FIBROSCAN

HEALTH TECHNOLOGY ASSESSMENT SECTION

MEDICAL DEVELOPMENT DIVISION

MINISTRY OF HEALTH MALAYSIA

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EXECUTIVE SUMMARY OF FIBROSCAN

INTRODUCTION

Liver fibrosis (LF) is characterized by the accumulation of an extracellular matrix, which distorts the hepatic architecture. The major etiologies of LF are viral-associated hepatitis, alcohol abuse, non-alcoholic steatohepatitis and autoimmune disease. The progression of LF increases the stiffness of liver and the resistance of liver blood flow resulting in liver failure and eventual liver cirrhosis which increases the risk of developing liver cancer. Once cirrhosis develops, liver function is impaired and liver transplantation is the only therapy to avoid a fatal condition. Therefore, an accurate assessment LF is very important in order to predict the prognosis and start the appropriate prophylactic therapy to prevent disease progression.

At present, liver biopsy (LB) is still the gold standard for the assessment of liver fibrosis. However, it is an invasive method associated with patient discomfort and, in rare cases, with serious complications. It is difficult to perform LB for all patients who need to be assessed repeatedly due to its invasiveness and prohibitive cost and its accuracy is limited because biopsy samples are usually too small to diagnose the disease accurately and diagnostic opinions often differ among pathologists because of significant intra- and interobserver variability.

Recently, transient elastography [redacted] has become available for the assessment of LF as a rapid noninvasive method, which can measure liver stiffness from outside of the body.

This technology review was requested from the office of Medical Development Division.

TECHNICAL FEATURES

Transient elastography (FibroScan) is performed with an ultrasound transducer probe mounted on the axis of a vibrator. Vibrations of mild amplitude and low frequency are transmitted by the transducer, inducing an elastic shear wave that propagates through the underlying tissues. Pulse-echo ultrasound acquisitions are used to follow the propagation of the shear wave and to measure its velocity, which is related directly to tissue stiffness (the elastic modulus): the stiffer the tissue, the faster the shear wave propagates. FibroScan takes <5 minutes to perform, and produces immediate, operator-independent results.

CONCLUSION

There is good evidence to show that FibroScan showed a better correlation with fibrotic area than the existing liver fibrosis markers, suggesting that Fibroscan can be used as an alternative to liver biopsy in assessment of liver fibrosis, as it is safe and has a sufficient diagnostic accuracy.

In conclusion, real-time elastography is a new and promising sonography-based noninvasive

method for the assessment of liver fibrosis in patients with chronic viral hepatitis. In combination with simple laboratory values, real-time elastography can further improve the discrimination of different fibrosis stages, which plays a decisive role in the management of patients with viral hepatitis.

The review showed that there were good evidences of effectiveness when using FibroScan. However, these are early results, so more research is needed. Most of the studies conducted to date are small, focus on a subset of patients with chronic liver disease which fail to consider the full range of non-invasive tests, and arrive at differing thresholds for discriminating among the degrees of fibrosis. It is also unclear whether the studies were independent of industry involvement.

However, future studies on larger patient cohorts are necessary for improvement and also validation of the elasticity scores and discriminating power of the fibroscan.

RECOMMENDATION

The potential for non-invasive fibrosis staging is promising, but which technology or combination of technologies will be most useful is unclear. It could be compelling to use FibroScan more frequently based on its rapid and non-invasive nature. However the degree to which FibroScan can replace liver biopsy is still unclear.

Based on the above review, more clinical research is warranted to provide further additional evidence of effectiveness for its use in diagnosing liver fibrosis, validation of the elasticity scores and discriminating power of the FibroScan

TITLE: FIBROSCAN

1. INTRODUCTION

Liver fibrosis (LF) is characterized by the accumulation of an extracellular matrix, which distorts the hepatic architecture [1-2]. The major etiologies of LF are viral-associated hepatitis, alcohol abuse, non-alcoholic steatohepatitis and autoimmune disease. The progression of LF increases the stiffness of liver and the resistance of liver blood flow [1, 3]. An insufficiency of liver blood flow results in liver failure and eventual liver cirrhosis which increases the risk of developing liver cancer. Once cirrhosis develops, liver function is impaired and liver transplantation is the only therapy to avoid a fatal condition [4]. Therefore, an accurate assessment LF is very important in order to predict the prognosis and start the appropriate prophylactic therapy to prevent disease progression.

At present, liver biopsy (LB) is still the gold standard for the assessment of liver fibrosis. However, it is an invasive method associated with patient discomfort and, in rare cases, with serious complications [5-6]. It is difficult to perform LB for all patients who need to be assessed repeatedly due to its invasiveness and prohibitive cost. In addition, accuracy of liver biopsy is limited because biopsy samples are usually too small to diagnose the disease accurately and diagnostic opinions often differ among pathologists because of significant intra- and interobserver variability and sampling errors [7- 8]. Furthermore, studies have shown a great sampling variability in biopsies if consecutive percutaneous samples were taken by redirecting the biopsy needle through a single entry sight and when comparing surgical samples with individual virtual biopsies or biopsy samples taken from the right and left hepatic lobes [7,9].

Recently, transient elastography [redacted] has become available for the assessment of LF as a rapid noninvasive method, which can measure liver stiffness from outside of the body [10-12].

2. OJECTIVE/ OBJECTIVES

To determine the safety and effectiveness (diagnostic accuracy) of the FibroScan.

3. TECHNICAL FEATURES

Transient elastography [redacted] is performed with an ultrasound transducer probe mounted on the axis of a vibrator. Vibrations of mild amplitude and low frequency are transmitted by the transducer, inducing an elastic shear wave that propagates through the underlying tissues. Pulse-echo ultrasound acquisitions are used to follow the propagation of the shear wave and to measure its velocity, which is related directly to tissue stiffness (the elastic modulus): the stiffer the tissue, the faster the shear wave propagates [13-15].

4. METHODOLOGY

4.1 SEARCH METHODS

PUBMED, PROQUEST and MEDLINE via EBSCO were searched using the keywords fibroscan, transient elastography, liver fibrosis, fibroscan safety, fibroscan effectiveness and efficacy, fibroscan adverse events either singly or in combination, with the limits to human study, year of publication from 2000 – 2008. In addition websites for existing HTA agency, society websites and cross-referencing of the articles retrieved were also carried out accordingly to the topic.

5. RESULTS AND DISCUSSION

From the search, forty articles were retrieved. Only twenty-two studies were relevant and taken as references. However, only one systematic review and four diagnostic accuracy studies were evaluated in this review.

The evidence were graded according to the US/Canadian Preventive Services Task Force (Appendix)

5.1 EFFECTIVENESS

A rapid review assessment under issues in emerging technologies by the Canadian Agency for Drugs and Technologies in Health [16] [level 1], showed that there were seven observational studies that addressed the relative performance of FibroScan, blood tests, or combinations thereof versus liver biopsy. Most of these were conducted in France. Four studies included less than seventy five patients in the statistical analysis, while the others include one hundred and eighty three to seven hundred and eleven participants. They were mainly hepatitis C viral (HCV) patients, one included patients with chronic liver disease, and one included only patients who are HIV and HCV co-infected. The studies suggested that FibroScan results were reproducible across operators and time. All the studies reported that FibroScan's diagnostic performance was good. This finding had sparked debate. Five studies present AUROC (area under the receiver operating characteristic curve) values, a commonly used index of diagnostic accuracy where values close to 1.0 represent high diagnostic accuracy. In terms of FibroScan's ability to discriminate degrees of fibrosis, as staged on the Metavir scale (F0 to F4 where F0=no fibrosis, and F4=cirrhosis), the AUROC ranges across the studies were F>2, 0.72 to 0.88; F>3, 0.90 to 0.91; and, F=4, 0.95 to 0.99. These results suggested that FibroScan performed well in identifying severe fibrosis or cirrhosis, but was less accurate in identifying lesser degrees of fibrosis. This was important because F2 was a threshold for initiating treatment. Two studies considered the performance of FibroScan relative to or with blood tests. Castera *et al.* [10] reported that the diagnostic accuracy of FibroScan, FibroTest®, (BioPredictive, Paris, France) and APRI (aspartate transaminase to platelets ratio index) are of the same order, and that diagnostic accuracy was maximized when FibroScan and FibroTest were used in tandem. Colletta *et al* [17] found FibroScan to be superior to FibroTest among HCV patients with normal aminotransferases.

In a study conducted by Mireen Friedrich-Rust, Mei-Fang Ong, Eva Herrmann et al [18] [level II-2], fifty-nine patients with chronic viral hepatitis and histologic results for fibrosis staging, twenty patients with chronic viral hepatitis and proven liver cirrhosis, and a control group of twenty healthy volunteers were included in a cross sectional study to investigate the assessment of liver fibrosis using this sonography-based real-time elastography (FibroScan). It was performed with conventional ultrasound probes during a routine sonography examination. In addition, aspartate transaminase–to–platelet ratio index (APRI) and routine laboratory values were included in the analysis. A specially developed program was used for quantification of tissue elasticity. The Spearman's correlation coefficient between the elasticity scores obtained from FibroScans and the histologic fibrosis stage was 0.48. This was highly significant ($p < 0.001$). The diagnostic accuracy (expressed as AUROC) were 0.75 for the diagnosis of significant fibrosis (F ≥ F2), 0.73 for severe fibrosis (F ≥ F3), and 0.69 for cirrhosis (F=4). Adding information from blood markers may improve the diagnostic accuracy of fibroScan. Therefore, a logistic regression analysis was performed including a few routine laboratory parameters. The best accuracy could be achieved by combining the elasticity score with platelet count and GGT. For a combined elasticity–laboratory score, the AUROC curves were 0.93, 0.95, and 0.91, respectively. Altogether, 80% of the patients with significant fibrosis (F ≥ F2) could be correctly identified with the real-time elastography (sensitivity). In patients with an elasticity score of less than 100.1(which is the cut-off value for the presence of significant fibrosis (F ≥ F2) according to METAVIR fibrosis stages), 78.6% of cases (negative predictive value) could be excluded.

In a study by Masaki Kawamoto et al [19] [level II-2], thirty patients who underwent a liver resection from January 2003 to May 2005 were examined in this cross- sectional study. Liver stiffness measured by using a FibroScan between 2003 to May 2005 was examined. All measurements were performed in the right lobe of the liver. The exact fibrotic area (FA) of liver fibrosis (LF) were assessed using a digital image analysis (DIA), the fibrotic area was stained blue. Serum hyaluronate, type IV collagen, and Hepatocyte growth factor (HGF) levels, and routine chemical laboratory tests were also measured. The correlation between FA and existing LF markers including FibroScan, hyaluronate, type IV collagen, and the aspartate transaminase to platelet ratio index (APRI) were compared. All markers correlated with FA. The correlation with the FibroScan findings was much higher than that with any other markers, even though the serum hyaluronate level was formerly believed to be the best available marker for evaluating LF. It was found that the biochemical data correlated with FA based on DIA. The diagnostic accuracy of FibroScan increased when it was used for severe fibrosis, whereas it decreases when it was used for a nearly normal liver. In this study, the diagnostic accuracy of FibroScan for livers with more than 20% FA (sensitivity= 100, specificity =95.5, AUC= 0.991) was better than that for livers with 10% FA (sensitivity= 100, specificity =76.9, AUC= 0.932). The reason why AUC of FibroScan for fewer FAs decreases may be due to the system itself. Wave velocity in liver was affected by fibrosis and watery distributions in liver. Liver atrophies in severe LF and cirrhosis may reduced the space to store watery contents.

In a study by Laurent Castéra, Julien Vergniol, Juliette Foucher et al.[20] [level II-2], 183 consecutive patients with chronic hepatitis C (METAVIR fibrosis stage F1, n = 47; F2, n=53; F3, n = 37; F4, n = 46) with an indication for percutaneous liver biopsy were recruited

between June 2003 and June 2004. The performance of FibroScan was prospectively assessed in patients with chronic hepatitis C, in comparison with and combined with currently available biochemical markers (Fibrotest; Biopredictive; and the aspartate transaminase to platelets ratio index [APRI]); a liver biopsy examination performed the same day served as the reference. The laboratory followed the preanalytical and analytical recommendations required to obtain fibrotest (FT) results. From the results it was found that values in AUROC of FibroScan, FibroTest, and APRI were of the same order (0.83, 0.85, and 0.78, respectively, for F > 2; 0.90, 0.90, and 0.84, respectively, for F > 3; and 0.95, 0.87, and 0.83, respectively, for F =4). The best performance was obtained by combining the FibroScan and FibroTest, with AUROC of 0.88 for F > 2, 0.95 for F > 3, and 0.95 for F = 4. When the FibroScan and FibroTest results concurred, liver biopsy examination confirmed them in 84% of cases for F > 2, in 95% for F > 3, and in 94% for F = 4.

In a study by Jose A. Carrión, Miquel Navasa,et al [21] [level II-2] , 124 HCV infected liver transplant recipients underwent 169 liver biopsies and 129 hepatic hemodynamic studies with determination of hepatic venous pressure gradient (HVPG). All patients underwent transient elastography. The aim of this study was to evaluate prospectively the diagnostic accuracy of transient elastography (FibroScan) to assess liver damage in HCV-infected liver transplant recipients. The results obtained by this noninvasive method have been compared with those obtained by liver biopsy, the current gold standard, and by HVPG. A strong positive association between the fibrosis stage and the liver stiffness value (Kruskal-Wallis <0.001) was obtained. The optimal cutoff value in this cohort was a liver stiffness value =8.5 kilopascals (kPa), whereby the Diagnostic accuracy of Transient Elastography (FibroScan) to predict liver fibrosis was found to be sensitivity 90%, specificity 81%, positive predictive value 79%, and NPV 92%, respectively. The AUROC for diagnosis of fibrosis >F2, >F3 and cirrhosis F=4 were 0.90, 0.93 and 0.98, respectively**.** There was a close direct correlation between hepatic venous pressure gradient (HVPG), and liver stiffness (Pearson correlation, 0.84; $P < 0.001$). The optimal liver stiffness cutoff value for diagnosis of portal hypertension (HVPG ≥6 mm Hg) was ≥8.74 kPa, with a sensitivity, specificity, positive predictive value, and NPV of 90%, 81%, 81%, and 90%, respectively. The AUROC for diagnosis of portal hypertension (HVPG≥ 6 mm Hg) was 0.93 and for significant portal hypertension was (HVPG ≥10 mm Hg) 0.94.

5.2 SAFETY

FibroScan is a non-invasive test, and no adverse events have been reported.

5.3 LIMITATIONS

Transient elastography has some limitations. First, the method cannot replace liver biopsy when diagnoses other than hepatitis C recurrence suspected. Although this is more common during the first months following transplantation, diseases such as de novo autoimmune hepatitis, nonalcoholic steatohepatitis, and chronic rejection can appear late after transplantation in patients with hepatitis C recurrence. Second, transient elastography cannot be performed in patients with high body mass index or with ascites (though ascites itself is in most instances a sign of cirrhosis/portal hypertension) [10-12]. Third, transient elastography does not distinguish between individual fibrosis stages, particularly when fibrosis is mild.

Although the intraoperator and interoperator reproducibility of the method is good, the coefficient of variation can be high in some patients [22].

5.3 OTHER ISSUES

FibroScan can be used to evaluate the extent of liver damage in all patients suffering from chronic liver disease, irrespective of the underlying cause, such as viral hepatitis, alcoholic liver disease and autoimmune hepatitis. It is painless and has none of the morbidity or mortality associated with needle biopsy of the liver. FibroScan offers several advantages over other techniques employed in the diagnosis of liver disease. Unlike with a needle biopsy of the liver, no anaesthetic is needed with FibroScan and the patient can be discharged immediately. However the operators need to be trained before using the device.

In the United Kingdom and France, FibroScan has been used in some private hospitals. There was no retrievable evidence to say whether FibroScan® is approved by FDA or having CE marked or not. However, FibroScan®is not currently licensed for use in Canada.

There were no retrievable health technology assessment reports from other HTA agencies other than from the Canadian Agency for Drugs and Technologies in Health.

6. CONCLUSION

Liver fibrosis can be caused by many diseases, but most of the studies examining the effectiveness of FibroScan have focused on patients infected with hepatitis C (HCV). Due to the rapid progression of liver fibrosis in transplant recipients and the need for frequent assessment of liver damage during follow-up, transient elastography may become an important tool for routine surveillance of hepatitis C recurrence in these patients. However morbid obesity or narrow intercostal spaces (the area between the ribs) preclude the use of fibroScan in 5% to 8% of patients.

There is good evidence to show that FibroScan showed a better correlation with fibrotic area than the existing liver fibrosis markers, suggesting that Fibroscan can be used as an alternative to liver biopsy in assessment of liver fibrosis, as it is safe and has a sufficient diagnostic accuracy.

The review showed that there were good evidences of effectiveness when using FibroScan. However, these are early results, so more research is needed. Most of the studies conducted to date are small, focus on a subset of patients with chronic liver disease which fail to consider the full range of non-invasive tests, and arrive at differing thresholds for discriminating among the degrees of fibrosis. It is also unclear whether the studies were independent of industry involvement.

However, future studies on larger patient cohorts are necessary for improvement and also validation of the elasticity scores and discriminating power of the fibroscan.

7. RECOMMENDATION

The potential for non-invasive fibrosis staging is promising, but which technology or combination of technologies will be most useful is unclear. It could be compelling to use FibroScan more frequently based on its rapid and non-invasive nature. The degree to which FibroScan can replace liver biopsy is still unclear.

The diagnostic performance of FibroScan is good for identifying severe fibrosis or cirrhosis, but it is less accurate for milder presentations. FibroScan is a promising technology, but large multi-centre trials comparing a range of emerging non-invasive fibrosis staging technologies are required. More clinical research is warranted to provide further additional evidence of effectiveness for its use in diagnosing liver fibrosis, validation of the elasticity scores and discriminating power of the FibroScan.

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9. APPENDICES

9.1. Appendix I- Levels of evidence scale

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization..

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE(Harris 2001)

Note: LE = Level of Evidence

9.3 Appendix 3 - search finding

Results of search on fibroscan:

Key words	**2008**	**2007**	**2006**	**2005**	**2004**	**2003**	**2002**	**total**
Fibroscan	17	20	23	2	-	1	-	
Transient elastography	32	44	16	8	4	4	3	
Fibroscan effectiveness	-	-	1	1	1	-	-	
Transient elastography effectiveness	1	1	1	-	-	-	-	
Fibroscan safety	-	-	1	-	1	-	-	
Transient elastography safety	-	-	-	-	-	-	-	
liver fibrosis diagnosis with fibroscan	12	15	20	4	-	1	-	
liver fibrosis diagnosis with Transient elastography	19	20	21	1	-	1	-	
liver fibrosis AND diagnos* AND transient elastography	19	24	12	4	-	1	-	
liver fibrosis AND diagnos* AND Fibroscan	-	-	-	-	-	-	-	