Development and evaluation of a nurse-led transient elastography service for the staging of hepatic fibrosis in patients with suspected chronic liver disease

R.B. McCORRY, N. PALANIYAPPAN, A. CHIVINGE, P. KAYE, M.W. JAMES and G.P. AITHAL

From the National Institute of Health Research: Biomedical Research Unit, Nottingham University Hospital NHS Trust, Nottingham NG7 2UH, UK

Address correspondence to R.B. McCorry MRCP, Department of Hepatology, National Institute of Health Research: Biomedical Research Unit, D Floor, South Block, Queen’s Medical Centre, Derby Road, Nottingham, Nottinghamshire NG7 2UH, UK. email: rogermccorry@hotmail.com

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Summary

Background and Aims: Establishing the presence of fibrosis and cirrhosis is an essential step in the management of patients with chronic liver diseases (CLD). Liver stiffness measurement (LSM) based on transient elastography (TE) correlates well with the stages of liver fibrosis and has been developed as a non-invasive alternative to liver biopsy. The studies performed to date have used physician operators. With the potential use of TE for screening of community-based populations for liver disease, we aimed to evaluate the performance of nurse operators.

Design: Retrospective analysis.

Methods: We reviewed the reliability and accuracy of LSMs performed by the nurse-led TE service at Queen’s Medical Centre, Nottingham between May 2009 and January 2011. Consecutive patients with suspected CLD who underwent LSM were included.

Results: Over the study period 585 LSMs were performed. Analysis was performed on the 208 patients where LSM could be compared with liver biopsy findings. Of these 11 (5.3%) had unreliable LSM results (less than 10 valid shots or success rate <60%). There were no LSM failures. Inadequate liver biopsy specimen led to exclusion in 26 (12.5%) patients. For the detection of significant fibrosis (Ishak stage >2), a sensitivity of 0.78 and specificity of 0.81 was obtained, with a cut-off value of 8 kPa. Using a cut-off value of 13 kPa for detection of cirrhosis, a sensitivity and specificity of 0.8 and 0.92 was obtained.

Conclusions: We have demonstrated that a nurse-led TE service can produce a low level of unreliable results and LSM failures, with comparable sensitivity and specificity for detecting significant fibrosis and cirrhosis to those reported in the literature. The demands on the use of TE could potentially be eased through the introduction of nurse-led service delivery.

Introduction

Most people with early chronic liver diseases (CLDs) do not have symptoms, and so the disease progresses to severe fibrosis and even cirrhosis without being detected. Establishing the presence and stage of liver fibrosis is an essential component of the management process in patients with CLDs. The role of liver biopsy in staging liver fibrosis, regarded as the gold standard until recently, is now being superseded by non-invasive imaging modalities.1 Transient elastography (TE) (Fibroscan, Echosens, Paris) measures the liver stiffness and the liver stiffness measurement (LSM) correlates with the stages

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of liver fibrosis.\textsuperscript{2,3} TE is a user-friendly technique that can be performed rapidly at the bedside, with immediate results.

However, if TE was to be integrated into routine clinical practice widely and consistently, the service cannot be reliant upon specialist clinicians providing it. Previous studies have almost exclusively reported the results of physician operators. Given that TE is a simple and highly reproducible test, that should not require significant expertise, it would appear ideally suited to non-physician operator service delivery. Here, in the first UK study assessing TE performance, we attempt to retrospectively analyse and validate the nurse-led TE service at the Medical Day Case Unit in Queens Medical Centre (QMC), Nottingham University Hospitals which was initiated in May 2009.

**Methods**

**Study population**

The decision to refer the patients for LSM and liver biopsy was made by the primary physician, usually a hepatologist. Between May 2009 and January 2011 consecutive adult patients suspected of having CLD by the assessing clinician, who underwent LSM on an outpatient basis, were retrospectively included in the study.

**Operator training**

Five nurses employed in the Day Case Unit of QMC, whose skill sets were comparable to state enrolled nurses elsewhere in the country, were identified for training in the use of TE. Each underwent one full day’s training with the Echosens representative. The indications for LSM were discussed and the representative described the relevant anatomical landmarks and provided instruction on how to use the probe. Each nurse performed four supervised LSMS during the initial training. The nurses performed a further 20 LSMS with a consultant hepatologist in attendance when point of application of TE probe and other performance measures of LSM (Figure 1) were monitored. Once the supervising consultant was satisfied with the nurses’ performance, they were allowed to operate independently.

**LSM**

All LSMS were performed with the patient lying in the dorsal decubitus position with the right arm held in maximal extension. Covered with coupling gel the tip of the transducer was placed on the skin at an intercostal space overlying the right lobe of the liver. A time-motion ultrasound image allowed the operator to locate a portion of liver at least 6-cm thick and free of large vascular structures. The probe button was then pressed to begin an acquisition. The software automatically rejected acquisitions that did not have a correct vibration shape or a correct follow-up of the vibration propagation. The median value of the successful acquisitions was deemed to be representative of the liver stiffness and was called LSM. As recommended by the manufacturer, if no value was obtained following 10 acquisitions LSM failure was documented. LSM was considered unreliable if there were fewer than 10 valid acquisitions, success rate was <60% or interquartile range was >30%.

A cut-off value of 8 kPa was used to determine the presence of fibrosis based on a recent study of LSMS in a healthy population that determined this to be a threshold (90th percentile) above which further investigation was indicated.\textsuperscript{4} A cut-off value of 13 kPa was used to determine the presence of cirrhosis based on a previous meta-analysis of LSM studies that identified this as the optimal cut-off.\textsuperscript{5}

**Liver biopsy**

In the patients who had undergone liver biopsy within 2 weeks of LSM, we used the fibrosis staging to assess the accuracy of LSM for the diagnosis of significant fibrosis and cirrhosis. Three experienced liver pathologists analysed all liver biopsy specimens. Liver biopsy specimens that measured <10 mm in length and biopsies that were deemed non-suitable for fibrosis assessment were excluded from the analysis. Liver fibrosis was staged using the Ishak score (0–6) in all cases.

**Data collection**

The tissue elastography machine was interrogated to provide LSM data on the study cohort. Further demographic data and the histology reports of the liver biopsies were obtained from our online database.

**Results**

Over the study period 585 LSMS were performed by nurses on the Medical Day Case Unit. In 208 patients LSM could be compared with liver biopsy findings. Their characteristics are summarized in Table 1. We excluded 26 patients (12.5%) because of inadequate liver biopsy specimens. There were no LSM failures (zero valid shots), although 11 patients (5.3%) had unreliable LSM results and were
also excluded (11 had less than 10 valid measurements and 1 patient had a success rate of <60%). Statistical analysis was performed on the 172 patients included (Figure 2). The mean age of the group was 47 (range 19–83) years and 62.8% were men. The indications for assessment were non-alcoholic fatty liver disease in 16.9% (n = 29), hepatitis C in 16.9% (n = 29), hepatitis B in 15.1% (n = 26), alcoholic liver disease in 13.9% (n = 24), mixed aetiologies in 8.1% (n = 14), autoimmune hepatitis in 4.1% (n = 7), cholestatic liver diseases in 5.2% (n = 9) and miscellaneous in 15.7% (n = 27).

Of the biopsies performed, 4.3% (n = 9) were performed via the transjugular route. Median biopsy length was 18 mm. The distribution of fibrosis stage was as follows: 57 subjects (33.1%) had no fibrosis, Ishak 1 in 39 subjects (22.7%), Ishak 2 in 21 subjects (12.2%), Ishak 3 in 13 subjects (7.6%), Ishak 4 in 10 subjects (5.8%) and cirrhosis (Ishak 5/6) in 30 subjects (17.4%).

The median LSM was 6.1 kPa (range 2.8–75 kPa). The mean number of measurements per patient was

### Table 1 Main characteristics of the 208 patients with paired liver biopsy and LSM

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>131 (63.0)</td>
</tr>
<tr>
<td>Female</td>
<td>77 (37.0)</td>
</tr>
<tr>
<td>Age (mean ± SD, years)</td>
<td>48 ± 14</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>36 (17.3)</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>28 (13.5)</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>30 (14.4)</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease</td>
<td>38 (18.3)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>9 (4.3)</td>
</tr>
<tr>
<td>Haemochromatosis</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Mixed</td>
<td>18 (8.7)</td>
</tr>
<tr>
<td>Others</td>
<td>42 (20.2)</td>
</tr>
<tr>
<td>Biopsy</td>
<td></td>
</tr>
<tr>
<td>Percutaneous</td>
<td>199 (95.7)</td>
</tr>
<tr>
<td>Transjugular</td>
<td>9 (4.3)</td>
</tr>
<tr>
<td>Length of biopsy (mean ± SD, cm)</td>
<td>1.70 ± 0.73</td>
</tr>
</tbody>
</table>
11.2 (range 10–28) and the mean success rate was 94% (range 64–100%). For cirrhosis (Ishak 5/6) the median LSM was 27.4 kPa (range 8.7–75 kPa). For significant fibrosis (Ishak >2) the median LSM was 14.2 kPa (range 4.3–75 kPa). In the absence of fibrosis (Ishak 0) the median LSM was 4.6 kPa (range 2.8–12.2 kPa).

Using the cut-offs for detection of the presence of fibrosis (Ishak >2) an LSM of >8 kPa produced a sensitivity and specificity of 0.78 [95% confidence interval (CI) 0.64–0.88] and 0.81 (95% CI 0.73–0.88), respectively. For the detection of the presence of cirrhosis (Ishak 5/6) LSM of >13 kPa produced a sensitivity and specificity of 0.8 (95% CI 0.61–0.92) and 0.92 (95% CI 0.86–0.96), respectively (Table 2).

**Discussion**

We have described the development and performances of a nurse-led and delivered LSM service using TE in a specialist centre setting. Our results were pooled for all aetiologies of liver disease reflecting a real-world hepatology experience that was representative of QMC’s referral base. The Hepatology Department provides a secondary and tertiary care service and, as previous audits demonstrate, generates large numbers of referrals from general practice.6,7 As well as being the first report of TE experience in a UK centre, our study is the first to demonstrate that nurses can achieve competency in LSM, producing results with high levels of reliability and accuracy comparable to previous studies reporting the performance of physician operators. Competence in performing LSM was attained following a brief training period with relatively small numbers of procedures performed under supervision. The study corroborates the findings of previous studies that have demonstrated that LSM correlates with liver biopsy for the detection of cirrhosis and significant fibrosis.

Given there was only, at most, a 2-week interval between LSM and liver biopsy, it was possible to minimize the likelihood of progression of fibrosis that could have rendered the comparison between techniques as meaningless. A major issue in TE research, which remains unresolved, is which LSM cut-off values to use for each stage of fibrosis. The cut-offs we employed were derived from a large, community-based population study and a meta-analysis, however, it is clear that cut-offs for both significant fibrosis and cirrhosis require prospective validation.3,4 The heterogeneous nature of the cohort, with a number of aetiologies of liver disease represented, also represents a potential limitation. Different aetiologies of liver disease may have different stiffness cut-offs for significant fibrosis or cirrhosis. For instance, earlier studies have reported cut-offs for cirrhosis ranging from 12.5 kPa9 for viral hepatitis to 21.5 kPa3 for the diagnosis of alcoholic cirrhosis. The cut-offs employed in our study for significant fibrosis and cirrhosis could be construed as non-specific, given the heterogeneity of the study cohort. Set cut-off values for the various aetiologies of liver disease do, of course, require validation.

The most recent meta-analysis of TE performance in the assessment of hepatic fibrosis included 40 studies with a median sample size of 123 (mean 184).9 Our sample size of 208 paired LSMs and

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<table>
<thead>
<tr>
<th>Fibrosis stage</th>
<th>Cut-off (kPa)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant fibrosis (Ishak ≥ 3)</td>
<td>&gt;8</td>
<td>77.78</td>
<td>81.36</td>
<td>65.63</td>
<td>88.89</td>
</tr>
<tr>
<td>Cirrhosis (Ishak ≥ 5)</td>
<td>&gt;13</td>
<td>80.00</td>
<td>92.3</td>
<td>68.57</td>
<td>95.62</td>
</tr>
</tbody>
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Figure 2. Flow chart of the study. After exclusion of patients without paired liver biopsies (LB), unreliable LBs (specimens <10 mm), unreliable LSMs (less than 10 valid shots or success rate <60%), 172 patients were selected.
liver biopsies would appear to be equivalent to previous studies. We have confirmed a low level of unreliable LSMs at 5.3% (11 of 208). The most frequent reason for unreliable results was fewer than 10 successful acquisitions (4.8%). Limitations introduced by random errors in the measurements are mitigated by taking the median value of at least 10 successful acquisitions as representative of the liver stiffness for that subject. In addition, none of the cohort studied experienced LSM failure. This compares favourably with a French study of 13,369 LSMs that quoted a failure rate of 3.1% and unreliable results in 15.8% of cases.10 This would suggest that adequate training in this group of non-physician operators does not require many procedures. The nurses in our centre were taught using a full day’s training programme and 20 supervised procedures. These nurses have been shown in this study to have acquired satisfactory skills to deliver consistent and reliable LSM in patients with CLDs. Our findings are in keeping with two previous studies where consistent LSM results were obtained after a training period of ~50 examinations.11,12 In contrast, Castéra et al.10 reported that operator experience (<500 examinations) influenced both LSM failure and unreliable results.

Detection of any significant fibrosis may be important to detect as this will identify CLDs with potential to progress in the long term. This group of patients are likely to benefit from effective interventions. We found that nurse operators detected ‘any significant fibrosis’ with a high degree of accuracy. Employing a cut-off of 8 kPa to detect the presence of significant fibrosis (Ishak >2), TE produced a sensitivity of 78% (95% CI 64–88%) and specificity of 81% (95% CI 73–88%). This compares favourably with the results of a meta-analysis based on nine studies that reported, for the diagnosis of significant fibrosis, pooled estimates for sensitivity of 70% (95% CI 67–73%) and specificity 84% (95% CI 80–88%).13

Detecting cirrhosis in patients with risk factors for chronic progressive liver disease is also important in clinical practice as these patients would benefit from surveillance for hepatocellular carcinoma and gastro-oesophageal varices, with intervention for the primary prevention of bleeding. In our study, TE performed best at differentiating cirrhosis (Ishak 5/6) from no cirrhosis with a sensitivity and specificity of 80% (95% CI 61–92%) and 92% (95% CI 86–96%), respectively, using a cut-off of 13 kPa. This is consistent with the same meta-analysis which reported that, for the diagnosis of cirrhosis, the pooled estimates for sensitivity were 87% (95% CI 84–90%) and specificity 91% (95% CI 89–92%).13

With the utility of TE expanding and the evolution of its role as a screening tool to identify liver disease in community-based populations,14 the demands on physician operators’ time will surely increase. LSM by TE involves a user-friendly technique that can be performed rapidly following only a brief training period to achieve competency. For these compelling reasons it would seem logical that the service be offered by non-physician operators. The major benefit of a nurse-led service is that it reduces the demands on physician resources, as their role is limited to training and supervision in the early part of the process. Our study demonstrates that a nurse-led TE service is not only possible, but can achieve levels of reliability and accuracy in diagnosing significant fibrosis and cirrhosis that are comparable to results obtained in studies involving physician operators. These personnel can be trained adequately by performing around 20 LSMs in a supervised setting. We are currently planning for service expansion to include a nurse-led TE service in the community using portable devices.

Conflict of interest: None declared.

References


