in Table 1. There were more men than women. Among the 38 patients included, chronic liver disease was related to HCV infection in 26 cases (68.4%) and to HBV infection in 12 cases (31.5%). Age at transplantation, duration of hemodialysis, duration of liver infection, duration of transplantation, angiotensin-converting enzyme inhibitor and/or angiotensin-II-receptor antagonist therapy, as well as its duration, are summarized in Table 1. Three out of the 38 patients (7.9%) had developed post-transplant diabetes mellitus, and were diabetic at liver fibrosis assessment.

Table 1. Characteristics of patients.

Number	38
HCV (%)	26 (68.4)
HBV (%)	12 (31.5)
ALAT (IU/l)	49.4 ± 48
Normal range: 0–34 female; 0–45 male	
HCV RNA (log IU/ml)	6.078 ± 1.21
HBV DNA (IU/ml)	<12
Age at transplantation (years)	39.02 ± 11.8
Gender (M/F)	28/10
Duration of hemodialysis (months)	89.9 ± 56.1
Duration of virus infection (months)	233 ± 56
Duration of transplantation at liver biopsy (months)	132.79 ± 48
HBV treatment	
Adefovir	8 (66.6)
Lamivudine	2 (16.6)
Adefovir + lamivudine	2 (16.6)
ACE inhibitors (%)	22 (57.2)
ARA (%)	14 (36.8)
Duration of ACE inhibitors and or ARA therapy (months)	72 ± 18.9
Liver biopsy METAVIR	
Activity (%)	
A0	9 (23.6)
A1	19 (50)
A2	8 (21)
A3	2 (5.2)
Fibrosis (%)	
F0/F1	10 (26.9)
F2	14 (36.8)
F3	7 (18.42)
F4	7 (18.4)

ACE, angiotensin-converting enzyme; ARA, angiotensin-II-receptor antagonist; HBV, hepatitis virus B; HCV, hepatitis virus C.

The liver biopsy gave the following fibrosis-grade distribution using the METAVIR score: F0/F1, $n = 10$ (26.9%); F2, $n = 14$ (36.8%); F3, $n = 7$ (18.42%); F4, $n = 7$ (18.4%). As shown in Table 1, mild liver disease with an F0/F1 METAVIR grade was observed in 10 patients (26.9%), and severe liver disease with a F3/F4 METAVIR grade was observed in 14 (36.8%) patients. Five out of the 12 (41.6%) HBV patients and seven out of the 26 (30.26%) HCV patients had severe liver fibrosis METAVIR F3/F4. Fourteen patients (36.8%) had intermediate-grade fibrosis, with an F2 METAVIR grade. According to Metavir activity, necroinflammatory activity, as seen in the liver biopsy, was mild (Table 1): A0/A1, $n = 28$ (73.6%); A2, $n = 8$ (21%); A3, $n = 2$ (5.2%). Most patients had a low serum ALT level (49.4 ± 48 IU/l) and none had an alcohol intake >20 g/day.

Comparison of fibrotest and fibroscan with liver biopsy

The optimal cut-off values for FT or LSM were chosen to maximize sensitivity, specificity, positive, and negative predictive values (NPV) with reference to the METAVIR grades obtained from the liver biopsy (Table 2). The ROC curves (Fig. 1) were analysed for all patients with mild liver disease (METAVIR grade <F2) and for those with severe liver disease (Fig. 2; METAVIR grade F3–F4). The corresponding area under the ROC curve for fibrosis stage <F2 was 0.69 (0.47–0.91) for FT, and 0.68 (0.45–0.90) for LSM (Fig. 1). The areas-under-curves for fibrosis stage F3–F4 were 0.55 (0.35–0.76) for FT and 0.69 (0.50–0.87) for LSM (Fig. 2).

The FT values ranged from 0.13 to 0.92. FT could not be measured in three cases (7.8%) because of elevated bilirubin caused by hemolysis of the blood sample or Gilbert's disease in two cases and because of increased haptoglobin and decreased α2-macroglobulin in a third infected patient. For mild histologic liver disease (Table 2) with a METAVIR grade <F2, the optimal cut off value of FT was 0.5, with a sensitivity of 68.2% (45–86), a specificity of 70% (34–93), a positive predictive value (PPV) of 83.3% (58–96), and a NPV of 50% (23–77). With respect to nonsignificant liver fibrosis (<F2), 80% of the patients with no significant liver fibrosis (<F2) were well classified with an FT cut-off value of <0.5. The optimal FT cut-off value was 0.69 (Table 2) for predicting severe liver disease (METAVIR grade F3/F4). This value gave a sensitivity of 30.8% (9.1–61.4) and a specificity of 84.2% (60.4–96.6). FT had a PPV of 57.1% (18.4–90.1) and an NPV of 64% (42.5–82) for predicting severe liver disease. There was a discrepancy between the

Table 2. Diagnostic accuracy of fibrotest and liver stiffness measurement in identifying renal-transplant patients with mild liver fibrosis METAVIR scores of F0/F1, or severe liver fibrosis METAVIR scores of F3/F4.

	Prediction of no significant fibrosis METAVIR < F2 (F0–F1) Liver biopsy (n = 10)		Prediction of severe fibrosis METAVIR ≥ F3 (F3–F4) Liver biopsy (n = 14)	
	Fibrotest < 0.5 (n = 10)	LSM < 7.1 kPa (n = 10)	Fibrotest > 0.69 (n = 13)	LSM > 9.5 kPa (n = 13)
Sensitivity (%)	68.2 (45.1–86.1)	69.2 (38.6–90.9)	30.8 (9.1–61.4)	69.2 (38.6–90.9)
Specificity (%)	70 (34.8–93.3)	73.9 (51.6–89.8)	84.2 (60.4–96.6)	73.9 (51.6–89.8)
PPV (%)	83.3 (58.6–96.4)	60 (32.3–83.7)	57.1 (18.4–90.1)	60 (32.3–83.7)
NPV (%)	50 (23–77)	81 (58.1–94.6)	64 (42.5–82)	81 (58.1–94.6)
Correctly classified (%)	8 (80)	9 (90)	8 (61.54)	8 (61.5)
Underestimated (%)	0	0	5 (38.46)	5 (38.46)
Overestimated (%)	2 (20)	1 (10)	0	0

LSM, liver stiffness measurement; PPV, positive predictive value; NPV, negative predictive value.

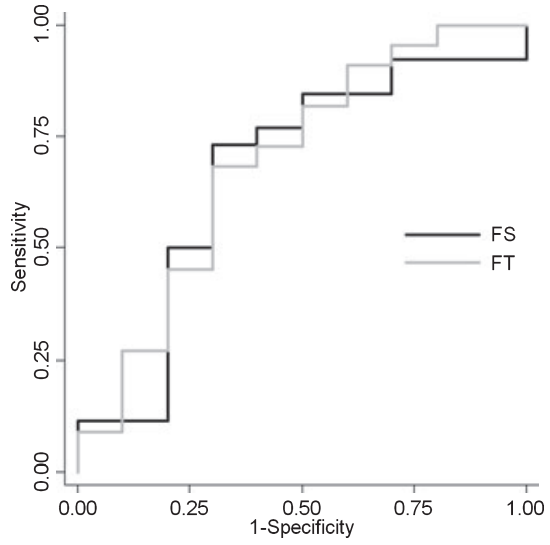

Figure 1 Diagnosis value of fibrotest and liver stiffness measurement to assess mild liver fibrosis METAVIR scores F0/F1. AUROC were 0.69 ± 0.11 for fibrotest (thin black line) and 0.68 ± 0.11 for liver stiffness measurement (bold black line).

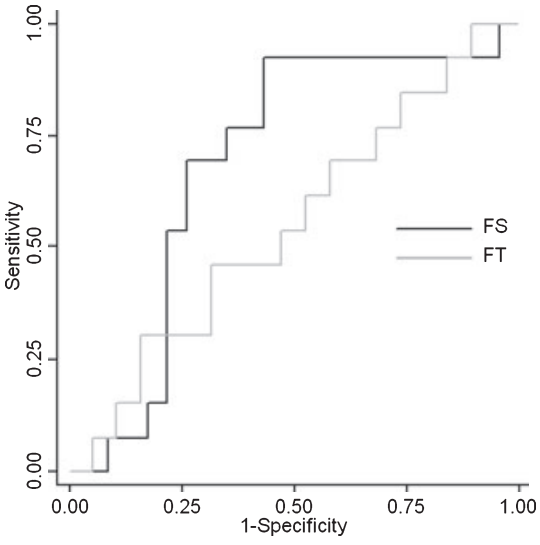

Figure 2 Diagnosis value of fibrotest and liver stiffness measurement to assess severe liver fibrosis METAVIR scores F3/F4. AUROC were 0.55 ± 0.10 for fibrotest (thin black line) and 0.69 ± 0.09 for liver stiffness measurement (bold black line).

FT and the histologic assessment of severe liver fibrosis (F3/F4) in five patients (38.46%). In all misclassified patients, liver fibrosis was underestimated by FT.

The diagnostic performance of LSM for fibrosis staging is summarized in Table 2. LSM by fibroscan was unsuccessful in one overweight patient (2.36%). In all other cases, the weight of the patients was normal with a body mass index of 24.7 ± 3.5.kg/m^2. Mild liver fibrosis ($F < 2$) was accurately predicted, with a cut-off value of 7.1 kPa. In patients with LSM lower than 7.1 kPa, the sensitivity was 69.2% (38–90) and the specificity was 73.9% (51–89) for the prediction of mild liver disease (<F2), with a PPV of 60% (32–83) and a NPV of 81% (58–94). Among the 10 patients in whom the LSM was <7.1 kPa, only one patient was misclassified. In this case, liver fibrosis was overestimated by LSM and histology showed liver peliosis.

The optimal cut-off value of LSM for assessing severe liver fibrosis (F3/F4) was 9.5 kPa. Using this value, the sensitivity and specificity were 69.2% (38.6–90) and 73.9% (51.6–89.8), respectively (Table 2). The PPV and NPV of LSM for predicting severe liver disease (F3/F4) were 60% (32.3–83.7) and 81% (58.1–94.6), respectively. But liver fibrosis was underestimated by LSM in five cases (38.46%) of the 13 patients with severe liver disease.

Discussion

The major objective of this study was to evaluate the suitability of FT and LSM for assessing liver fibrosis as compared with liver biopsy. The optimal cut-off values for FT and LSM were set to maximize sensitivity and specificity with reference to the grade of fibrosis, as given by a liver biopsy. Two cut-off values: 0.5 (FT) and 7.1 kPa (LSM) for mild fibrosis METAVIR scores of F0/F1, and 0.69 (FT) and 9.5 kPa (LSM) for severe liver fibrosis METAVIR scores of F3/F4. Using these values, AUROC for mild-fibrosis stage was similar for FT (0.69) and LSM (0.68). Almost all patients with mild fibrosis, as assessed by liver biopsy, were well-classified by FT (80%) and LSM (90%). The liver fibrosis of two patients was overestimated by FT, whereas LSM overestimated fibrosis in only one patient. However, the liver biopsy of one of these two patients showed considerable liver peliosis and, in this case, the increased FT and LSM values were probably not linked to severe liver fibrosis. We found, for the first time, that LSM accurately predicted mild liver fibrosis in kidney-transplant patients: once this one patient had been excluded, all other patients were well-classified. These results are similar to those of Varaut *et al.* [15], who used FT to examine a small population of 14 kidney recipients.

Conversely, FT and LSM were not sufficiently accurate for detecting patients with severe liver disease METAVIR scores of F3/F4, as assessed by liver biopsy. AUROC for LSM (0.69) was better than for FT (0.55) for this stage of fibrosis. More useful in clinical practice than AUROC, we found that few of the patients (61.5%) with severe liver disease, as assessed by a liver biopsy, were well classified by FT or LSM. LSM and FT always underestimated liver fibrosis and misclassified these patients. In kidney-transplant patients with HBV or HCV infection, FT and LSM poorly predicted severe fibrosis, and had a surprisingly high number of false negatives in contrast to previously published from HCV or HBV nontransplanted populations [8,13]. Harada *et al.* [16] showed that LSM was good at predicting liver fibrosis in a very different population of 46 HCV liver-transplant patients, though; they used a cut-off value of 15.4 kPa for predicting severe liver fibrosis of ≥3. This value is much higher than that reported in previously published studies on general HCV populations [8,12,13]. The accuracy of FT and LSM was not influenced by the type of virus infection and among the five misclassified patients, three had HCV and two had HBV infection.

Most of our patients had mild necroinflammatory activity and very low serum ALT values. In agreement with our study, it has been shown that diagnostic value of FT, when applied to HCV-infected patients with normal ALT values and significant fibrosis ≥F2 is poor [17], with a PPV of 33% and a NPV of 62%: these are very much comparable to our results. Conversely, LSM with a cut-off of 8.7 kPa was very accurate in predicting significant liver fibrosis ≥F2 in a population with normal serum ALT [17]. Cut-offs from 7.1 to 8.4 kPa have been reported to be associated with significant liver fibrosis METAVIR scores of F3/F4 [12,13]. However, the number of misclassified patients would be higher if the lowest cut-off (7.1 kPa) were used for patients with normal ALT values [17], as suggested by Castera *et al.* [18]. In our study, compared with 7.1 kPa, a 8.4-kPa cut-off gave a lowest sensitivity (59.2%) and an equivalent specificity (80%). A recent study [19] found that the evaluation of liver fibrosis by LSM is influenced by serum ALT level. A decrease in ALT values was an independent factor influencing LSM. They also found that the LSM was significantly ($P < 0.001$) lower in cirrhotic patients with normal serum ALT activity than in those with elevated ALT [19]. In our study, HCV- or HBV-infected transplant patients with severe liver fibrosis, as assessed by biopsy, had low ALT values and well compensated liver disease without any clinical, biochemical or ultrasound signs of cirrhosis. Hence, the risk of underestimating liver fibrosis in HCV or HBV kidney-transplant patients using FT or LSM is in agreement with previous studies that have shown reduced noninvasive marker scores in an inactive viral infection, such as HCV-infected patients with a sustained virologic response [20], and in HBV-infected patients treated with Lamivudine [21]. Moreover, renin–angiotensin inhibitors were used to treat most of our patients, and some recent data from animals [22] and cirrhotic patients [23] indicate that these treatments have an antifibrotic effect with reduced serum hyaluronate. Although serum hyaluronate is not included in the FT, the concentrations of other serum markers used in noninvasive fibrosis tests could be influenced by these inhibitors, which are generally used in kidney diseases.

In conclusion, the noninvasive methods, LSM and FT, accurately identify kidney-transplant patients infected by HBV or HCV without significant liver fibrosis. However, the use of these noninvasive methods for the identification of transplant patients with severe liver fibrosis needs to be approached with caution as most of these patients have mild necro-inflammatory liver disease and low ALT values. LSM and FT are promising tools to help clinicians to identify the subgroup of patients with viral hepatitis needing a liver biopsy after kidney transplantation. Our study included only a small number of patients; a large prospective multi-center trial on kidney-transplant patients is required to validate these noninvasive methods in clinical practice.

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Authorship

LA: performed the noninvasive test, designed the study and wrote the paper. NK: did the follow-up of the patients and wrote the paper. DB: participated to the noninvasive tests performance. MD: did the histologic analysis of liver biopsies. FA: did the virologic tests. VLC: did the statistical analysis. LR: participated to the study design, did the follow-up of the patients, and reviewed the paper.

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