

FACTORS ASSOCIATED WITH FAILURE OF LIVER STIFFNESS MEASUREMENT USING TRANSIENT ELASTOGRAPHY

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REZUMAT

Scopul lucrării: Măsurarea durității hepatice prin elastografie impulsională utilizând FibroScan®-ul este o nouă metodă non-invazivă de evaluare a fibrozei hepatice. Nu totdeauna se pot obține măsurători valide (MV). Scopul lucrării a fost evaluarea prevalenței și a factorilor care au influențat eșecul evaluării prin FibroScan. **Material și metodă:** Studiul a inclus 1461 pacienți cu hepatopatii cronice de diverse etiologii. S-a considerat evaluare eșuată dacă nu au putut fi obținute 10 MV. Am analizat factorii asociați cu eșecul evaluării. **Rezultate:** Din cei 1461 pacienți, în 6,9% (101) din cazuri nu s-au putut obține MV. Rata de eșec a fost semnificativ statistic mai mare la femei - 9,1% (64/704), decât la bărbați - 4,9% (37/757) ($p=0,0019$, $OR=1,946$). Vârsta medie în grupul cu evaluare eșuată a fost $54,2\pm 10,1$ ani, semnificativ mai mare decât la cei cu MV ($50,6\pm 14,1$ ani) ($p<0,0001$). Indexul de masă corporală (IMC) în grupul cu evaluare eșuată a fost $30,9\pm 5,4$ kg/m², semnificativ mai mare decât în grupul cu MV ($26,1\pm 4,6$ kg/m²) ($p<0,0001$). Prezența steatozei hepatice la examinarea ecografică și talia pacienților nu au influențat rata de succes (15,5% din pacienții cu MV au avut steatoză vs. 15,8% din cei cu evaluare eșuată, $p=0,8874$, $OR=1,025$; respectiv talia medie a fost $166,5\pm 9,3$ cm în grupul cu evaluare eșuată vs. $168,6\pm 19,1$ cm la cei cu MV, $p=0,0745$). **Concluzie:** La 6,9% dintre cei 1461 pacienți evaluați prin FibroScan nu am putut obține MV. Sexul feminin, vârsta înaintată și IMC ridicat au fost semnificativ statistic asociate cu imposibilitatea obținerii de MV.

Cuvinte cheie: elastografie impulsională, duritatea hepatică, boală cronică de ficat, FibroScan

ABSTRACT

Objective: Liver stiffness measurement (LSM) using transient elastography (FibroScan® device) is a novel rapid, non-invasive technique that evaluates liver fibrosis. In some cases, however, no elasticity measurement is obtained. The aim of this study was to assess the prevalence and factors associated with failure of LSM in patients with chronic liver disease. **Material and methods:** Our study included 1461 patients with chronic liver disease of diverse etiologies. Failure was defined if 10 valid measurements (VM) could not be obtained. We analyzed the factors associated with failure. **Results:** From the 1461 patients, failure to obtain a VM was observed in 6.9% (101) of the cases. The proportion of failure among women was significantly higher - 9.1% (64/704), than in men - 4.9% (37/757) ($p=0.0019$, $OR=1.946$). The mean age in the failure group was 54.2 ± 10.1 , significantly higher than in the VM group (50.6 ± 14.1) ($p<0.0001$). The mean body mass index (BMI) in the failure group was 30.9 ± 5.4 kg/m², extremely significant higher than in the VM group (26.1 ± 4.6 kg/m²) ($p<0.0001$). The height of the patients and the presence of steatosis on ultrasound examination did not influence the chance to obtain VM (166.5 ± 9.3 cm in the failure group vs. 168.6 ± 19.1 cm in the VM group - $p=0.0745$) and 15.5% of the patients in the VM group had steatosis, vs. 15.8% in the failure group, $p=0.8874$, $OR=1.025$). **Conclusion:** Failure to obtain valid LSM was observed in 6.9% of the patients. Female gender, older age and higher BMI were statistically significantly associated with failure to obtain valid LSM.

Key words: transient elastography, liver stiffness, chronic liver disease, FibroScan

INTRODUCTION

In the evaluation of chronic hepatitis (viral and non-viral), liver fibrosis is a very important factor associated with prognosis. Hence, the necessity of a precise evaluation of the severity of fibrosis, in order

to perform a correct staging and to take a decision regarding the treatment.

Currently, the biopsy examination of the liver is considered to be the "gold standard" method to evaluate fibrosis.¹ Nevertheless, the liver biopsy (LB) has its shortcomings: intra- and interobserver variability,^{2,3} sampling variability,⁴ and, last, but not least, the fact that LB is an invasive method, with morbidity and mortality greater than zero.

Considering all these facts, non invasive methods for the evaluation of liver fibrosis were developed in the last few years, in order to replace LB, among them the liver stiffness (LS) evaluation by means of transient elastography (TE) using a FibroScan® device (EchoSens, Paris, France).^{5,6} The system consists of a probe with an ultrasonic transducer mounted on the

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axis of a vibrator. This vibrator induces a wave of mild amplitude and low frequency to the tissue. Thus, an elastic shear wave is created that propagates in the tissue and in the meantime a pulse-echo ultrasound is performed to follow the shear wave and measures its velocity. The velocity of propagation is directly related to the tissue stiffness. The harder the tissue, the faster the shear waves propagates.⁷ With this method we can detect and measure the LS in normal and pathological individuals, the results being measured in kiloPascals (values between 2.5 and 75 kPa).

This method was first developed in France,⁸ but later on, several studies from different parts of the world were published, confirming its value.^{7,9,10}

In order to be able to use TE in clinical practice, valid measurements (VM) have to be obtained in the majority of evaluated cases, the method has to be reproducible (small inter- and intra-observer variability) and also to establish in which domains the method has the most reliable results.

MATERIAL AND METHODS

Our study included 1461 successive patients with chronic liver disease of diverse etiologies, admitted in the Department of Gastroenterology and Hepatology from Timisoara, during a 10 months period (June 2007 - March 2008). In all these patients we performed LS measurement (LSM) by TE, using a FibroScan[®] device (EchoSens, Paris, France). LS measurements were performed according to the classical methodology by three physicians who had previously performed at least 50 examinations, which are considered to be sufficient for a proper training.¹¹⁻¹³

The measurements were made in the right lobe of the liver through the intercostal spaces, on patients lying in the dorsal decubitus position with the right arm in maximal abduction. The tip of the probe transducer was covered with coupling gel and placed on the skin, between the ribs at the level of the right lobe of the liver. The operator, assisted by ultrasound time-motion and A-mode images provided by the system, located a portion of the liver that was at least 6 cm thick and free of large vascular structures. Once the area of measurement had been located, the operator pressed the probe button to begin an acquisition. Ten successful acquisitions were performed on each patient.

The success rate was calculated as the ratio of the number of successful acquisitions over the total number of acquisitions. In each patient 10 valid measurements were performed, after which a median value of the LS was obtained, measured in kPa. Only in patients in which LSM had a success rate of at

least 60%, with IQR<30%, the measurements were considered reliable. Failure was defined if 10 valid measurements (VM) could not be obtained with a success rate of at least 60% and with IQR<30%.¹⁴

All the patients underwent abdominal ultrasound examination, performed by five experienced physicians. Liver steatosis was diagnosed based on classical ultrasound signs (“bright” liver with “posterior attenuation” as compared to the normal echogenicity of the right kidney). Patients with ascites were excluded from our study since LS measurement can not be performed if a layer of liquid is interposed between the probe and the liver.¹²

We analyzed the factors associated with failure. For a statistical study of quantitative variables, the mean and standard variation were calculated, and for the qualitative ones, the percentage was calculated. The percentages were compared by Fisher exact test. The statistical significance of the risk factors was assessed with Fisher exact test. Female gender and the presence of steatosis were considered risk factors for failure of LSM. The statistical analysis was performed using Microsoft Excel and GraphPad Prism programs.

RESULTS

Our group included 1,461 successive patients, 704 women and 757 men, mean age 51.0 ± 14 years. From the 1461 patients, failure to obtain valid LSM was observed in 6.9% (101) of the cases, so that valid measurements were obtained in 93.1% of cases (1360 patients).

The proportion of failure among women was significantly higher compared to men, 9.1% (64/704) vs. 4.9% (37/757) ($p=0.0019$, OR=1.946). (Fig.1)

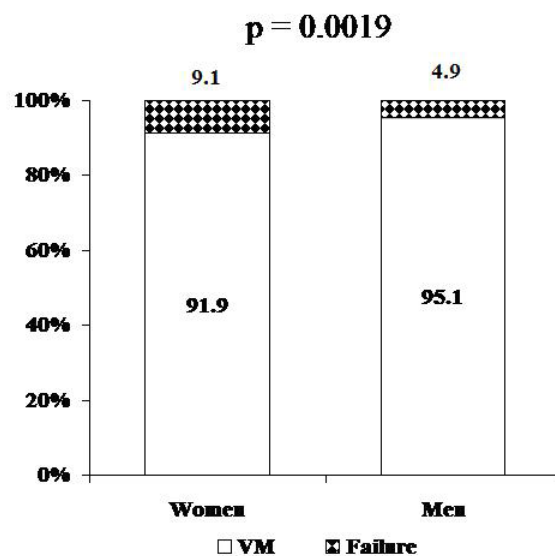


Figure 1. The influence of gender on the rate of valid LSM by means of TE (FibroScan).

The mean age in the failure group was 54.2 ± 10.1 years, significantly higher than in the VM group (50.6 ± 14.1 years) ($p < 0.0001$). (Fig. 2)

The mean body mass index (BMI) in the failure group was 30.9 ± 5.4 kg/m², extremely significantly higher than in the VM group (26.1 ± 4.6 kg/m²) ($p < 0.0001$). (Fig. 2)

We did not find significant differences between the mean height in the failure group (166.5 ± 9.3 cm) vs. the VM group (168.6 ± 19.1 cm), $p = 0.0745$. (Fig. 2)

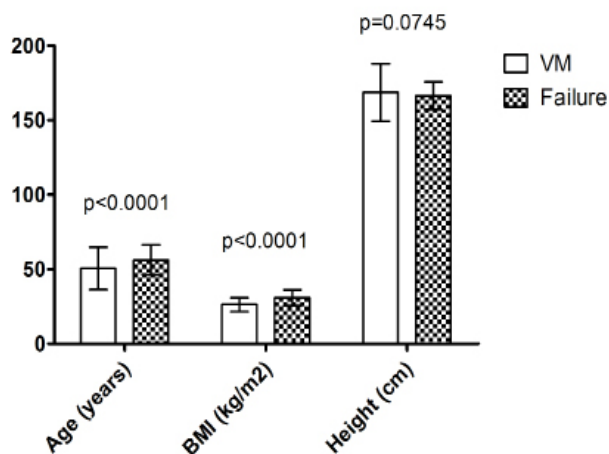


Figure 2. The influence of age, BMI and height on the rate of valid LSM by means of TE (FibroScan).

The presence of steatosis on ultrasound examination did not influence the chance to obtain VM: 15.5% of the patients in the VM group had steatosis (211/1360), vs. 15.8% in the failure group (16/101), ($p = 0.8874$, OR=1.025). (Fig. 3)

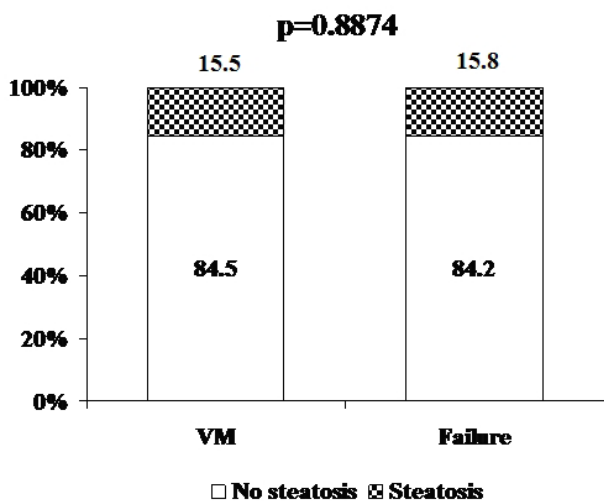


Figure 3. The influence of steatosis on the rate of valid LSM by means of TE (FibroScan).

DISCUSSION

Since the beginning of the clinical use of this method, the rate of VM has been studied. As expected, it is not 100%, failure to obtain VM being associated with the presence of obesity and with the lack of adequate intercostal spaces.¹²

In a prospective study performed by Foucher et al. on 2,114 LSM by means of TE, failure to obtain VM was reported to occur in 4.5% of the cases.¹⁵

In a study performed by Roulot et al on 429 healthy individuals who underwent TE evaluation by means of FS, failure to obtain VM was observed in 4.6% of the cases. The failure rate increased with BMI, reaching 88% for values above 40 kg/m².¹⁶

In a German study performed on 147 patients with various chronic liver diseases, valid LSM were obtained for 135 (92%), thus with a failure rate of 8%.¹⁷

In an Italian study aimed to assess the reproducibility, inter and intra-observer concordance of TE evaluation of LS, in which 200 patients were evaluated by repeated FibroScan LSM, very low rates (2.4%) of indeterminate results were observed, almost exclusively associated with high BMI (> 28 kg/m²).¹⁸

In a prospective, multicentric study performed by Ziolo et al. on 327 patients with chronic HCV hepatitis, who were evaluated in order to compare LSM to the liver biopsy, 23 patients were excluded because reliable measurements of LS could not be obtained, resulting in a failure rate of approximately 7%.¹⁹

In another study performed by Foucher et al. on 758 patients who were evaluated in order to assess the performance on TE for the diagnosis of cirrhosis, in 6.2% of the cases VM could not be obtained, mostly due to overweight.²⁰

In a large, multicentric study, that enrolled 1257 patients with chronic liver disease of diverse etiologies, who underwent LSM and LB within 6 months, 118 patients were excluded because reliable LSM could not be obtained, resulting in a failure rate of 9.4%.²¹

As presented above, failure rates in obtaining valid LSM by TE range between 2.4% and 9.4% in different studies.^{8,15-22} The failure rate in our group was 6.9%, not very different from the published data, as presented in Table 1.

Regarding factors associated with failure, a study performed by Kettaneh and al on 935 HCV patients evaluated by means of TE and liver biopsy (assessed according to Metavir score), showed after a multivariate analysis that the probability of a VM (correlated with the histological score) was higher if the operator was experienced (with more than 50 FibroScan evaluations performed), if the patient was young (OR 0.96/year

CI 95% 0.95-0.97 $p < 0.0001$) and not obese (OR 0.19 if obese CI 95% 0.12-0.29, $p < 0.0001$).²³

Table 1. Failure rates for LSM in various studies:

Author	Published	Nr. of cases	Failure rate of LSM
Fraquelli et al.	Gut 2007	200	2.4%
Foucher et al.	J Gastroenterol Hepatol 2006	2,114	4.5%
Roulot et al.	J Hepatol 2008	429	4.6%
Foucher et al	Gut 2006	758	6.2%
Şirli et al.	Current study	1,461	6.9%
Ziol et al.	Hepatology 2005	327	7%
Erhardt et al.	Dtsch Med Wochenschr 2006	147	8%
Gómez-Domínguez et al.	Aliment Pharmacol Ther 2006	103	8.7%
Ganne-Carrie et al.	Hepatology 2006	1,257	9.4%

In our study, also, the age of the patient seems to influence the chance to obtain VM, since the mean age in the failure group was significantly higher than in the VM group (54.2 ± 10.1 years vs. 50.6 ± 14.1 years, $p < 0.0001$).

Also, in a large, prospective study by Foucher et al.¹⁵, the univariate analysis showed that failure was associated with: BMI > 28 (OR 9.1, CI 95% 5.8-14.0, $p < 0.001$), diabetes mellitus (OR 2.1, CI 95% 1.2-3.7, $p = 0.01$), age > 50 years (OR 4.0, CI 95% 2.7-6.3, $p < 0.0001$), steatohepatitis (OR 3.4, CI 95% 1.7-6.9, $p = 0.001$). Failure to obtain VM was not operator dependent and was not associated with the gender of the patient, or with the level of transaminases. In the multivariate analysis, the only factor associated with failure to obtain VM was BMI > 28 (OR 10.0, CI 95% 5.7-17.9, $p = 0.001$).

In our study, the presence of steatosis on ultrasound examination did not influence the chance to obtain VM (15.5% of the patients in the VM group had steatosis, vs. 15.8% in the failure group, $p = 0.8874$, OR = 1.025).

Similar to other studies, in our group obesity was statistically significant associated with failure to obtain VM, the BMI was extremely significant higher in the failure group as compared to the VM group (30.9 ± 5.4 kg/m² vs. 26.1 ± 4.6 kg/m², $p < 0.0001$).^{15,16,18,23}

In contrast with the studies performed by Foucher et al and Kettaneh et al, that showed that the gender of the patient does not influence the rate of VM, in our

study the failure rate was statistically significant higher in women than in men (9.1% vs. 4.9%) ($p = 0.0019$, OR = 1.946), meaning that in our group, failure to obtain valid LSM tends to occur twice as often in women than in men.^{15,23} Since in our group women had a significantly lower mean BMI than men (26.2 ± 5.1 kg/m² vs. 26.8 ± 4.5 kg/m², $p = 0.0032$), we can speculate that fat distribution and smaller intercostal spaces are responsible for the higher failure rate in women in our group of patients.

CONCLUSION

The LS evaluation by means of FibroScan® is a method in which reliable measurements can be obtained in the great majority of scanned patients. Female gender, older age and higher BMI were statistically significant associated with failure to obtain valid LSM.

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