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The Role of Ultrasound Shear Wave Elastography in the Management of Liver Disease

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FUNDER:

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GLOSSARY OF ABBREVIATIONS:

ACRU:	Archive & Corporate Records Unit
CRF:	Clinical Research Facility
JRCO:	Joint Research & Compliance Office
NAFLD:	Non Alcoholic Fatty Liver Disease
NAS:	NAFLD Activity Score
NASH:	Non Alcoholic Steatohepatitis
LS:	Liver Stiffness
REC:	Research Ethics Committee
TE:	Transient Elastography

KEYWORDS:

Ultrasound, Fibroscan, Liver Biopsy, Transient Elastography, Liver Disease

STUDY SUMMARY:

TITLE: The Role of Ultrasound Shear Wave Elastography in the Management of Liver Disease

DESIGN: Comparative imaging study

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RESEARCH QUESTION: How accurate are the results of transient elastography (imaging) techniques in evaluating liver stiffness and liver disease

POPULATION: Patients with liver disease undergoing liver biopsy as part of their clinical care

ELIGIBILITY: Aged between 18 and 75 and ability to give informed consent

RATIONALE FOR THE STUDY:

To correlate liver stiffness assessed by the Philips EPIQ 7^{TM} Ultrasound System, the Siemens Acuson (ARFI) ultrasound system, and by Fibroscan^{TM} (which is currently the best validated technique), and compare the results of these 3 imaging techniques to histological results in patients with chronic liver disease of different aetiologies.

To correlate spleen stiffness measured by the Philips EPIQ 7^{TM} Ultrasound System and the Siemens Acuson (ARFI^{TM}) with the presence of esophageal varices in patients with cirrhosis.

BACKGROUND:

The cirrhotic process of liver injury is the end-stage of hepatic fibrosis which results from progressive accumulation of extracellular matrix during the wound-healing response to repeated injury of the liver (2).

Mortality and morbidity rates increase exponentially once cirrhosis develops. A large prospective study (n = 838, median follow-up 50 mo) of chronic hepatitis C (CHC) patients showed that the standardised mortality rate for non-cirrhotic patients younger than 50 was 3.1, whereas cirrhotic patients had a standardized mortality rate of 26.2 in the same age group (3). Therefore, the ability to reliably rule out cirrhosis may be considered an important characteristic of any test designed to assess liver fibrosis. Cirrhosis also is related to an increased risk of liver related morbidity (4) as well as mortality (5). A systematic review showed an increase in mortality risk with development of each successive decompensation - varices, variceal bleed and ascites (5). The overall survival was only 64%. Moreover, the rate of progression of fibrosis to liver cirrhosis can be variable. A study of 2235 treatment naïve HCV patients showed a median time of 30 years to development of cirrhosis but the rate of progression was faster in heavy alcohol users, older patients, males and patients with high indices of inflammatory activity on biopsy (6). Liver-related mortality and decompensation is expected to continue to increase over the next decade, due to the projected increase in the number of patients with cirrhosis in the population (7). Therefore, a prompt assessment of the degree of severity of fibrosis, an accurate and timely diagnosis of liver cirrhosis and management of complications is important in guiding management of therapy in chronic liver disease. Liver biopsy is often required (8,9), but it is an invasive procedure, with a risk of severe complications (1/4000–10,000), (8,9,13). In addition, its accuracy is prone to sampling error (14) and inter-and/or intra-observer diagnostic discrepancies occur in up to 10–20% of liver biopsies (15).

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Ultrasound-based transient elastography (TE) is one of the first non-invasive imaging methods that has been used in common practice. The technique is based on low frequency vibrations: shear waves produced by the ultrasound machine propagate through the tissue and produce an elastic deformation, with the premise that liver stiffness (LS) measurements reflect the degree of hepatic fibrosis. Displacement is reflected in the variation of the acquired echo signals. Several meta-analyses have assessed LS measurements by TE as a predictor of significant fibrosis in patients with chronic hepatopathies (16, 17).

Since its development, the use TE has been evaluated for many etiologies of chronic liver disease (16,17). A large meta-analysis included 40 studies and patients with chronic hepatitis B, C, alcohol and other causes of cirrhosis. In this analysis, TE had a pooled sensitivity of 83% and specificity of 89% for the diagnosis of cirrhosis (F4 on biopsy) (18). However, the limitations of this technique include the requirement for expensive equipment, and lack of standardised cut-offs for diagnosis of fibrosis stages (18). The diagnostic accuracy of TE is lowered in obese patients, in presence of ascites and elevated ALT levels (19,20).

Siemens-based ARFI^{TM} system and Philips Elast PQ^{TM} use conventional US to generate a shear wave directly within the liver tissues. This allows the sonographer to obtain both conventional US images and also specify a region of interest (ROI) for estimation of liver stiffness. The propagation velocity of the shear wave is reported in meters per second, and correlates with the liver stiffness. The direct generation of shear wave within the liver tissue holds advantages over TE since it is not subject to the chest/abdominal wall distortion of the waves. Moreover a multricentric study showed that ARFI is not affected by presence of ascites and less affected by elevated ALT levels (21).

A meta-analysis showed that ARFI had excellent accuracy for the diagnosis of cirrhosis (AUC 0.91 for F4). At a cut-off value of 1.87 m/s, ARFI had 84% sensitivity and 92% specificity for the diagnosis of cirrhosis (22).

While Fibroscan^{TM} (Echosens, Paris, France) and the Siemens-based ARFI^{TM} system are at different stages of validation, Elast PQ^{TM} from Philips is an ultrasound-based technique, which has recently been developed, meriting further assessment.

According to the EASL guidelines non-invasive methods are not merely an alternative to biopsy for staging fibrosis, but also predictive of the incidence of liver-related complications of liver fibrosis, including HCC development. However, further studies focusing on diverse etiologies of chronic liver disease are needed (23).

Esophageal varices (EVs) resulting from portal hypertension are a serious and important complication of cirrhosis. Current guidelines recommend screening endoscopy for all patients with cirrhosis. (24). However, the majority of patients undergoing screening endoscopy either do not have varices or have varices that do not require prophylactic treatment as the prevalence of esophageal varices (25). In order to avoid unnecessary invasive screening endoscopic examinations, noninvasive methods for diagnosing EVs in cirrhotic patients are required. Several studies showed that the spleen stiffness measurement could be correlated with the presence of esophageal varices. (26, 27, 28).

AIMS & OBJECTIVES:

1. To correlate liver stiffness assessed by the Philips EPIQ 7^{TM} Ultrasound System, the Siemens Acuson (ARFI) ultrasound system, and by Echosens Fibroscan^{TM} (which is

currently the best validated technique), and compare the results of these 3 imaging techniques to histological results in patients with chronic liver disease of different aetiologies.

2. To determine cut-off values of the liver stiffness (LS) measurements that correlate to the histological fibrosis stage.

3. To detect variations of the liver stiffness (LS) measurements correlated to different parameters:

   - diagnostic blood tests (aminotransferases, alkaline phosphatase, GGT, total bilirubin, cholinesterase, serum albumin level and prothrombin index; aspartate transaminase–platelet ratio index (APRI));
   - blood pressure
   - anthropometric parameters:
   - body mass index (BMI), waist circumference (WC), triceps skinfold thickness (TSF) and waist-hip ratio (WHR)
   - ethnic and gender differences

4. To assess quality parameters (IQR and SR) for the liver stiffness (LS) measurements

5. To distinguish non-alcoholic steatohepatitis (NASH) from non-alcoholic fatty liver disease (NAFLD).

SECONDARY OBJECTIVE:

1. To correlate spleen stiffness with the presence of complications of cirrhosis, such as oesophageal varices.

STUDY DESIGN:

This is an imaging study to compare the results of 3 imaging techniques (Philips Shear Wave Ultrasound, Siemens Acuson ARFI and Echosens Fibroscan) to clinical diagnostic results of liver biopsies.

100 patients will be studied with Philips Ultrasound System, Siemens ARFI Acuson and Fibroscan™ immediately prior to the liver biopsy.

INCLUSION CRITERIA:

- Able and willing to provide written informed consent;
- Aged between 18 and 75;
- Chronic liver disease;
- About to undergo a liver biopsy as part of standard routine clinical care, or if a liver biopsy has already recently been performed, is willing to come in for a specific research visit for the 3 scans;
- Willing to consent to medical notes and diagnostic test results being reviewed, captured, and recorded by the clinical research study team.

EXCLUSION CRITERIA:

- Unable or unwilling to give written informed consent;

- Aged under 18 or over 75;
- No evidence of liver disease;
- Pregnancy;
- Patients with pacemakers fitted.

STUDY PROCEDURES:

Up to 100 patients with liver disease who have been referred for a liver biopsy will be scanned, immediately prior to their liver biopsy, with the Philips Ultrasound System, Siemens Acuson S2000 ARFI Ultrasound System, and Echosens Fibroscan. These 3 scanning procedures are non-invasive, will take no longer than 20 minutes in total, and will be performed by the study doctors in the same unit as where the patients are attending for their liver biopsy.

Philips and Siemens Ultrasound: For each patient 30 valid measurements will be taken by a trained operator, who will be blinded to the results of the Fibroscan. Patients will be in the supine position and fasted for up to 6 hours. 10 measurements will be taken on the right lobe of the liver, and 10 on the left lobe of the liver and a median value calculated. The operator will take some of the measurements in approximately the same area where the biopsy will be performed. The measurements will be taken in the area where the liver tissue is at least 6 cm thick and free of large blood vessels. A measurement depth of 2 cm below the liver capsule will be chosen to standardize the examination. The operator will track the location of each measurement. 10 valid measurements will then also be taken on the spleen. Spleen size will be measured (area and longitudinal diameter). Maximum spleen bipolar diameter will also be taken.

Fibroscan: For each patient 10 valid measurements will be taken by a trained operator. Patients will be in the supine position and fasted for at least 6 hours. Measurements will be taken in the right lobe of the liver by the intercostal approach with a standard Mprobeor XL probe. The median value of ten valid measurements (SR >60% and IQR < 30%) will be used.

Liver Biopsy Results: All biopsy specimens will be analysed by an experienced pathologist as standard diagnostic clinical care. Liver fibrosis stages will be evaluated semi quantitatively according to the Metavir and Ishak scores. Steatosis will be assessed according the number of hepatocytes with fatty degeneration. Liver fibrosis will be staged on aF0–F4 scale according to the Kleiner histological scoring system. The NAFLD Activity Score (NAS) will be calculated according to Kleiner. All liver biopsies will be clinically indicated and will therefore be part of a patient's routine clinical care. Diagnostic results of the liver biopsy will be sourced from the patient's medical notes and will be compared to the results of the 3 imaging techniques. If a patient has already had a recent liver biopsy and consents to participating in this study, they will be invited to attend a 30 minute visit to the Hepatology Clinical Research Facility so that they can have the 3 scans performed.

SUBJECT RECRUITMENT:

The aim is to recruit up to 100 participants for this study. All patients attending the weekly Cirrhosis Clinic in the Hepatology CRF will be considered for participation in this study, so too will all patients who are referred to the Hepatology Unit for a clinically indicated diagostic

liver biopsy. The study doctors will liaise and work closely with the nurses who manage the Cirrhosis Clinic and biopsy lists.

Relevant sections of the patients' medical notes will be reviewed by clinically trained members of the study team who hold substantive or honorary contracts with Imperial College Healthcare NHS Trust.

Written informed consent will be obtained from each participant. Participants will be given the Patient Information Sheet and this will be explained in full to them before Informed Consent is sought. Patients will have a minimum of 24 hours in order to read the Patient Information Sheet and they will be given the opportunity to ask as many questions as they like. The doctor taking consent will be the main study doctor and all study doctors will be fully GCP accredited.

WITHDRAWAL OF SUBJECTS:

Subjects are free to withdraw consent at any time and this will not affect their clinical care. Data captured up until the point of withdrawal of consent will still be used in the study.

DATA COLLECTION, DATA HANDLING & RECORD KEEPING:

Explicit consent for access to relevant sections of medical records by members of the research team will be gained. Transfer of study relevant information on magnetic/optical media or networks will only be in encrypted form, according to local NHS ICT protocols. Where data is stored on NHS computers, appropriate access controls will be in place to ensure that access to confidential research information is restricted to those who need access. Paper records (consent forms etc) will be stored securely on NHS premises. This will be within a locked filing cabinet or cupboard in a locked office to which only the senior research team has access.

The Data Protection Act and Caldicott principles will be adhered to at all times.

Data will be pseudoanonymised as soon as possible. Data recorded on the case record form (CRF) will be identified by a unique reference number, this will only be linked to the individual patient separately, in a secure database held by the recruiting clinicians. CRFs and other trial documentation will be labelled only with this unique identifier.

Identifiable patient data will only be stored on secure computers which may only be accessed by the clinicians involved in the patients' clinical care. A unique identifying numerical code which is distinct from the NHS number or hospital record number will be assigned. The unique identifier will be used for all research data stored on investigator's computers. This pseudoanonymised data will be kept on NHS and University computers. Such data will be encrypted to the local ICT requirements. Paper records (consent forms etc) will be stored securely on NHS premises.

Only members of the research team who hold a relevant NHS Trust contract will have access to the relevant sections of medical records of those who agree to participate. Explicit consent for this access will be sought from each participant on the consent form. Information gleaned from such access will remain entirely confidential, and will only be recorded anonymously in study records.

It is Imperial College policy that all data relating to research, including consent forms, are kept for 10 years.

AT THE END OF THE STUDY:

Once the study results have been generated, the study documents will be archived at Imperial College's archive facility (ACRU - Archive and Corporate Records Unit) which is based at Imperial's Charing Cross Campus. Full records of the archive transfer will be kept within the Hepatology Department in the Clinical Trials and Clinical Research Manager's office, but only the Chief Investigator or his nominated deputy will be allowed to access these records once archived.

STOPPING/DISCONTINUATION RULES:

The study is due to continue for two years.

RESEARCH GOVERNANCE, MONITORING, ETHICS & R&D APPROVAL:

The study will be conducted in compliance with the Research Governance Framework for Health and Social Care and Good Clinical Practice. The study will be conducted in accordance with the approvals of the Research Ethics Committee and the Joint Research & Compliance Office of Imperial College London & Imperial College Healthcare NHS Trust.

INDEMNITY:

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this.

SPONSOR:

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

REPORTING & DISSEMINATION:

Results of the study will be disseminated by conference presentation and peer review publication and will be reported annually to REC.

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