SuperSonic Imagine’s
Innovative Solutions for Clinical Liver Disease

Global Product Marketing & Education
October 2016
Liver Disease is a Growing Global Problem

The Facts:

• Liver fibrosis is a GLOBAL problem impacting 300-700 million people (5-10% of the world’s population).

• The most common causes are:

  **Hepatitis B virus** (HBV), **Hepatitis C** (HBV), **Alcohol** and **Non-alcoholic Fatty Liver Disease** (NAFLD) including **Non-alcoholic Steatohepatitis** (NASH).


Global Prevalence of HBV

240 million people worldwide
Global Prevalence of HCV

180 million people worldwide
## Prevalence of HCV per Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Income classification</th>
<th>Most prevalent genotypes</th>
<th>Anti-HCV (%)</th>
<th>No. Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>Upper-middle</td>
<td>1,2,6</td>
<td>2.2</td>
<td>29,791,212</td>
</tr>
<tr>
<td>India</td>
<td>Lower-middle</td>
<td>1,3</td>
<td>1.5</td>
<td>18,216,960</td>
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<td>Egypt</td>
<td>Lower-middle</td>
<td>4</td>
<td>14</td>
<td>11,826,360</td>
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<td>Indonesia</td>
<td>Lower-middle</td>
<td>1,2</td>
<td>3.9</td>
<td>9,436,986</td>
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<tr>
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<td>5,367,834</td>
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<tr>
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<td>6,409,840</td>
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<td>Nigeria</td>
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<tr>
<td>Japan</td>
<td>High</td>
<td>1,2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cameroon</td>
<td>Lower-middle</td>
<td>1,2,4</td>
<td></td>
<td></td>
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<tr>
<td>Brazil</td>
<td>Upper-middle</td>
<td>1,3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>Low</td>
<td>1,4</td>
<td></td>
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<tr>
<td>Philippines</td>
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<tr>
<td>Italy</td>
<td>High</td>
<td>1,2</td>
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<tr>
<td>Ukraine</td>
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<td>1</td>
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<td>Uzbekistan</td>
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<td>Turkey</td>
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<tr>
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<td>1,2,4</td>
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<tr>
<td>Thailand</td>
<td>Upper-middle</td>
<td>1,3,6</td>
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</tr>
</tbody>
</table>

**World's Population**

![Graph showing number of people infected with HCV per country, categorized by income level.](image-url)
The Clinical Challenge:
What do clinicians want?

A faster, easier, safer and non-invasive alternative to liver biopsy.

A validated tool to screen for liver fibrosis/cirrhosis, AND the ability to stage fibrosis with a score.

A method which allows for repeated serial evaluations. This is critical for monitoring new anti-viral HCV drugs and NAFLD-NASH.

A method which is low cost for the patient, AND provides a good reimbursement and return on investment.

- Current costs: Up to $300,000 over a patients lifetime

There is global consensus that a non-invasive, accurate, validated, and economical test for early detection and staging is needed.
Our Solution:
The Aixplorer® ultrasound system for Liver Fibrosis
Aixplorer’s Key Pillars

“One Probe Solution”
Unique ShearWave Technology

“60 Second Exam”
Faster Workflow

“Clinically Proven”
Superior Performance and Accuracy

“Higher Reimbursement”
4 times Transient Elastography
Now there is a Solution
Aixplorer® with ShearWave™ Elastography

Our Solution:

• **SuperSonic Imagine’s** unique technology can provide liver fibrosis screening, staging and monitoring.

• The 60 second ShearWave™ Elastography exam – **fast, easy, clinically proven** and **cost effective**:
  
  • Simple 1 image acquisition and 3 measurement workflow
  
  • Quick Q-Box™ Analysis Tools with Stability Index to assure quality
  
  • Clear and concise Liver Report package
One Probe Solution
XC6-1 Single Crystal Curved Array Transducer

• “One Probe Solution” for All Patient Types:
  • Reliable – One probe lasts a lifetime. No need for annual recalibration.
  • Excellent SWE™ penetration down to 10 cm in obese patients. Maximum imaging to depths beyond 30 cm!
  • No failures due to ascites.
  • Single crystal technology for maximum sensitivity and image clarity.
  • Lightweight, ergonomic design.
60 Second Exam
Non-Invasive & Quantitative Liver Fibrosis Assessment

- Large color-coded ShearWave™ area for easy visualization of the heterogeneity and extent of liver fibrosis.

- Simple blue to red color scale for easy qualitative interpretation of stiffness.

- Q-Box™ quantitative tools allow rapid quantitative measurement of tissue stiffness.

- Stability Index for accurate and confident quantitative results.
60 Second Exam
4 Easy Steps

1. Position the patient in a supine or slight left oblique position, hand above head, and activate the XC6-1 probe.

2. Firmly press the probe to enlarge the intercostal space. When a clear B-mode image of the liver is seen up to 8 cm of depth, activate SWE™ and ask the patient to pause breathing.

3. Acquire 5-10 seconds of real-time SWE images. Press Freeze.

4. Choose an image with clear parenchyma free of vessels. Press Q-Box™. Position the ROI in an area where the Stability Index (SI) reads 90% or higher. Press Save.

Repeat this procedure 3 times to acquire 3 valid, independent SWE™ images of the same scanning view.
The Aixplorer®: Clinically Proven for Liver Fibrosis
Liver stiffness values measured with SWE in Hepatitis C patients

<table>
<thead>
<tr>
<th>METAVIR Scores</th>
<th>Stiffness values (IQR)</th>
<th>Fibrosis assessment (METAVIR)</th>
<th>Cut-off values</th>
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<tr>
<td>F0-F1</td>
<td>5.1-6.8</td>
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<td></td>
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<tr>
<td>F2</td>
<td>7.2-8.3</td>
<td>F≥2</td>
<td>7.1</td>
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<tr>
<td>F3</td>
<td>9.2-10.1</td>
<td>F≥3</td>
<td>8.7</td>
</tr>
<tr>
<td>F4</td>
<td>12.8-18.8</td>
<td>F=4</td>
<td>10.4</td>
</tr>
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</table>

Clinically Proven
Liver Fibrosis Assessment with SWE™

HCV Patients

NAFLD Patients

(% Patients with BMI > 25 kg/m²)

Clinically Proven
Liver Fibrosis Assessment with SWE™

- Correlation coefficient between liver stiffness measured non-invasively and liver fibrosis scoring

<table>
<thead>
<tr>
<th></th>
<th>SWE™</th>
<th>TE</th>
<th>ARFI VTTQ</th>
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<tr>
<td>Ferraioli¹</td>
<td>0.83</td>
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<td>Cassinotto²</td>
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<tr>
<td>Gerber³</td>
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<td>0.73</td>
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<td>Samir⁴</td>
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<tr>
<td>Dhyani⁵</td>
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</tr>
<tr>
<td>Franchi⁶</td>
<td>0.83</td>
<td></td>
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</tr>
</tbody>
</table>

Clinically Proven
SWE™ Multicenter Retrospective Study

First Results of the Multicenter Retrospective Study on Liver Fibrosis Assessment with SWE™
15 International Sites / 1340 patients

ShearWave™ Elastography delivers excellent results in managing chronic liver disease patients

In HBV patients, SWE™ delivers increased sensitivity in the assessment of significant fibrosis and cirrhosis (≤F1 vs. ≥F2)

In HCV patients, SWE delivers excellent sensitivity in the evaluation of cirrhosis (≥F4)

ShearWave™ Elastography delivers excellent diagnostic assessment of all fibrosis stages

NAFLD and NASH patient assessment superior in severe fibrosis (≤F2 vs. ≥F3)
Quantitative Elasticography of Liver Fibrosis and Spleen Stiffness in Chronic Hepatitis B Carriers: Comparison of Shear-Wave Elastography and Transient Elastography with Liver Biopsy Correlation

ShearWave™ Elastography has Higher Accuracy and Technical Success than the FibroScan® in Hepatitis B patients

ShearWave™ Elastography yields narrower IQR ranges and tighter probability curves in the risk prediction of alcoholic fibrosis and cirrhosis

Clinically Proven Liver Fibrosis Assessment with SWE™ vs. FibroScan®

ShearWave™ Elastography is More Accurate than the FibroScan® in Hepatitis C patients

Accuracy of Real-Time Shear Wave Elastography for Assessing Liver Fibrosis in Chronic Hepatitis C: A Pilot Study

Confidential
Clinically Proven
Liver Fibrosis Assessment with SWETM vs. FibroScan®

ShearWaveTM Elastography Clinically Outperforms the FibroScan® in Chronic Liver Disease Patients

ShearWaveTM Elastography is more Technically Successful and has Better Performance than the FibroScan® in the Detection of Portal Hypertension in Cirrhosis
“I can reduce my biopsy numbers by 90% during initial fibrosis staging when I use the Aixplorer’s® real-time, quantitative ShearWave™ Elastography from SuperSonic Imagine”

“This is especially helpful for my patients who are eligible to receive the new antiviral treatments for HCV. This quick, non-invasive exam improves the overall patient experience.”

Dr. James Trotter
Medical Director of Liver Transplantation
Baylor University Medical Center
Dallas, Texas

“The advent of ShearWave™ Elastography, has ushered in an era of fewer liver biopsies for the Hepatitis C patient, while allowing the clinician to evaluate, monitor and effectively treat these patients without the risks of an invasive biopsy.”

Dr. Ravi Ravinuthala
Ohio Gastroenterology & Liver Institute
Cincinnati, Ohio
The Clinical Challenge:
Liver Steatosis
What is Steatosis?

- Steatosis, or fatty liver, describes the accumulation of excess fat in the liver, usually above 5%.
- Steatosis is the hallmark of most prevalent liver diseases, including alcoholic and nonalcoholic fatty liver disease (NAFLD).

Steatosis / NAFLD > 5% may progress to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis and liver cancer.

- Steatosis also reduces the viral response in hepatitis C treatment, complicates liver surgery, and raises overall risk to cardiovascular events.
The Clinical Challenge
Obesity and Steatosis

The Facts:

- NAFLD and NASH, and their progression was relatively unknown in etiology until 10 years ago.
- Today, more than 25% of the world’s population is at risk with NAFLD, 3% with NASH.
- NAFLD/NASH has very high prevalence in the Americas, Asia-Pacific, the Middle East and Europe.
- Approximately 10%-25% of patients with NAFLD will develop NASH. 5%-8% of those will develop liver cirrhosis within 5 years. Furthermore, 12.8% of patients with liver cirrhosis will develop hepatocellular carcinoma (HCC) within 3 years.
- NAFLD/NASH is a silent killer, growing at an epidemic rate in proportion to obesity. From 1980-2013 obesity increased by 10% in adults and by 47% in children.

USA Predilection for Liver Fibrosis

USA Statistics:

• 700,000-1.4 million persons are estimated to be infected with the HBV virus
• 3.2 million persons are chronically HCV-infected
• 27-34% of all Americans are estimated to have NAFLD

USA Data: http://www.cdc.gov/hepatitis/statistics/2013surveillance/commentary.htm
The Clinical Challenge
Obesity and Steatosis

A Global Effort to Address the Epidemic of Fatty Liver Disease

“Left unchecked, obesity will make the current generation of children the first in human history to have a life span shorter than that of their parents.”

David Satcher, MD, PhD
The Clinical Challenge
Assessment of Liver Steatosis

Early detection of steatosis at the 5% level.

Low cost.
Non-invasive. Safe. Well tolerated.
Serial assessment during treatment and beyond.
Globally available.

A non-invasive, accurate, validated, and economical test to detect, assess and monitor steatosis is needed.
Our Solution: The Aixplorer® ultrasound system for Liver Steatosis
Hepatorenal Ratio for Steatosis Assessment: B-Mode Ratio Tool

- Quantifies brightness of the liver with renal cortex.
- Significantly improves the assessment of fatty liver compared to traditional “guess-imation”.
- Fast and easy to use. Requires only B-mode.

Clinically Proven

- Ultrasound Hepatic-Renal Ratio was found to be an excellent predictor of liver fat content.
- Able to discriminate between levels of steatosis with high sensitivity and specificity.\(^1\)
- The addition of ultrasound attenuation parameter (e.g. CAP) only improved the accuracy by 1.8%.\(^2\)
- Can be done on DICOM images.\(^3\)

- No additional cost
- Compare to FibroScan CAP tool at +$22k.

The Aixplorer®: Clinically Proven for Liver Steatosis
Clinically Proven Ultrasound Meta-Analysis for the Detection of Steatosis

Diagnostic Accuracy and Reliability of Ultrasonography for the Detection of Fatty Liver: A Meta-Analysis
49 Publications / 4720 patients

Ultrasonography allows for reliable and accurate detection of moderate-severe fatty liver, compared to histology.

The Hepato-Renal brightness (HRI) performed best with a sensitivity of 98% and specificity of 93%.

Other measures of ultrasound brightness e.g. hepatic or portal vessel walls significantly outperformed ultrasound beam attenuation (CAP), sensitivity 59%, specificity 95%.

By Ruben Hernandez,1,2,3,4 Muriana Lazescu,5,6 Susanne Bonenkamp,1 Babar Kamil,7 Frederick L. Brancati,1,2,8 Aliro Guillar,1,5,8 and Jennifer M. Clark1,5,8

Ultrasonography is a widely accessible imaging technique for the detection of fatty liver, but the reported accuracy and reliability have been inconsistent across studies. We aimed to perform a systematic review and meta-analysis of the diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver. We used MEDLINE and Embase from October 1967 to March 2010. Studies that provided clear tabulations of ultrasonography versus histology or standard imaging techniques, or that provided reliability data for ultrasonography, were included. Study variables were independently abstracted by three reviewers and double checked by one reviewer. Forty-nine (4720 patients) studies were included for the meta-analysis of diagnostic accuracy. The overall sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of ultrasonography for the detection of moderate-severe fatty liver, compared to histology (gold standard), were 84.8% (95% confidence interval: 79.5-88.9), 93.6% (87.2-97.6), 13.3 (6.4-27.6), and 0.16 (0.03-0.62), respectively. The area under the summary receiving operating characteristics curve was 0.93 (0.91-0.95). Reliability of ultrasonography for the detection of fatty liver showed kappa statistics ranging from 0.54 to 0.92 for intra-rater reliability and from 0.64 to 1.00 for inter-rater reliability. Sensitivity and specificity of ultrasound was similar to that of other imaging techniques (i.e., computed tomography or magnetic resonance imaging). Statistical heterogeneity was present even after stratification for multiple clinically relevant characteristics. Conclusion: Ultrasonography allows for reliable and accurate detection of moderate-severe fatty liver, compared to histology. Because of its low cost, safety, and accessibility, ultrasound is likely the imaging technique of choice for screening for fatty liver in clinical and population settings. (Hepatology 2011;54:1082-1090)
Clinically Proven
Liver Steatosis Assessment with Hepatorenal Ratio

Sonographic Hepatorenal Ratio: A Noninvasive Method to Diagnose Nonalcoholic Steatosis

Valéria Pereira de Almeida e Borges, MD1, Angelica L. D. Diniz, PhD,1 Helina P. Couto, PhD2, Haroldo L. G. Rocha, MD,1,2,3 Senior Barbara Andrade, MD1
1 Universidade Federal de Uberlândia, Uberlândia, Minas Gerais, Brazil
2 Universidade Federal da Bahia, Salvador, Bahia, Brazil

Received 13 May 2013; accepted 13 August 2013

ABSTRACT: Purpose. To evaluate the accuracy of the sonographic hepatorenal ratio (HRR) in the diagnosis of fatty liver.

Keywords: fatty liver; ultrasonic hepatorenal ratio; liver biopsy; nonalcoholic steatosis

Hepatorenal ratio is the strongest predictor of liver fat content.

The Hepatic Renal Ratio is the strongest predictor of liver fat content.

Ultrasound hepatic-renal ratio and hepatic attenuation rate for quantifying liver fat content

Significant correlation was found between HRR and histologic steatosis (r=0.80). The cutoff for predicting steatosis was 1.24 (sensitivity 92.7%; specificity 92.5%).

The Hepatic Renal Ratio is the strongest predictor of liver fat content.

Hepatorenal Index as an Accurate, Simple, and Effective Tool in Screening for Steatosis

OBJECTIVE. The Hepatorenal Index has been reported to be a sensitive and noninvasive test to quantify steatosis, but it is cumbersome and time-consuming and requires specialized software. The aim of this study was to improve and simplify the hepatorenal index calculation and determine whether it is an effective tool for differentiating patients with steatosis from those without steatosis, thereby eliminating the need for biopsy in a large number of patients.

MATERIALS AND METHODS. Our study included 351 patients who had undergone ultrasound-guided percutaneous liver biopsy at our institution. Sensitivity and specificity were calculated using receiver operating characteristic curves based on comparisons of hepatorenal index and liver histology.

RESULTS. Of the 351 patients, 14 had >5% liver fat on biopsy and 337 had <5% liver fat on biopsy. The hepatorenal index was calculated using software based on comparisons of hepatorenal index and liver histology.

CONCLUSIONS. The Hepatorenal Index is an accurate, simple, and effective tool in screening for steatosis.
“The hepatorenal index is a simple, reliable, and cost-effective screening tool for identifying patients who should not undergo liver biopsy for evaluation of steatosis.”

Dr. Richard H. Marshall
Assistant Professor of Clinical Radiology
LSU School of Medicine
New Orleans, Louisiana

“The use of the hepatorenal sonographic index facilitates quantification of liver steatosis, even in small degrees, and is not affected by fibrosis or steatohepatitis. It is reproducible and operator-independent and easily can be made available and applicable in routine clinical practice.”

Dr. Muriel Webb
Department of Gastroenterology
Sourasky Medical Center
Tel Aviv, Israel
## Advantages of Aixplorer®
Comparison to Fibroscan®

<table>
<thead>
<tr>
<th>Aixplorer®</th>
<th>FibroScan®</th>
<th>Aixplorer Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One Probe Solution</strong>&lt;br&gt;XC6-1 probe works in a broad range of patients</td>
<td>Fails under common conditions of obesity and ascites¹&lt;br&gt;Requires 3 probes with annual recalibration/replacement¹</td>
<td><strong>Superior Workflow</strong>&lt;br&gt;<strong>Fewer Failed Exams</strong></td>
</tr>
<tr>
<td><strong>60 Second Exam</strong>&lt;br&gt;Real-time Imaging over a large 2D area&lt;br&gt;As few as 3 acquisitions&lt;br&gt;Qualitative and Quantitative ShearWave™ Analysis&lt;br&gt;Steatosis Assessment with B-mode Ratio&lt;br&gt;Fully validated connectivity options</td>
<td>5-10 Minutes per case&lt;br&gt;Requires minimum of 10 acquisitions&lt;br&gt;Higher technical failure rate due to blind positioning and small target area&lt;br&gt;CAP tool adds add’l $26k cost&lt;br&gt;Limited connectivity</td>
<td><strong>Higher Patient Throughput</strong>&lt;br&gt;<strong>Lower Cost</strong></td>
</tr>
<tr>
<td><strong>Clinically Proven</strong>&lt;br&gt;In HBV, HCV, NAFLD and General Liver Disease and Cirrhosis</td>
<td>Higher Technical Failure Rates&lt;br&gt;Proven lower accuracy</td>
<td><strong>Clinically Superior Performance and Accuracy</strong></td>
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<tr>
<td><strong>Higher Reimbursement</strong></td>
<td>Low Reimbursement&lt;br&gt;Annual Calibration Costs</td>
<td><strong>Increased Return on Investment</strong></td>
</tr>
</tbody>
</table>

¹ Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. Radiology; Volume 276: Number 3—September 2015
SuperSonic Imagine’s ShearWave™ Elastography provides solutions at ALL stages of liver disease.

Main Causes:
- HBV, HCV
- Alcohol
- Obesity (NAFLD-NASH)

Progressing over 5 to 50 years

Screening

Staging

Diagnosis

Removal of Underlying Cause; Drug Therapy

Monitoring
Thank you!