The XL probe: a luxury or a necessity? Risk stratification in an obese community cohort using transient elastography

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Abbreviations:

ALT, alanine aminotransferase; AUDIT, Alcohol use disorders identification test; BMI, body mass index; CLD, Chronic liver disease; EASL, European Association for the study of Liver; kPa, kilopascals; LSM, liver stiffness measurement; NAFLD, non-alcoholic fatty liver disease; SCD, Skin capsular distance; TE, transient elastography; WHO, World Health Organisation

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Echosens™ provided a loan of the XL probe at the start of the study. No financial assistance was provided. Echosens™ had no role in the study design, the collection or interpretation of the data.

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Author Contributions:
R Harris, TR Card, T Delahooke, GP Aithal, IN Guha were involved in the study design and concept, implementation of the study in primary care, interpretation of results and editing of the manuscript. R Harris analysed the data set and wrote the initial manuscript draft. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. IN Guha is the guarantor.

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Abstract

Background

Transient elastography is a non-invasive tool which can stratify patients at risk of chronic liver disease. However, a raised body mass index has been independently associated with a failed or unreliable examination.

Objective

To analyse the performance of two probes (M/XL) on a portable transient elastography device within an obese community population.

Method

Prospective study with recruitment from a primary care practice. Patients identified with a risk factor for chronic liver disease were invited to a community based risk stratification pathway for transient elastography readings with both probes. A threshold of ≥8.0kPa defined elevated liver stiffness.

Results

477 patients attended the pathway. 21% of patients had no valid measurements with the M probe. There was a significant difference between the probes in the proportion achieving ≥10 valid readings (M vs XL probe: 66.2% vs 90.2%; p = <0.001) and in their reliability (M vs XL probe: 77.4% vs 98.5%; p= 0.028). Unreliable readings with the M probe increased as the body mass index increased. The XL probe re-stratified 5.2% of patients to have a normal reading.

Conclusion

The XL probe on a portable device significantly improves the applicability of transient elastography within a community based risk stratification pathway.

Key Summary

Summarise established knowledge

1. Transient elastography (TE) is an extensively validated diagnostic tool for stratifying the severity of liver disease.
2. However, a raised body mass index has been independently associated with a failed or unreliable examination, a potential limitation when using transient elastography in a community based risk stratification pathway.
3. The XL probe has been developed specifically for obese patients and with it now available on the portable device this could increase the applicability of transient elastography as a risk stratification tool.
4. Considering its increasing utilisation in clinical care, there remains a paucity of data on the relationship between the M and XL probe when used on the same patient.

Significant/ new findings

1. This is the first study which has demonstrated the feasibility and success of using both probes in the community within a risk stratification pathway.
2. Use of the XL probe significantly increased the number of valid (M vs XL probe: 66.2% vs 90.2%) and reliable readings (M vs XL probe: 77.4% vs 98.5%) that were obtained.

3. Use of the correct probe is essential to ensure the patient is risk stratified correctly. The XL probe re-stratified 5.2% of patients to have a normal TE reading according to our definition for clinically significant liver disease.
4. Within a risk stratification pathway, the XL probe is not an optional extra, but a necessity in a population setting where a raised BMI is becoming routine.

Introduction

Chronic liver disease (CLD) has risen up the public health agenda due to increasing mortality rates and the preventable burden of disease within the general population caused in the majority by lifestyle related risk factors (1).

Case finding strategies to tackle these issues have been suggested (2, 3) but are not routinely implemented. Yet, use of non-invasive tests such as transient elastography (TE) as a risk stratification tool for liver disease have previously been demonstrated to be successful (4, 5). Advantages of TE include its ease of use, provision of timely results, diagnostic accuracy and that it is non-invasive. The convenience of a portable machine also allows risk stratification to occur within the community rather than a hospital setting (6).

However, a raised body mass index (BMI) has been independently associated with a failed or unreliable TE examination using the standard 'M' probe (7-9) with successful readings reported in only 75% of obese patients (BMI ≥ 30kg/m^2) (10). A potential limitation when using TE in a risk stratification pathway. This is concerning given the increasing proportion of the general population who are overweight (65% of men and 58% of women in England (11)). The XL probe has been developed specifically for obese patients and with it now available on the portable device this could increase the applicability of TE within a risk stratification pathway.

The aim of this study was to analyse the performance of the M and XL TE probes among those with a BMI ≥ 28kg/m^2 within a risk stratification pathway based in the community.

Methods

Study setting and population

This is a prospective study with recruitment from a primary care practice in Leicester, England. The study ran from January 2015 until March 2016. Local regulatory approval was obtained on 10th April 2013 from the Leicester Research Ethics Committee (13/EM/0123) and written informed consent was gained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. The study has been registered on the ClinicalTrials.gov website (NCT02037867)

Commented [RH1]: A declaration of the study registered on a public clinical trials registry

Clinical, anthropometric and biochemical data was obtained from the electronic primary care records (SystmOne, TPP, UK) within which data is stored as searchable numerical values and prospectively coded 'Read codes'.

Recruitment occurred via an invitation to attend a community based risk stratification pathway for CLD which has been previously described (6). Patients were initially identified from the electronic primary care records. Adults (≥ 18 years) with one or more lifestyle related risk factors for CLD at the start of the study were invited. These included:

1. Hazardous alcohol use – defined as >14 units/week for women and >21 units/week for men, or an AUDIT questionnaire score ≥ 8 (12), or presence of a Read code for alcohol misuse.
2. Type 2 diabetes - presence of a Read code related to the diagnosis
3. BMI ≥28.0 kg/m^2 – presence of a numerical value recorded within the past 5 years. A lower BMI cut off for obesity (≥28.0 kg/m^2) was agreed a priori for all patients included within the study due to the increased prevalence of people with Asian ethnicity in this population. This is in accordance with the World Health Organisation (13) who recommend different cut off points for the Asian population due to a higher risk of type 2 diabetes and cardiovascular disease at a lower BMI compared to European populations. A lower cut off ensured that patients of Asian ethnicity whose BMI was lower than the traditional cut off for obesity (30.0 kg/m^2) but who were still at high risk of CLD were invited to attend.

Patients meeting any of the following criteria were ineligible and not invited to attend the risk stratification pathway: 1. Contraindication to undertaking a TE reading (e.g. pregnancy, implantable cardiac device) 2. Known diagnosis of CLD 3. Known malignancy or other terminal illness 4. Patients unable to consent to investigation or housebound and unable to attend.

Transient elastography

TE is a non-invasive diagnostic test which calculates the degree of liver stiffness by propagation of an elastic shear wave. Correlation between its results and stages of liver fibrosis has been extensively evaluated and validated in all major aetiologies of CLD (14).

The TE device can be either static or portable but until recently the XL probe has only been available with the static device. Three experienced operators performed all the TE examinations as per the manufacturer's recommendations and had completed >100 examinations prior to the study using the portable FibroScan® 402 device (Echosens, Paris). The technique for obtaining a TE reading and the differences between the probes has been previously described (15, 16). Ten valid measurements were collected with both probes with the median value reported as the liver stiffness measurement in kilopascals (kPa). Examinations unable to record any valid readings were deemed technical failures. As an indicator of variability the ratio of the interquartile range of the liver stiffness to the median value (IQR/M) was also recorded. Examinations were compared to the reliability criteria outlined by Boursier et al (17) and recommended by the manufacturer. To avoid confusion all examinations which are 'very reliable' or 'reliable' will be referred to in the subsequent text as reliable.

A TE reading was attempted with both probes for all patients with a BMI ≥28.0 kg/m^2. A threshold of ≥8.0kPa was agreed a priori to define elevated liver stiffness consistent with clinically significant liver disease. This threshold has been used within other community based screening programmes (4) and has been demonstrated to have a high negative predictive value for advanced fibrosis (10).

Statistical methods

Statistical analysis was completed using Stata version 14.2 (StataCorp LP). Baseline characteristics of the study cohort are presented as numbers (percentage) if categorical

data or medians (IQR) for non-normally distributed continuous data. A comparison of the performance of both probes was made using the chi squared test and the Wilcoxon signed rank test for categorical and non-normally distributed continuous data respectively.

The difference in the number of reliable and unreliable readings between the two probes using the criteria outlined by Boursier (17) was compared using the chi squared test. Readings between the two probes were also compared in accordance with how this would affect risk stratification. A patient was considered to be re-stratified if the XL probe reading was <8kPa when the M probe reading had been ≥8kPa (in line with our definition of clinically significant liver disease). Correlation between the liver stiffness measurements obtained by both probes was calculated and a linear regression analysis was completed to further characterise this relationship. Multivariable regression analysis was carried out to estimate the effect of potential confounding variables. Agreement between the probes was further analysed using a Bland-Altman plot. To identify variables independently associated with re-stratification univariate and multivariate logistic regression models including the covariates age, gender, BMI, hypertension, hypercholesterolaemia, the reliability of the M probe reading, Type 2 diabetes and Hazardous alcohol use as a risk factor were conducted.

Results

Patient characteristics

The primary care practice had a total adult population of 4150 with 1167 patients identified to have at least one risk factor and eligible to be invited to attend the risk stratification pathway. Of these, 720 patients attended of which 477 had a BMI ≥28.0 kg/m^2 and had attempted TE readings with both probes (Patient characteristics outlined in table 1). Fifty percent of the patients were male and the median age was 58 years (IQR 47-68). The majority of the patients were white (72.5%) although this was lower than the general population (87.2% in the UK) due to the high percentage of patients with Asian ethnicity (24.6%) in the community in which the risk stratification pathway was implemented. Seventy three percent of the cohort had a BMI ≥28.0 kg/m^2 as their only risk factor whilst 10.9% and 15.4% also had hazardous alcohol use or type 2 diabetes as an additional risk factor; 2.1% of patients had all three risk factors. The median BMI was 31.4 (IQR 29.4-34.7).

Reliability of the probes

The XL probe increased the number of valid TE readings (Table 2); 21% of the patients had no valid measurements with the M probe. There was a significant difference in the proportion who had ≥10 valid readings between the M and XL probes (66.2% vs 90.2%; p <0.001); 76% of the patients with <10 valid readings with the M probe had ≥10 readings with the XL probe.

A significant difference was also seen in the reliability with >96% of patients with an unreliable M probe reading obtaining a reliable XL probe reading (Table 3). According to the reliability criteria (17) only 0.84% of the patients did not obtain a reliable reading with either probe (Table 3). The number of reliable measurements increased with the XL probe and a

significant difference was observed between the two probes (M vs XL probe: 77.4% vs 98.5%; p= 0.028). The number of unreliable readings increased with the M probe as the BMI increased whilst with the XL probe the number of unreliable readings remained low across all BMI categories.

The TE readings between the probes were highly correlated (R^2 0.78, p value <0.001) (Figure 1). A Bland-Altman plot (Figure 2) demonstrated this and revealed a larger difference at higher mean values (Pitman's test of difference in variance: r=0.656, p value = <0.001). In multivariable analysis no appreciable confounding of this relationship was found with any of the studied variables (BMI, Gender, Ethnicity, Age, Type 2 diabetes as a risk factor, Hazardous alcohol use as a risk factor). In general, the XL probe readings were lower than those obtained with the M probe with linear regression analysis returning the following estimate: XL = (0.59 x M) + 1.73.

Use of both probes within the community risk stratification pathway

The XL probe ensured 21% of patients obtained a TE reading who otherwise would have been deemed a technical failure if only the M probe was available. The XL probe also re-stratified 5.2% of patients to have a normal TE reading according to our definition for clinically significant liver disease (Table 4). The percentage of patients re-stratified increased as the BMI increased. BMI was the only variable in a multivariate logistic regression which was significantly associated with re-stratification. For every 1kg/m^2 increase in BMI the odds of being re-stratified increase by 19% (Table 5).

Discussion

Key findings

Within a risk stratification pathway, an ideal tool would reliably identify patients at high risk of disease and exclude those who are normal. However, as we have demonstrated use of TE with only the M probe as a risk stratification tool in an obese cohort could potentially lead to a large number of patients with an invalid or unreliable TE reading.

Despite 93.1% of patients who had a TE reading with both probes being risk stratified equivalently, 1 in 5 patients within this obese community cohort had no valid readings with the M probe. Use of the XL probe significantly improved the number of valid and reliable TE readings that were obtained.

Linear regression analysis suggests there is a good correlation between the probes with the readings from the XL probe relating to that of the M probe in line with the equation (XL = (0.59x M) + 1.73). The XL probe readings are lower than the M probe which is consistent with other findings in the literature (16, 18). The Bland-Altman plot demonstrates this difference when using both probes in the same individual and that this difference is larger the greater the mean reading.

Strengths and limitations

Whilst other studies (16, 19) have compared both probes in a hospital setting we have demonstrated the feasibility of using both probes in a community risk stratification pathway. Ten valid measurements were obtained in 66.3% of patients using the M probe and in 90.2% with the XL probe. This performance compares favourably to other studies (16, 19) despite being used in a community rather than a hospital setting.

The percentage of reliable readings is lower than other studies which have risk stratified using TE in the community (Baba *et al* (20): 98.3%; You *et al* (21) 97%). This is likely due to the increased number of patients with obesity in our cohort compared to the unselected general population used within these studies. This highlights the importance of having access to the XL probe in order to maximise the numbers of patients who could be risk stratified.

A limitation is the inability to comment on the diagnostic performance of TE within this population and healthcare setting. We were unable to compare the two TE probe readings against histological findings although a liver biopsy does have its own documented limitations (22). Myers *et al* (16) analysed the performance of both TE probes against histological outcomes in an overweight cohort and identified optimal liver stiffness cut offs with the M probe (≥7.8kPa) and the XL probe (≥6.4kPa) for diagnosing ≥ F2 fibrosis. It is worth noting that according to our equation, conversion of an M probe cut off of 7.8kPa yields an XL probe cut off of 6.3kPa which is remarkably close to the value derived by Myers *et al*.

However, it has been reported that the disparity between the two probes is eliminated when the M probe is re-calibrated to measure an equivalent depth to the XL probe (16). Similarly, when the stiffness is made homogeneous using phantom liver models the difference between the probe readings disappears (16). Histological specimens demonstrate a greater amount of fibrous tissue around the subcapsular region which can be out of proportion to the remainder of the parenchyma (23). This suggests that the lower readings observed with the XL probe may be due to a deeper area of the liver being scanned. A recent update of the device automatically selects the "appropriate" probe based on skin capsular distance (SCD). Our data shows the difference in readings which might occur if this guidance is not followed and consequently the potential error in risk stratification of patients (24). Thus choosing the correct probe is not for the sole reason of obtaining a reliable scan. Though our linear regression equation shows a clear relationship numerically between results from the two probes, it does not imply one probe can be substituted for another. The relationship between the probes at higher stages of fibrosis may differ, as highlighted by the Bland Altman plot.

At present, it is assumed that the same liver stiffness cut off can be used if the "appropriate" probe has been chosen. A validation study of the XL probe is required to ensure this assumption is correct and that the liver stiffness measurement obtained is reliable and correlates with the histological diagnosis. As we were unable to measure SCD and did not have any histological comparisons we are unable to validate the XL probe in this study but are aware of emerging evidence.

Relevance to clinical practice

There is an urgent need to tackle the growing epidemic of CLD and actively identity those patients who are at increased risk of liver related disease and death (25). With new guidelines recommending screening for patients at high risk of CLD (3) tools which are accessible and easily utilised are imperative. Our results suggest that a valid and reliable M probe reading is unlikely to underestimate the degree of liver fibrosis and consequently should not mis-stratify patients who have undiagnosed CLD. This is supported by the close correlation observed between the results from the two probes. However, access to the M probe alone would limit the applicability of TE within a community based risk stratification pathway. The adjunct of the XL probe with the portable device is an important advance to this technology to achieve a non-invasive test which can be universally applied to all patients at risk (26).

Whilst the added cost to a health care commissioner may be of concern this must be weighed up against the cost of a false positive result, a screening failure or even the cost to the health care system as a whole if the patient was to remain undiagnosed. Health economic analyses of proposed case finding strategies would be useful to determine the added economic value of having the XL probe available on a portable TE device.

Even if the XL probe is accessible, there still remains uncertainty over when it should be utilised to ensure a reliable reading is obtained. The manufacturer recommends measuring the SCD to determine which probe to use but this is not always possible in a community setting. This was indeed the case in our current study. Other studies have demonstrated a

patient's BMI to be a reasonable surrogate for SCD. Our results demonstrate that 25% of patients with a BMI>30 kg/m^2 had an unreliable reading with the M probe. This therefore could be a practical threshold in which the XL probe should be considered ahead of the M probe. Alternatively, the M probe may soon become redundant if the XL probe is able to provide more reliable readings in a general population who are increasingly overweight and at risk of CLD.

Lastly, assuming that the same liver stiffness cut off can be used for both probes, identification of the most appropriate probe would also ensure that the patient is risk stratified correctly. Within this study cohort alone, 1 in 20 patients may have been risk stratified incorrectly. Importantly in the multivariable logistic regression, BMI was the only variable which was significantly associated with re-stratification. Thus, the XL probe is now not an optional extra but a necessity in a population setting where obesity is becoming routine.

Conclusion

A reliable and valid M probe reading is unlikely to mis-stratify patients within a community based risk stratification pathway. The addition of the XL probe optimises the applicability of TE within a case finding strategy by significantly increasing the number of patients with reliable readings and ensuring they are risk stratified correctly, particularly in an obese cohort. Clinicians should be aware of the additional benefits the XL probe can offer in a population where obesity prevalence is increasing.

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