Clinical Applications of Acoustic Radiation Force Impulse (ARFI) Elastography

(ARFI elastography 之臨床應用)

# Effects of hepatic necroinflammation on liver stiffness measurement

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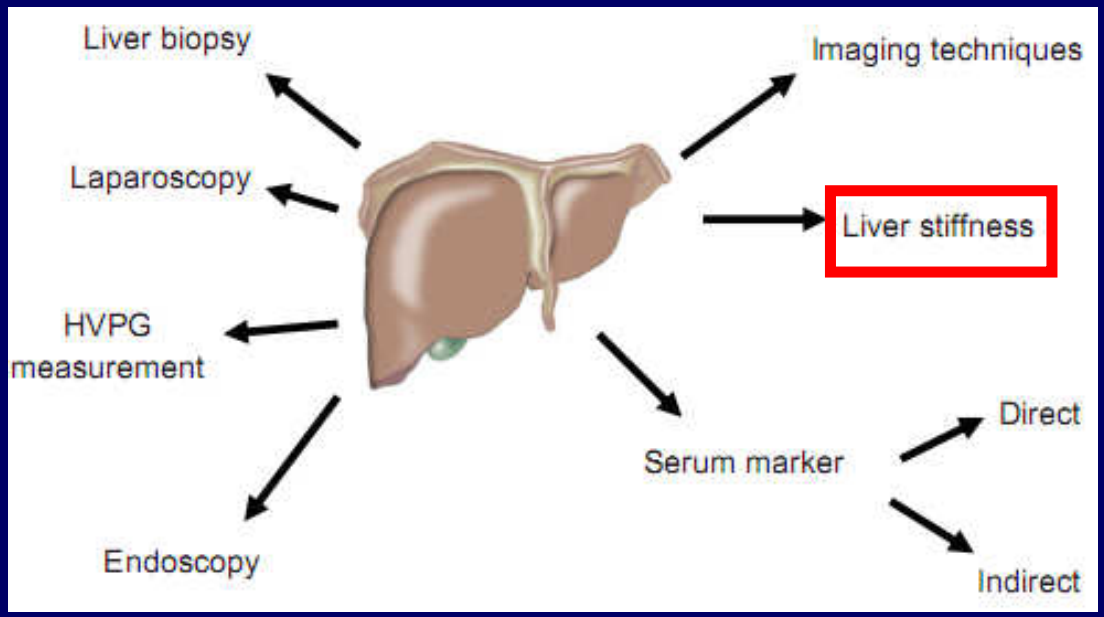
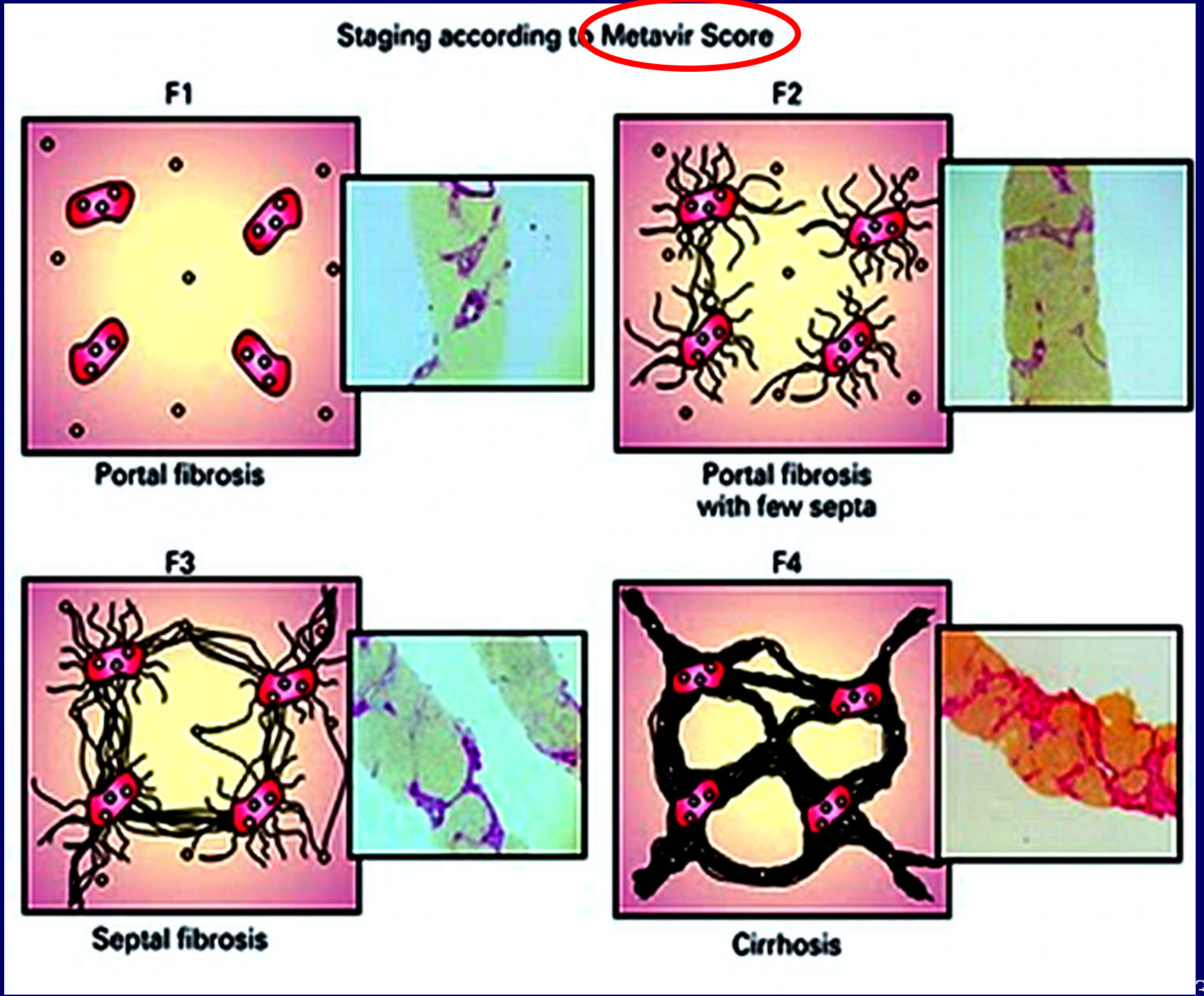
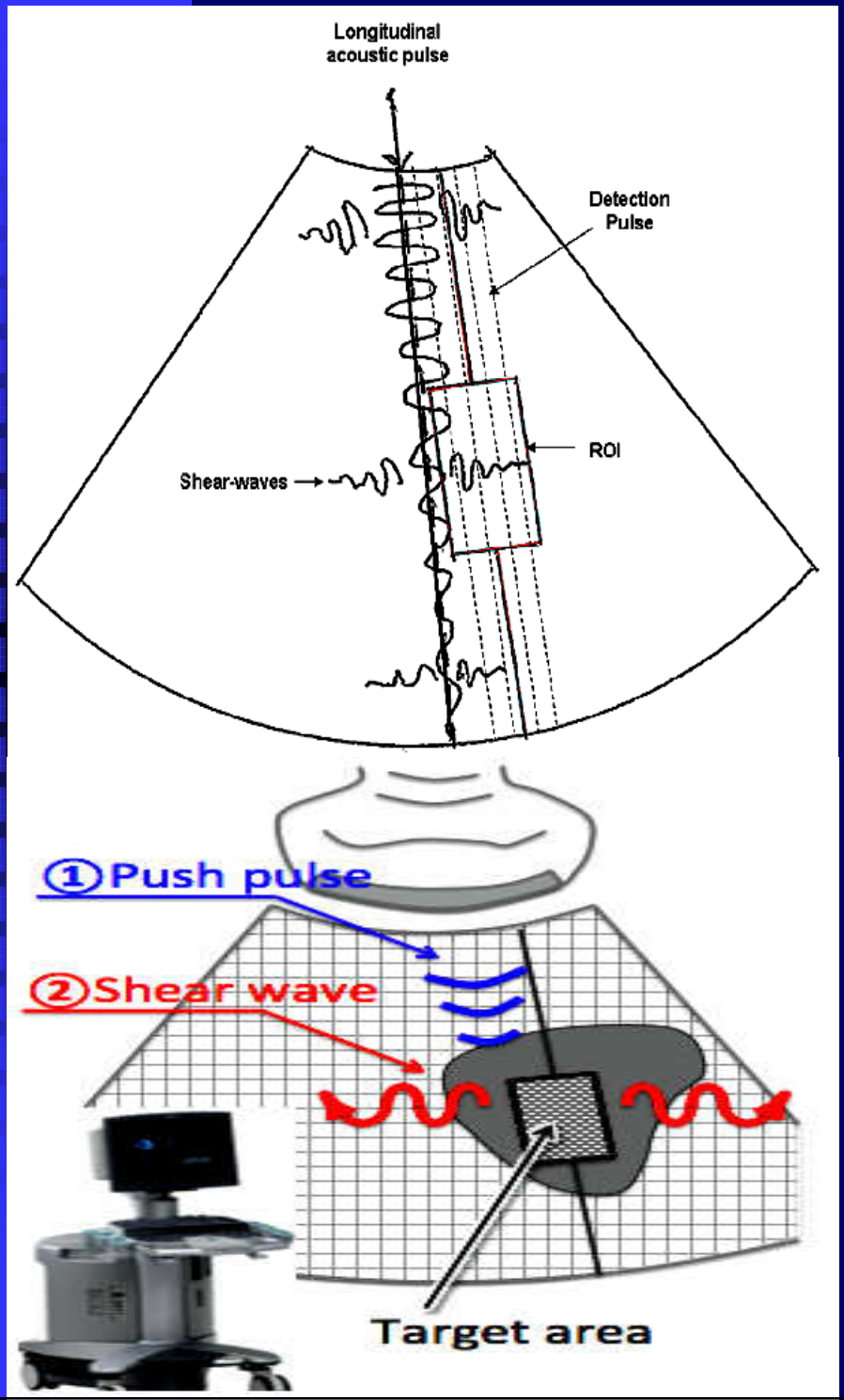
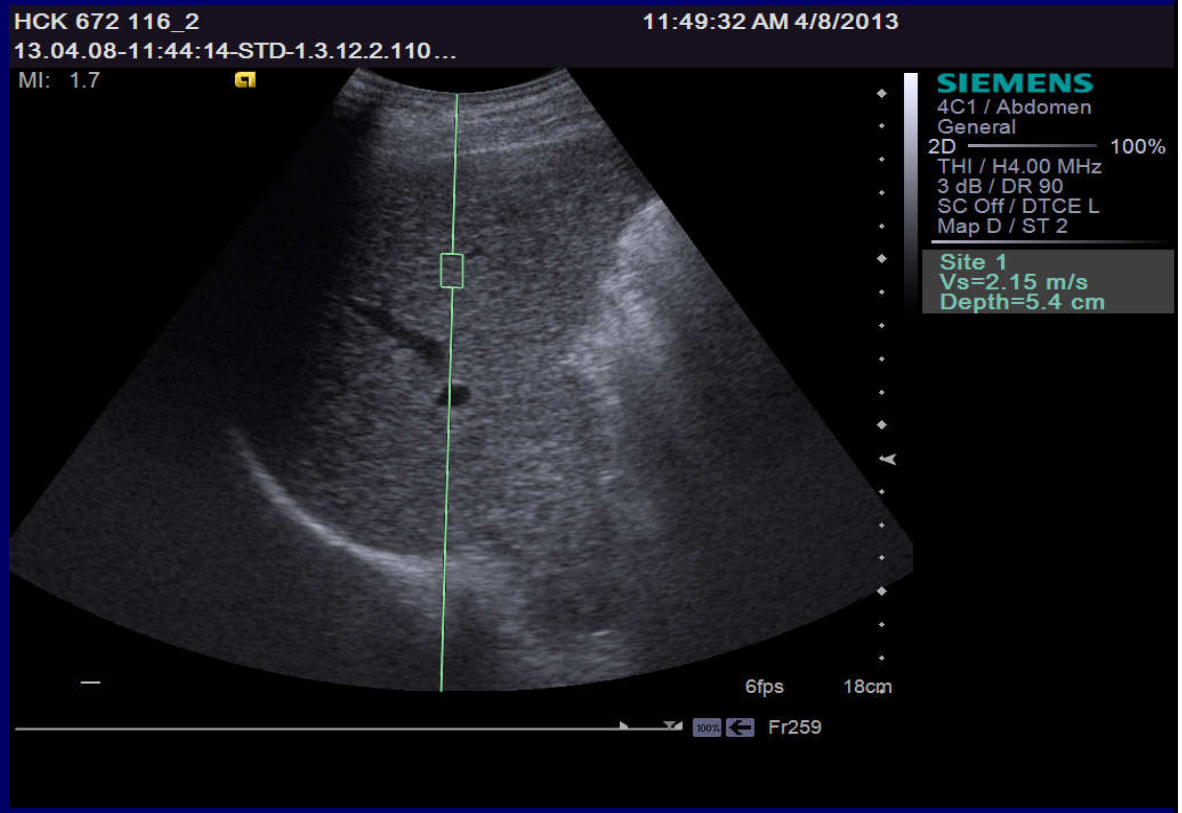



Mueller et al.
Hepatic Medicine-Evidence and Research 2012
Liver stiffness- a novel parameter for the diagnosis of liver disease


Staging according to Metavir Score
F1
Portal fibrosis
F2
Portal fibrosis
with few septa
F3
Septal fibrosis
F4
Cirrhosis

# ARFIE-LSM




Acuson S2000 with
a Siemens 4C1 curved array,
4.00 MHz for B-mode,
2.67 MHz for push pulses
and 3.08 MHz for detection pulses

**Table 1 Diagnostic performance and suggested cutoff values of liver stiffness measurement for the diagnosis of histologic cirrhosis (F4)**

| Ref. | Biopsies (*n*) | Prevalence of cirrhosis (F4) | Etiologies | Proposed cutoff values (kPa) | Sensitivity | Specificity | NPV | PPV | Positive LR | Negative LR | AUROC |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Castéra *et al*[4], 2005 | 183 | 25% | HCV | 12.5 | 87% | 91% | 95% | 77% | 9.7 | 0.1 | 0.95 |
| Fraquelli *et al*[23], 2007 | 200 | 12% | All | 11.9 | 91% | 89% | 98% | 53% | 8.3 | 0.1 | 0.9 |
| Arena *et al*[24], 2008 | 150 | 19.3% | HCV | 14.8 | 94% | 92% | 98% | 73% | 11.3 | 0.07 | 0.99 |
| Ziol *et al*[25], 2005 | 251 | 19% | HCV | 14.6 | 86% | 96% | 97% | 78% | 23.1 | 0.1 | 0.97 |
| Chan *et al*[26], 2009 | 161 | 25% | HBV | 13.4 | 60% | 93% | 88% | 75% | 85 | 0.43 | 0.93 |
| Marcellin *et al*[27], 2009 | 173 | 8% | HBV | 11 | 93% | 87% | 99% | 38% | 7 | 0.08 | 0.93 |
| Wong *et al*[28], 2010[1] | 238 | 23.5% | HBV | 9.0 (normal ALT)<br>12.0 (elevated ALT) | 54% | 99% | 67% | 98% | 3.3 | 0.7 | 0.88 |
| de Lédinghen *et al*[29], 2006 | 72 | 23.6% | HCV-HIV | 11.8 | 100% | 92.7% | 82% | 100% | 13.7 | 0 | 0.97 |
| Nobili *et al*[30], 2008[1] | 52 | 5.8% | NAFLD | 10.2 | 100% | 100% | 100% | 100% | ∞ | 0 | 1 |
| Wong *et al*[31], 2010 | 246 | 10.1% | NAFLD | 10.3 | 92% | 88% | 99% | 46% | 7.5 | 0.09 | 0.95 |
| Nahon *et al*[32], 2008 | 174 | 53.7% | ALD | 22.7 | 84% | 83% | 82% | 85% | 5.24 | 0.19 | 0.87 |
| Corpechot *et al*[33], 2006 | 95 (66 PBC, 29 PSC) | 16% | PBC/PSC | 17.3 | 93% | 95% | 99% | 78% | 18.6 | 0.1 | 0.96 |
| Carrión *et al*[34], 2006 | 124 | 11% | HCV-LT | 12.5 | 100% | 87% | 100% | 50% | 7.7 | 0 | 0.98 |
| Witters *et al*[36], 2009 | 66 | NA | Cystic fibrosis | 6.5 | 100% | 81% | NA | NA | NA | NA | 0.92 |
| Coco *et al*[75], 2007 | 228 | 20.2% | HCV/HBV | 14 | 78% | 98% | 82% | 98% | 39 | 0.2 | 0.96 |
| Ganne-Carrié *et al*[106], 2006 | 775 | 15.5% | All | 14.6 | 79% | 95% | 96% | 74% | 15.8 | 0.1 | 0.95 |
| Foucher *et al*[107], 2006 | 354 | 13.3% | All | 17.6 | 77% | 97% | 92% | 91% | 25.7 | 0.2 | 0.96 |
| Gómez-Domínguez *et al*[108], 2006 | 94 | 17% | All | 16 | 89% | 96% | 98% | 80% | 22.3 | 0.1 | 0.94 |
| Vergara *et al*[109], 2007 | 169 | 38.5% | HCV-HIV | 14.6 | 93% | 88% | 94% | 86% | 7.8 | 0.1 | 0.95 |
| Rigamonti *et al*[110], 2008 | 95 | 17% | HCV-LT | 12 | 93% | 93% | 99% | 74% | 14 | 0.1 | 0.9 |
| Yoneda *et al*[111], 2007 | 67 | 7.5% | NAFLD | 17 | 100% | 98% | 95% | 64% | 50 | 0 | 0.99 |

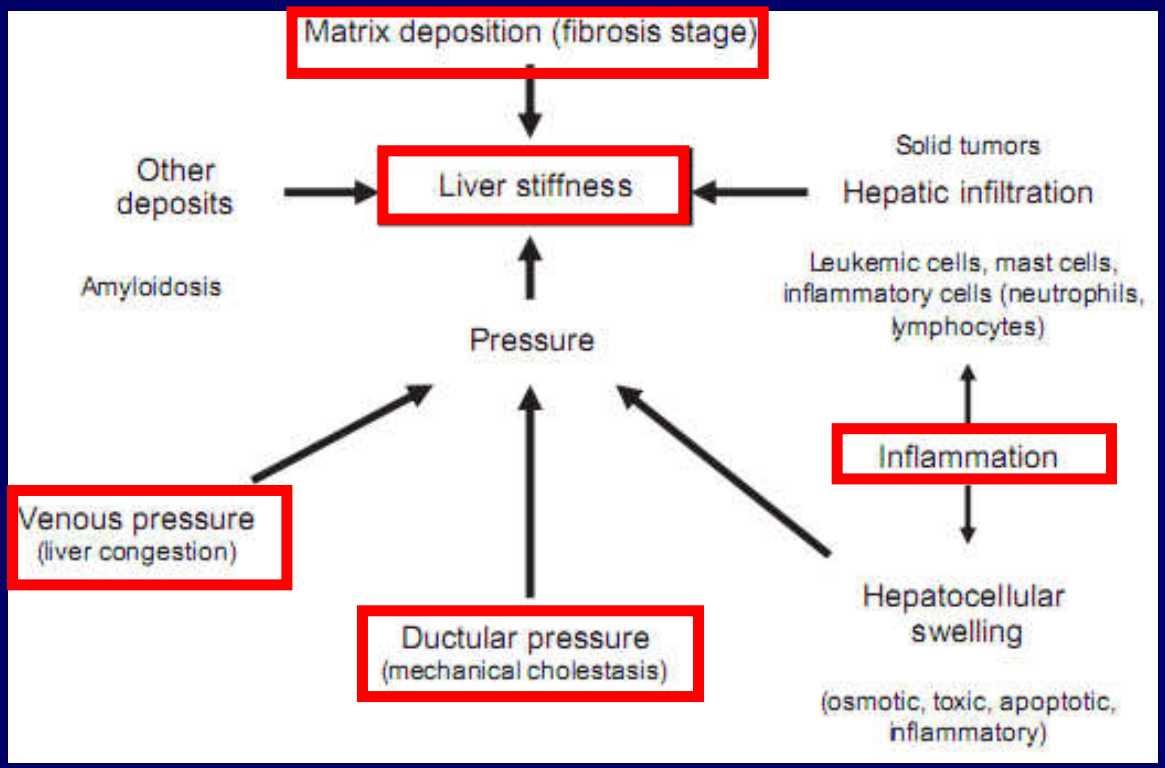
# Spectrum of Clinical Applications of ARFIE

- Liver fibrosis staging
- Noninvasive baseline evaluation and chronological surveillance
- Prognostication
- Treatment decision making
- Patient counseling
- Exclusion of cirrhosis

- In the chronically injured liver, fibrogenesis is the complex dynamic interplay among various hepatic cell types and mediators in which the process of perpetuation follows initiation.
- With the clinical application of magnetic resonance (MR) and ultrasound-based LSM, studies using MR elastography (MRE), FibroScan, and ARFI elastography have demonstrated significant correlations between liver stiffness and liver fibrosis.
- However, liver stiffness and liver fibrosis are not equivalent…➡

Chen et al. BMC GE 2012 Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in patients with chronic hepatitis C

# LSM




Mueller et al.
Hepatic Medicine-Evidence and Research 2012
Liver stiffness- a novel parameter for the diagnosis of liver disease

- Among the various host factors that affect LSM values, necroinflammation is most common in clinical settings.

- The swelling of hepatocytes, interstitial edema, and the infiltrates of inflammatory cells may increase LS in patients with acute hepatitis…

The effects of hepatic necroinflammatory activity on liver stiffness measurement (LSM) have varied in previous studies.

Positive correlation (dominant to date)

- Yoon et al.
- Chen et al.

...

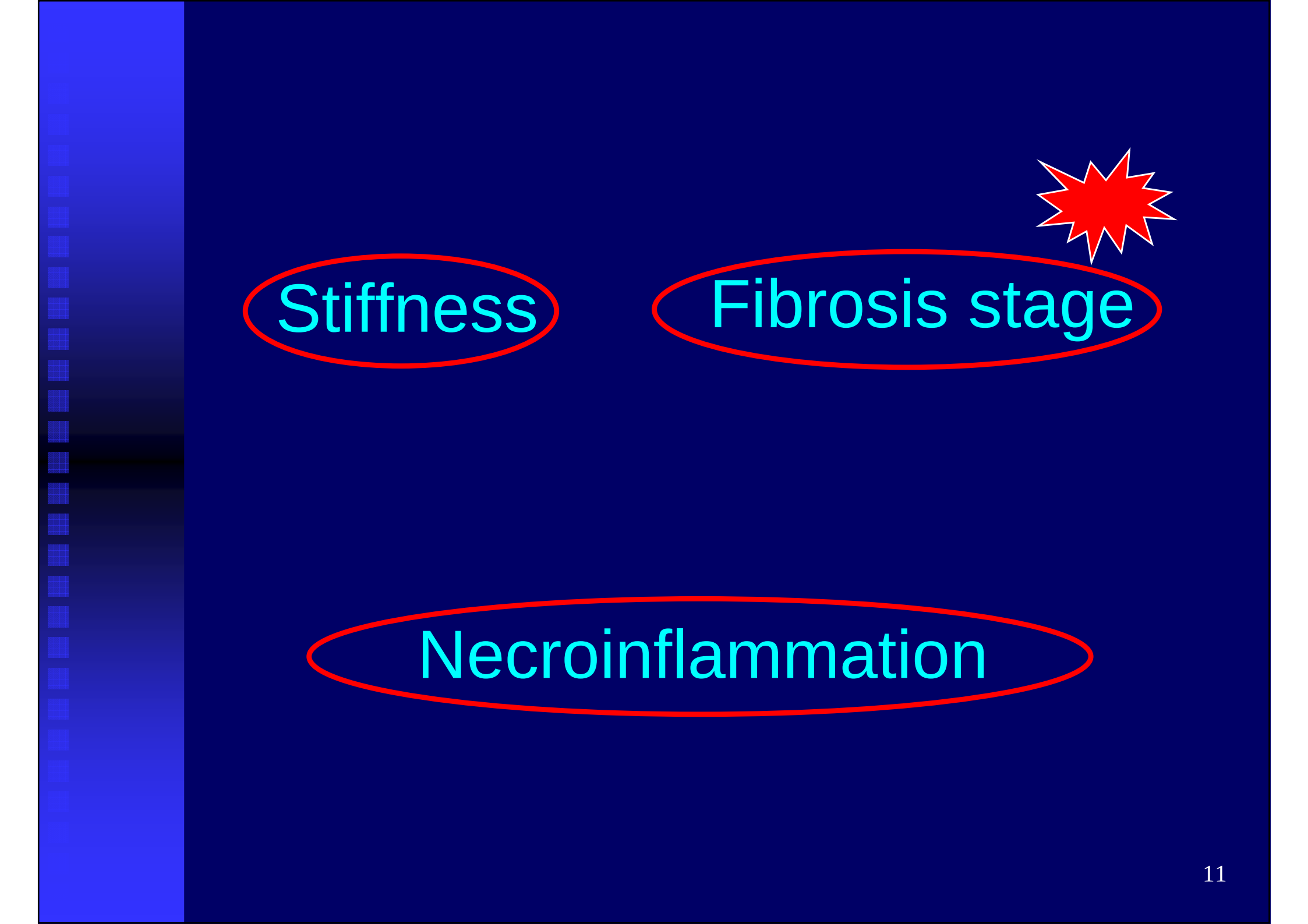
Insignificant correlation (only 2 reports)

- Rizzo et al.
- Colombo et al.

...

Negative correlation (only 1 report)

- Harata et al.


Stiffness
Fibrosis stage
Necroinflammation

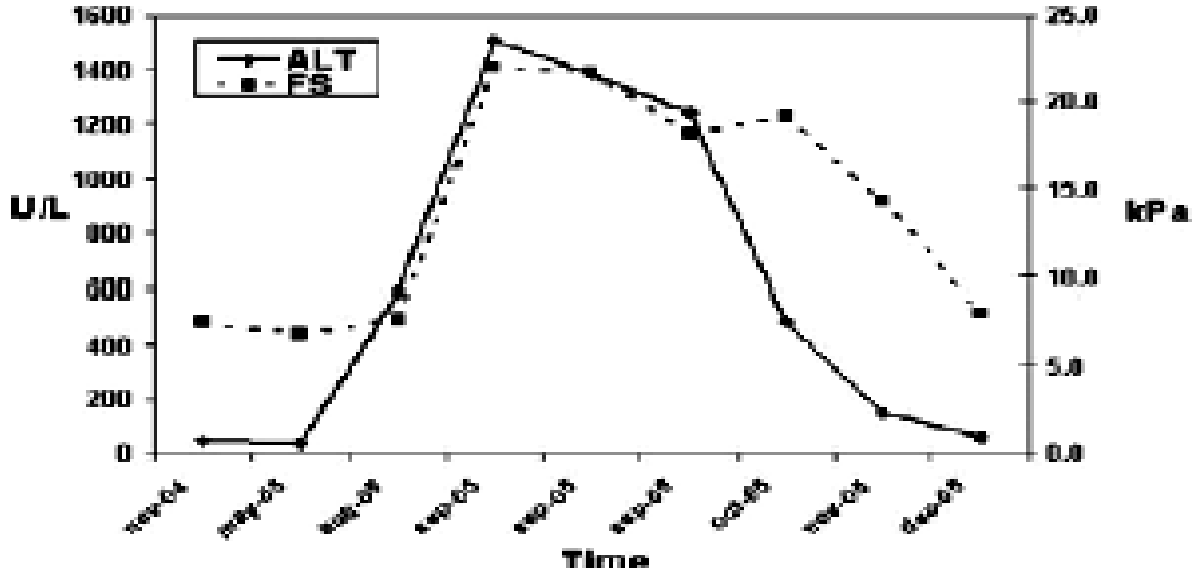



Fig. 3 Variations of FibroScan® values during the hepatitis exacerbation of a patient with chronic hepatitis B without fibrosis (METAVIR F0). At the ALT peak, liver stiffness values increased above the 14 kPa cut-off and decreased slowly thereafter to baseline values.

Coco et al. J Viral Hepatol 2007
Transient elastography-a new surrogate marker of liver fibrosis influenced by major changes of transaminases

- Despite the variation among previous investigations, several recent studies have demonstrated the necroinflammatory effects on liver stiffness by evolving analyses.

- In a longitudinal study using FibroScan, Sagir et al. observed false positivity for cirrhosis (cutoff > 12.5 kPa) in 15 of 20 non-cirrhotic patients with acute liver damage of various etiologies. In 6 patients, the LSMs dropped below 12.5 kPa with normalized ALT levels during follow-up…

# 15 cases > 12.5 kPa

**Table 1. Baseline Characteristics, Etiology of Acute Hepatitis, Stage of Fibrosis, and Initial Liver Stiffness in All Patients**

| Patient | Sex | Age (Years) | Etiology of Acute Hepatitis | Liver Biopsy Performed | Stage of Fibrosis (METAVIR) | ALT (IU/L) | Bilirubin (mg/dL) | AP (IU/L) | Initial Liver Stiffness (kPa) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 48 | HBV | Yes | F2 | 2510 | 27,89 | 149 | 67.8 |
| 2 | F | 37 | HBV | No | – | 1549 | 0.8 | 165 | 8.6 |
| 3* | M | 42 | HBV | No | – | 1550 | 2.96 | 84 | 21.3 |
| 4 | M | 64 | HBV | No | – | 779 | 5.82 | 323 | 26.3 |
| 5 | F | 72 | HBV | No | – | 5382 | 23.72 | 343 | 19.4 |
| 6 | M | 28 | HBV | No | – | 2084 | 30.28 | 172 | 27.7 |
| 7 | M | 61 | HBV | No | – | 1409 | 0.8 | 130 | 6.1 |
| 8 | M | 18 | HBV | No | – | 1931 | 10.68 | 294 | 7.1 |
| 9 | F | 21 | HAV | No | – | 1696 | 2.23 | 232 | 4.4 |
| 10 | F | 43 | Toxic | Yes | F1 | 151 | 31.8 | 170 | 52.3 |
| 11 | F | 34 | Toxic | Yes | F1 | 689 | 12.98 | 212 | 21.1 |
| 12 | M | 49 | Toxic | Yes | F1 | 193 | 21.38 | 220 | 39.7 |
| 13 | M | 59 | Toxic | Yes | F1 | 151 | 29.98 | 525 | 21.5 |
| 14 | M | 39 | Toxic | Yes | F2 | 250 | 2.57 | 602 | 34.8 |
| 15 | M | 81 | Toxic | Yes | F2 | 441 | 24.12 | 169 | 72 |
| 16 | F | 49 | Toxic | Yes | F1 | 2106 | 3.51 | 160 | 15.7 |
| 17 | F | 25 | Toxic | No | – | 171 | 14.98 | 416 | 6.3 |
| 18 | M | 26 | Autoimmune | Yes | F1 | 1931 | 2.44 | 123 | 45 |
| 19 | F | 64 | Autoimmune | Yes | F1 | 1045 | 0.84 | 273 | 13.6 |
| 20 | F | 47 | Autoimmune | Yes | F1 | 1096 | 16.29 | 428 | 29.2 |

Toxic hepatitis was due to nitrofurantoin (patient 10), prophylthiouracil (patient 11), amphetamine (patient 12), sirolimus (patient 13), efavirenz (patient 14), flumatid (patient 15), lamictal (patient 16), and opipramol (patient 17). The cutoff value for cirrhosis was 12.5 kPa. AP indicates alkaline phosphatase; F, female; HAV, hepatitis A virus; HBV, hepatitis B virus; and M, male.

*Patient 3 had a flare of chronic hepatitis B.

Sagir et al. Hepatology 2007

Transient elastography is unreliable

for detection of cirrhosis in patients with acute liver damage

**Table 2. Initial ALT and Liver Stiffness During the Acute Phase of Hepatitis and After Resolution of Acute Hepatitis**

| | Acute Phase | | After Resolution of the Acute Hepatitic Phase | |
|---|---|---|---|---|
| Patient | Initial Liver Stiffness (kPa) | ALT (Units/mL) | Liver Stiffness (kPa) | ALT (Units/mL) |
| 3* | 21.3 | 1550 | 11.6 | 28 |
| 4 | 26.3 | 779 | 7,9 | 12 |
| 5 | 19.4 | 5382 | 6.9 | 5 |
| 10 | 52.3 | 151 | 8.3 | 23 |
| 13 | 21.5 | 151 | 4.8 | 11 |
| 19 | 13.6 | 1045 | 6.8 | 30 |

The cutoff value for cirrhosis was 12.5 kPa.
*Patient 3 had a flare of chronic hepatitis B.

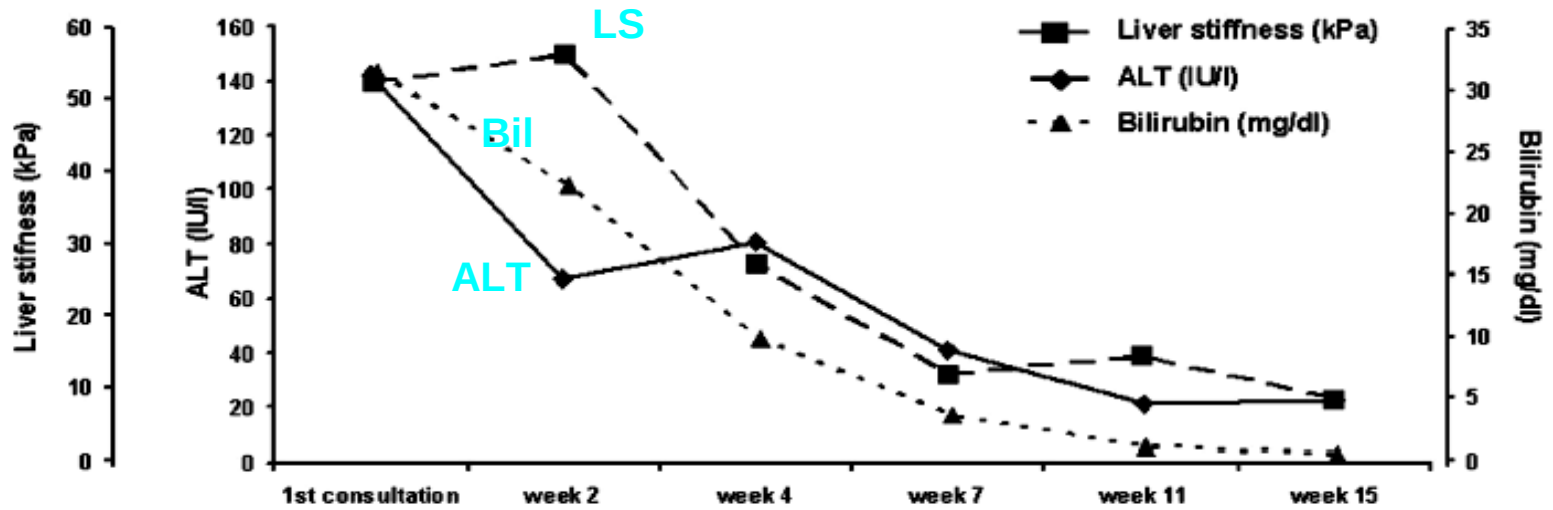



Fig. 1. Development of ALT, bilirubin, and liver stiffness during the course of nitrofurantoin-induced acute toxic hepatitis (patient 10).

Sagir et al. Hepatology 2007

Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage

- Using a longitudinal analysis, Arena et al. demonstrated significant correlations between sequential serum ALT levels and LSM results at different time points.

- Although these studies showed the need for caution when analyzing LSM in patients with necroinflammatory flares, they did not include regression estimates…

**Table 2. Sequential Determinations of Aminotransferase Levels (ALT, AST) and LSM During the Course of Acute Hepatitis**

| Patients (n, etiology) | I | | | II | | | III | | |
|---|---|---|---|---|---|---|---|---|---|
| | ALT | AST | LSM | ALT | AST | LSM | ALT | AST | LSM |
| 1, HBV | 2590 | 1477 | 10.1 | 1000 | 650 | 6.1 | 42 | 28 | 4.8 |
| 2, HCV | 917 | 813 | 8.8 | 367 | 123 | 5.9 | 70 | 32 | 4.9 |
| 3, HAV | 1437 | 980 | 9.8 | 713 | 435 | 7.4 | 75 | 79 | 5.4 |
| 4, HBV | 1057 | 911 | 12.6 | 317 | 347 | 12 | 80 | 72 | 6.5 |
| 5, HAV | 1117 | 616 | 8.8 | 234 | 41 | 8.8 | 45 | 32 | 5.5 |
| 6, HAV | 1291 | 632 | 7.2 | 543 | 276 | 4.8 | 78 | 56 | 4.2 |
| 7, HCV | 1175 | 618 | 10.4 | 198 | 111 | 8.8 | 48 | 35 | 6.9 |
| 8, HAV | 3159 | 1776 | 15.3 | 1147 | 832 | 12.1 | 62 | 78 | 6.8 |
| 9, HAV | 2154 | 1785 | 8.8 | 199 | 97 | 6.4 | 42 | 33 | 5.4 |
| 10, HBV | 1432 | 588 | 8.5 | 202 | 65 | 7.4 | 65 | 39 | 6.1 |
| 11, HAV | 2266 | 1628 | 10.2 | 1104 | 756 | 8 | 45 | 76 | 6.5 |
| 12, HBV | 1156 | 521 | 14 | 500 | 230 | 10.8 | 45 | 60 | 6.4 |
| 13, HAV | 2594 | 1720 | 15.3 | 1243 | 842 | 11.2 | 54 | 65 | 6 |
| 14, HCV | 628 | 455 | 11.4 | 301 | 147 | 6.2 | 25 | 26 | 6.1 |
| 15, HBV | 3191 | 2963 | 31 | 1540 | 1027 | 18.5 | 60 | 75 | 10 |
| 16, HBV | 5170 | 2521 | 21.3 | 2357 | 835 | 16 | 60 | 78 | 6.5 |
| 17, HBV | 2399 | 2735 | 14.4 | 1024 | 852 | 9.2 | 52 | 73 | 6.5 |
| 18, HBV | 2356 | 1298 | 9.9 | 987 | 564 | 8.9 | 80 | 52 | 6.2 |
| Mean values | 2004.9 ± 1115.4 | 1335.4 ± 795.9 | 12.7 ± 5.7 | 776.4 ± 580.6 | 457.2 ± 337.1 | 9.4 ± 3.6 | 57.1 ± 15.6 | 54.9 ± 20.3 | 6.2 ± 1.2 |

Aminotransferase levels and liver stiffness measurements at the 3 different time points: I. peak increase in aminotransferase; II. aminotransferase 50% or less of the peak; III. aminotransferase levels ≤ 2 ULN. Results are expressed in U/L for aminotransferase and in kPa for LSM. Mean values were reported ± SD. Abbreviations: LSM, liver stiffness measurement; ALT, aspartate aminotransferases; AST, alanine aminotransferases.

Arena et al. Hepatology 2008

Acute viral hepatitis increased liver stiffness values measured by transient elastography

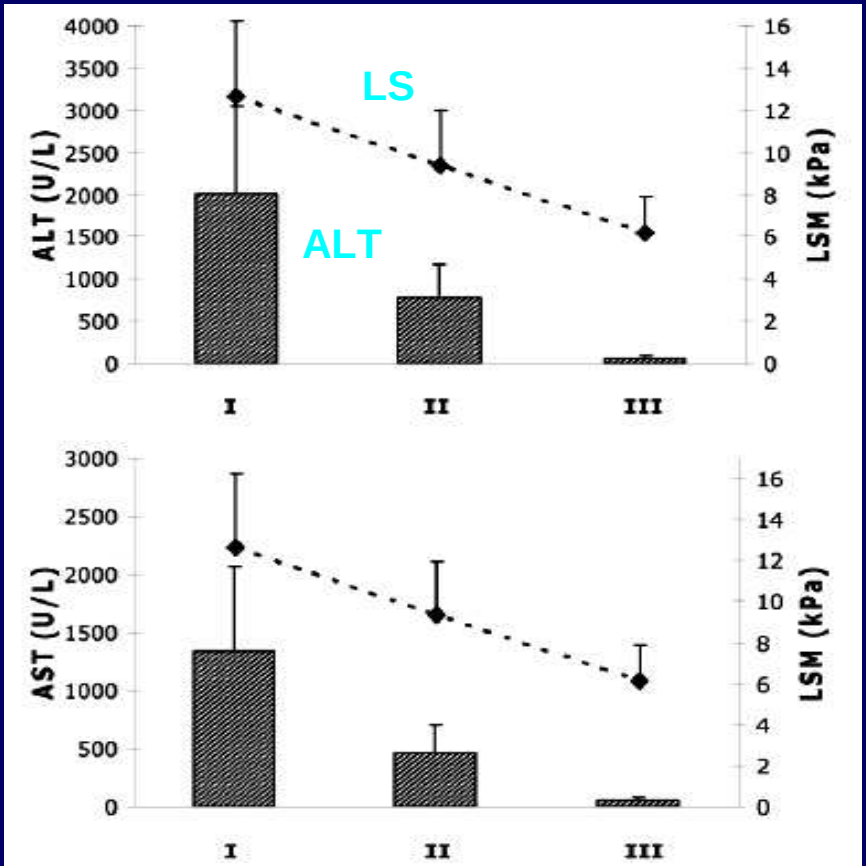



Fig. 1. Sequential relationship between aminotransferase levels (ALT and AST) and LSM at different time points (I. peak increase in aminotransferase; II. aminotransferase 50% or less of the peak; III. aminotransferase levels ≤ 2 ULN). The mean aminotransferase concentrations are reported in the primary y-axis in shaded columns, and the mean liver stiffness values (dashed line) are shown in the secondary y-axis. ALT, aspartate aminotransferases; AST, alanine aminotransferases; LSM, liver stiffness measurement; kPa, kilopascal.

Arena et al. Hepatology 2008

Acute viral hepatitis increased liver stiffness values measured by transient elastography

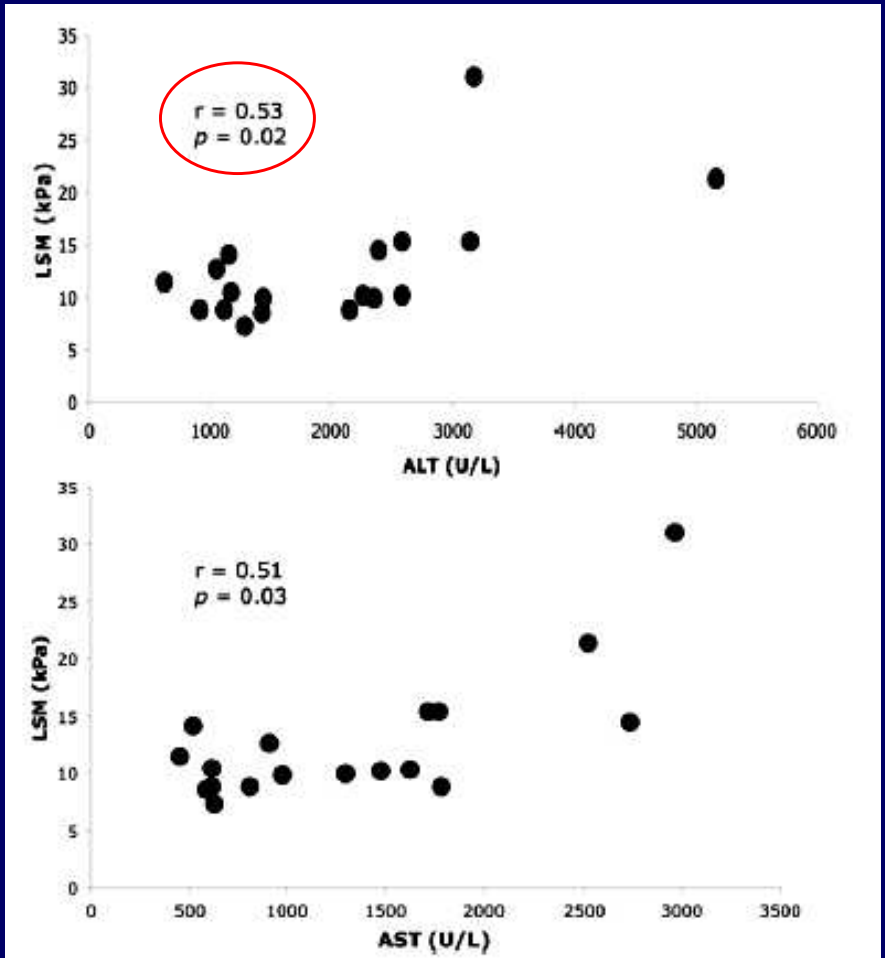



Fig. 2. Relationship between aminotransferase (ALT and AST) and LSM in whole patient population at the onset of acute viral hepatitis. ALT, aspartate aminotransferases; AST, alanine aminotransferases; LSM, liver stiffness measurement; kPa, kilopascal.

Arena et al. Hepatology 2008

Acute viral hepatitis increased liver stiffness values measured by transient elastography

- Seo et al. demonstrated that peak ALT levels significantly explained peak LSMs in 31 patients in acute hepatitis A via linear regressions adjusting for age and sex… ➡

n = 31, AHA

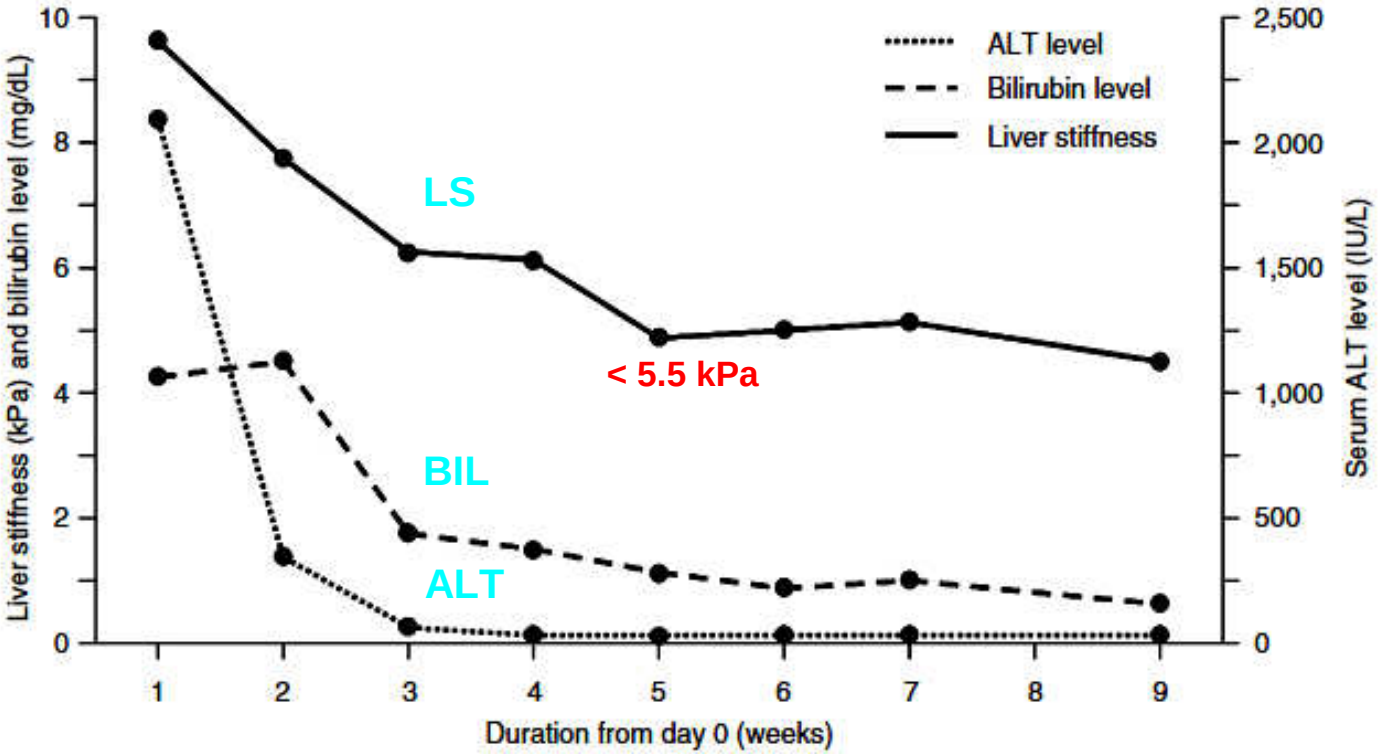



Figure 3. Changes in serum levels of ALT and BIL, and LSMs during the course of AHA.

Seo et al. Scand J Gastroenterol 2010
Dynamic changes in liver stiffness
during the course of acute hepatitis A

< 5.5 kPa

Table III. Linear regression analyses of peak LSMs and duration until normalization of LSMs.

| | Peak LSMs | | Duration until normalization of LSMs | |
|---|---|---|---|---|
| Variable | $P^a$ | β (95% CI) | $P^a$ | β (95% CI) |
| BMI | 0.879 | | 0.913 | |
| Peak ALT level | 0.003 | 0.002 (0.001–0.003) | 0.109 | |
| Peak BIL level | 0.969 | | 0.012 | 3.731 (0.892–6.570) |
| Peak INR | 0.001 | 11.301 (5.028–17.573) | 0.010 | 26.640 (6.929–46.350) |
| ALT level on peak-LSM day | <0.001 | 0.003 (0.001–0.004) | 0.912 | |
| BIL level on peak-LSM day | 0.324 | | <0.001 | 4.902 (2.520–7.284) |
| INR on peak-LSM day | <0.001 | 21.178 (13.699–28.658) | 0.283 | |
| Duration from Day 0 to peak-LSM day | 0.122 | | 0.813 | |
| Duration from Day 0 to peak-ALT day | 0.538 | | 0.645 | |
| Duration from Day 0 to peak-BIL day | 0.879 | | 0.470 | |
| Duration from Day 0 to peak-INR day | 0.977 | | 0.278 | |
| Duration from peak-ALT day to peak-LSM day | 0.136 | | 0.805 | |
| Duration from peak-BIL day to peak-LSM day | 0.232 | | 0.846 | |
| Duration from peak-INR day to peak-LSM day | 0.125 | | 0.995 | |

[a]Age and sex were adjusted.

Seo et al. Scand J Gastroenterol 2010
Dynamic changes in liver stiffness during the course of acute hepatitis A

- A cross-sectional study by Lee et al. showed that LSM using FibroScan in 158 patients was independently associated with histological necroinflammatory grading, but irrespective of serum ALT levels…

n = 158, CLD

- METHODS: We studied 158 patients with chronic liver disease who underwent transient elastography and liver biopsy sampling. Histologic findings on fibrosis and necroinflammatory activity in the biopsy specimens were evaluated according to the Korean Society of Pathologists Scoring System. Routine biochemical tests were performed according to standard methods.

- RESULTS: Liver stiffness was strongly correlated with liver fibrosis stage (Spearman coefficient=0.636, P<0.001), lobular activity (Spearman coefficient=0.359, P<0.001), and portoperiportal activity grade (Spearman coefficient=0.448, P<0.001). Liver stiffness was significantly associated with serum levels of total bilirubin (P=0.025), direct bilirubin (P=0.049), gamma-glutamyl transpeptidase (P=0.014), platelet count (P=0.004), albumin (P<0.001), and international normalized ratio (P<0.001). Multivariate analysis showed that fibrosis stage (B 3.50, P=0.009) and lobular activity grade (B 3.25, P=0.047) were independently associated with liver stiffness.

Lee da M et al.

Korean J Hepatol 2009

Factors associated with liver stiffness in chronic liver disease

- Fung et al reported a poor PPV (as low as 10%) for LSM by using FibroScan to diagnose true cirrhosis in 102 HBV-infected patients (median ALT: 89, range: 46-501 IU/L), among whom 32 patients had an LS value greater than 11.0 kPa... ➡

## Study Highlights

**WHAT IS CURRENT KNOWLEDGE**

- ✓ Transient elastography is useful as a non-invasive method for assessing liver fibrosis in chronic hepatitis B.
- ✓ Severe hepatitis flares can affect liver stiffness.

**WHAT IS NEW HERE**

- ✓ Transient elastography has an excellent negative predictive value for cirrhosis in chronic hepatitis B.
- ✓ Moderate inflammatory activity can also affect liver stiffness measurements and the accuracy of transient elastography.
- ✓ A cutoff of $< 7.1$ kPa can be used to exclude underlying significant fibrosis in chronic hepatitis B.
- ✓ Patients with occult hepatitis B infection have liver stiffness values that are similar to those in healthy subjects.

Fung et l. AJG 2010

Correlation of liver stiffness and histological features in healthy persons and in patients with occult hepatitis B, chronic active hepatitis B, or hepatitis B cirrhosis

- Multiple logistic regressions by Myers et al. showed that serum ALT levels greater than the optimal cutoff value 60 IU/L from ROC analysis were significantly correlated with the discordance (at least 2 stages between FibroScan and biopsy)...➡

n = 251, CLD

**Table 1.** Characteristics of patients according to discordance of at least two fibrosis stages between biopsy and liver stiffness measurement

| Variable | All patients ($n=251$) | Non-discordant results ($n=216$) | Discordant results ($n=35$) | *P*-value |
|---|---|---|---|---|
| Female sex | 34% (85) | 34% (74) | 31% (11) | 0.85 |
| Age, years | 49 (42–55) | 49 (42–55) | 52 (43–56) | 0.59 |
| Race | | | | |
| Caucasian | 60% (150) | 57% (124) | 74% (26) | 0.07 |
| Asian | 30% (76) | 33% (71) | 14% (5) | |
| Other/unknown | 10% (25) | 10% (21) | 11% (4) | |
| Aetiology | | | | |
| Hepatitis C | 53% (133) | 51% (111) | 63% (22) | 0.08 |
| Hepatitis B | 27% (68) | 30% (64) | 11% (4) | |
| NAFLD | 20% (50) | 19% (41) | 26% (9) | |
| BMI, kg/m$^2$* | 26 (23–30) | 25 (22–29) | 30 (25–33) | 0.0003 |
| Obesity (BMI $\geq 30$ kg/m$^2$)* | 26% (65) | 22% (48) | 51% (18) | 0.001 |
| Diabetes mellitus | 8% (20) | 7% (16) | 11% (4) | 0.50 |
| ALT, U/L† | 61 (39–92) | 59 (38–92) | 78 (60–93) | 0.01 |
| AST, U/L† | 44 (32–68) | 43 (31–65) | 54 (35–89) | 0.02 |
| Platelets, $\times 10^9$/L† | 222 (176–266) | 223 (178–261) | 207 (156–281) | 0.54 |
| APRI† | 0.53 (0.35–0.89) | 0.50 (0.34–0.85) | 0.65 (0.39–1.87) | 0.06 |
| Liver fibrosis F3-F4 at biopsy | 20% (51) | 22% (47) | 11% (4) | 0.18 |
| Necro-inflammation A2–A3‡ | 59% (117) | 58% (100) | 65% (17) | 0.53 |
| Steatosis > 33%‡ | 17% (39) | 16% (31) | 24% (8) | 0.32 |
| Biopsy length, cm§ | 2.4 (1.7–2.8) | 2.4 (1.7–2.8) | 2.2 (1.7–2.8) | 0.81 |
| Liver stiffness, kPa | 7.7 (5.3–11.6) | 6.8 (5.1–9.9) | 13.8 (11.8–21.3) | 0.0001 |
| Valid shots $\geq 10$ | 98% (246) | 98% (212) | 97% (34) | 0.53 |
| Success rate, %¶ | 100 (91–100) | 100 (91–100) | 100 (91–100) | 0.45 |
| IQR/median stiffness (IQR/M) | 0.16 (0.10–0.24) | 0.15 (0.09–0.23) | 0.23 (0.15–0.29) | 0.0007 |
| Interval between LSM and biopsy, days | 18 (0–60) | 16 (0–62) | 23 (5–44) | 0.81 |

14%

Myers et al. Liver Int 2010
Prevalence, risk factors and causes
of discordance in fibrosis staging
by transient elastography and liver biopsy

**Table 4.** Operating characteristics of the discordance risk score for discordance of at least two fibrosis stages between liver biopsy and transient elastography*

| Score (*n*) | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) | Accuracy, % (95% CI) |
|---|---|---|---|---|---|
| ≥0 (250) | 100 | 0 | 14 (10–19) | 0 | 14 (10–19) |
| ≥1 (208) | 97 (85–100) | 19 (14–25) | 16 (12–22) | 98 (87–100) | 30 (24–36) |
| ≥2 (87) | 71 (54–85) | 71 (65–77) | 28 (20–39) | 94 (89–97) | 71 (65–77) |
| ≥3 (22) | 34 (19–52) | 95 (92–98) | 55 (32–76) | 90 (85–93) | 87 (82–91) |

*1 point is assigned for each of BMI ≥30 kg/m$^2$, ALT ≥60 U/L and IQR/M ≥0.17. BMI missing in one patient.

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

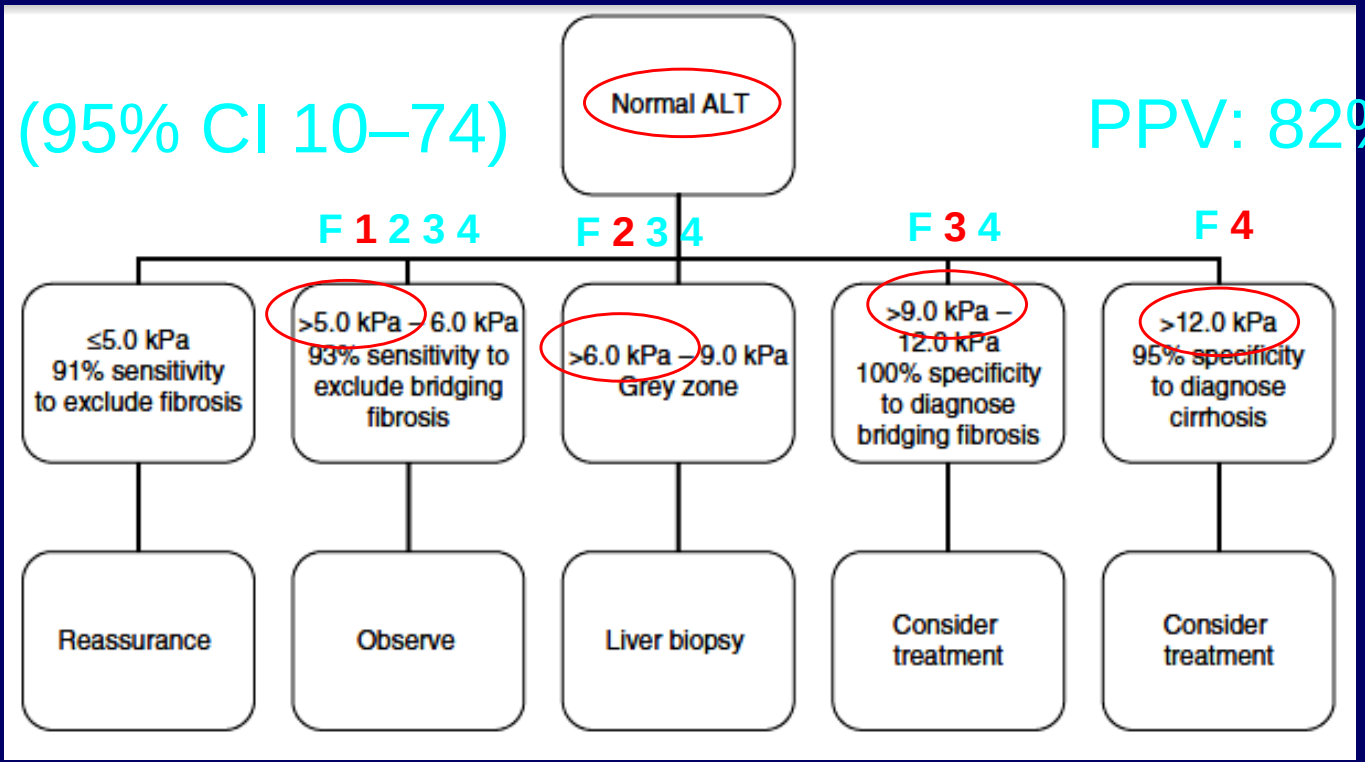
Myers et al. Liver Int 2010
Prevalence, risk factors and causes
of discordance in fibrosis staging
by transient elastography and liver biopsy

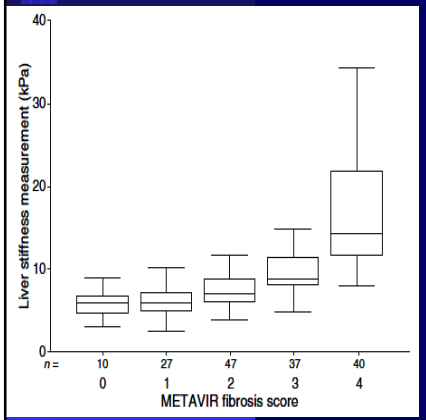
- Algorithms using distinct sets of cutoff values stratified by reference and elevated serum ALT levels have been developed, … ➡

n = 161, CHB

NPV: 38% (95% CI 10–74)

PPV: 82% (48–97)

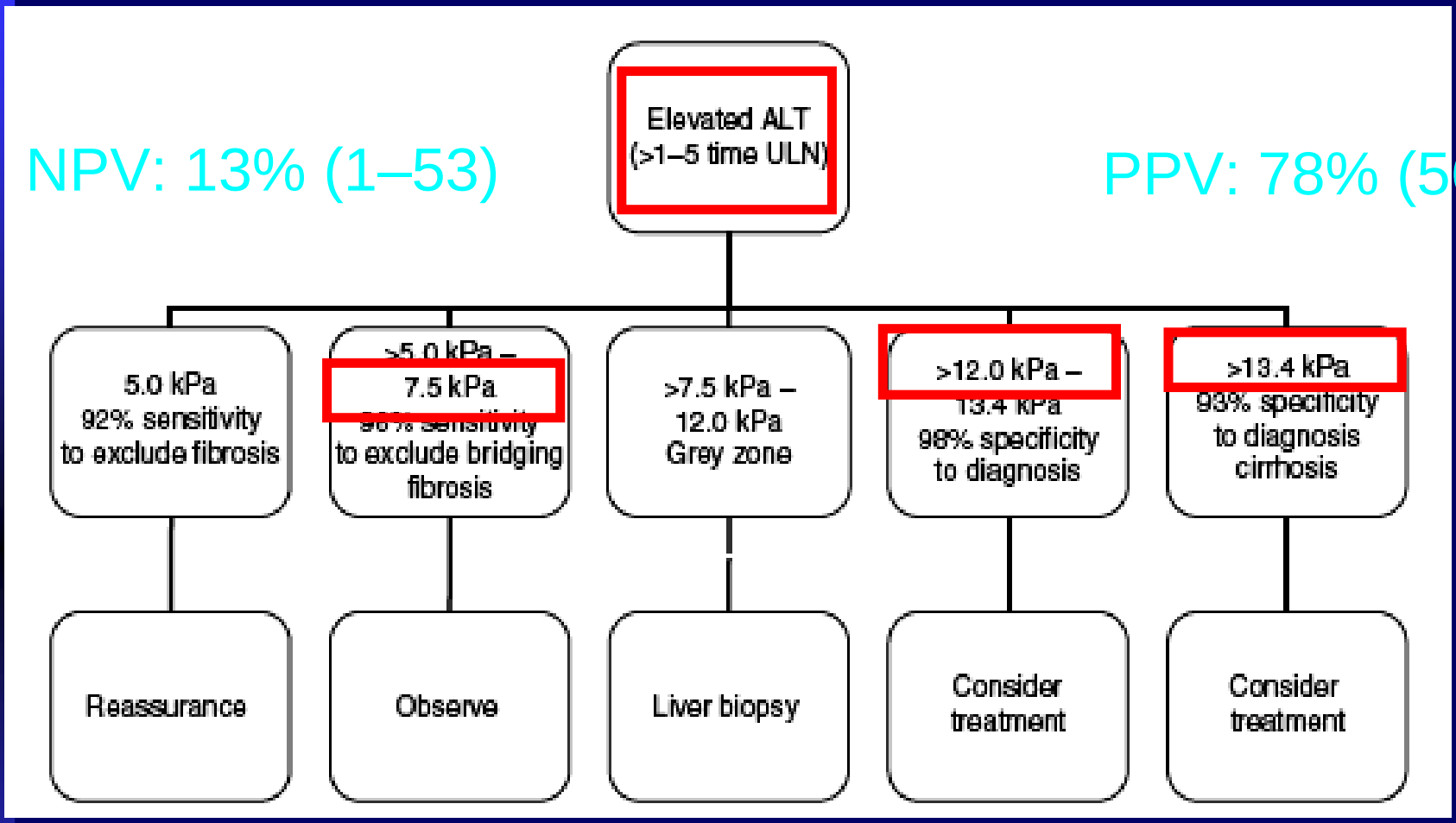



Chan et al. J Viral Hepat 2009
Alanine aminotransferase-based algorithms
of liver stiffness measurement
by transient elastography (Fibroscan)
for liver fibrosis in chronic hepatitis B

NPV: 13% (1–53)

PPV: 78% (56–92)




Chan et al. J Viral Hepat 2009
Alanine aminotransferase-based algorithms
of liver stiffness measurement
by transient elastography (Fibroscan)
for liver fibrosis in chronic hepatitis B

n = 391, CHB

**Table 2.** Comparisons and uni/multivariate analysis of variables to identify independent factors for predicting cirrhosis

| | Patients with F ≤ 3 (*n* = 151) | Patient with F4 (*n* = 179) | Univariate analysis | Multivariate analysis |
|---|---|---|---|---|
| Variables | | | | |
| Age (years) | 36.42 ± 13.75 | 49.73 ± 9.15 | < 0.001 | NS |
| Sex (male:Female) | 86:65 | 93:86 | 0.364 | – |
| BMI (kg/m$^2$) | 23.32 ± 3.35 | 23.44 ± 3.00 | 0.863 | – |
| LSM (kPa) | 7.53 ± 2.70 | 20.99 ± 14.37 | < 0.001 | < 0.001 |
| White cell count (10$^9$/L) | 6.208 ± 1.892 | 5.142 ± 2.012 | < 0.001 | NS |
| Haemoglobin (mmol/L) | 2.22 ± 0.25 | 2.10 ± 0.27 | 0.002 | NS |
| Platelet count (10$^9$/L) | 218.88 ± 58.75 | 137.33 ± 45.7 | < 0.001 | 0.001 |
| Prothrombin time (INR) | 1.01 ± 0.11 | 1.09 ± 0.12 | < 0.001 | NS |
| Total bilirubin (μmol/L) | 17.00 ± 5.95 | 21.08 ± 4.76 | < 0.001 | NS |
| Albumin (g/L) | 44.7 ± 4.3 | 40.4 ± 6.4 | 0.740 | – |
| AST (U/L) | 63.03 ± 33.43 | 48.52 ± 40.70 | 0.079 | – |
| ALT (U/L) | 109.9 ± 59.09 | 49.09 ± 32.28 | 0.001 | NS |
| Bun (mmol/L) | 4.37 ± 1.19 | 4.80 ± 2.68 | 0.218 | – |
| Creatinine (μmol/L) | 81.26 ± 13.25 | 79.50 ± 15.89 | 0.472 | – |
| Spleen diameter (cm) | 9.47 ± 1.35 | 11.47 ± 1.94 | < 0.001 | < 0.001 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; INR, international normalized ratio; NS, not significant.

Kim et al. Liver Int 2010

A novel liver stiffness measurement-based prediction model for cirrhosis in hepatitis B patients

LSPI = (LSM x spleen diameter / platelet count) x 100

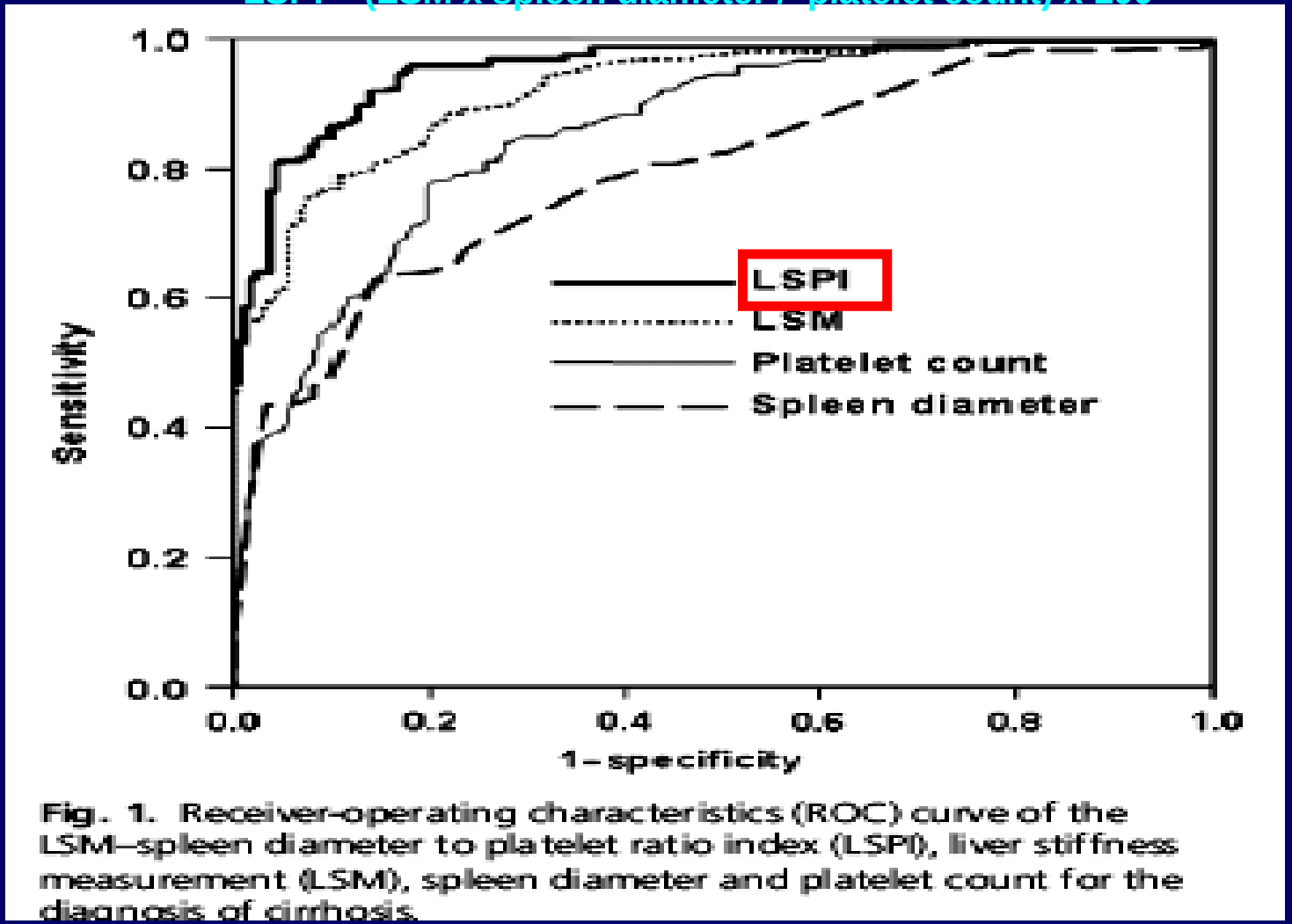



Fig. 1. Receiver-operating characteristics (ROC) curve of the LSM–spleen diameter to platelet ratio index (LSPI), liver stiffness measurement (LSM), spleen diameter and platelet count for the diagnosis of cirrhosis.

Kim et al. Liver Int 2010

A novel liver stiffness measurement-based prediction model for cirrhosis in hepatitis B patients

Table 4. Validation of the suggested predictive threshold values of the LSM–spleen diameter to platelet ratio index for the prediction of cirrhosis in each group from bootstrap samples

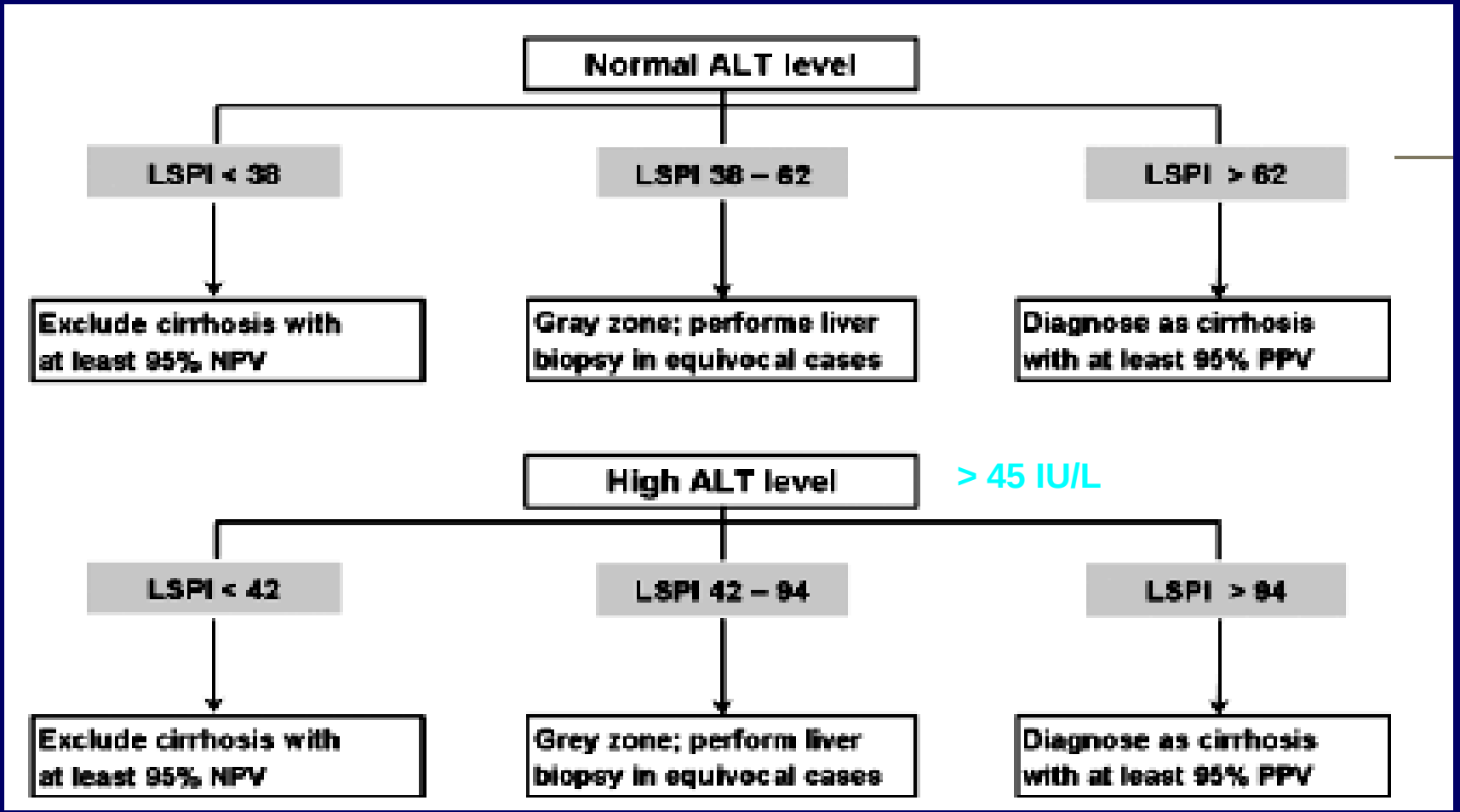
| | LSPI | NPV (%) | PPV (%) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| Normal ALT level | | | | | |
| Lower limit (at least 95% NPV) | 38 | 95.8 (83.8–99.3) | 82.8 (73.1–90.2) | 98.0 (92.1–99.7) | 68.8 (53.8–81.4) |
| Upper limit (at least 95% PPV) | 62 | 81.3 (68.7–90.5) | 95.5 (87.8–98.8) | 85.9 (75.8–92.9) | 93.8 (83.6–98.3) |
| High ALT level > 45 IU/L | | | | | |
| Lower limit (at least 95% NPV) | 42 | 95.1 (84.8–98.9) | 73.3 (61.9–83.0) | 96.3 (88.3–99.2) | 67.3 (54.1–78.8) |
| Upper limit (at least 95% PPV) | 94 | 76.4 (65.5–85.3) | 96.4 (86.0–99.4) | 67.4 (53.8–79.2) | 97.6 (90.7–99.6) |

In parentheses, 95% CI.

ALT, alanine aminotransferase; LSPI, LSM–spleen diameter to platelet ratio index; NPV, negative predictive value; PPV, positive predictive value.

Kim et al. Liver Int 2010

A novel liver stiffness measurement-based prediction model for cirrhosis in hepatitis B patients

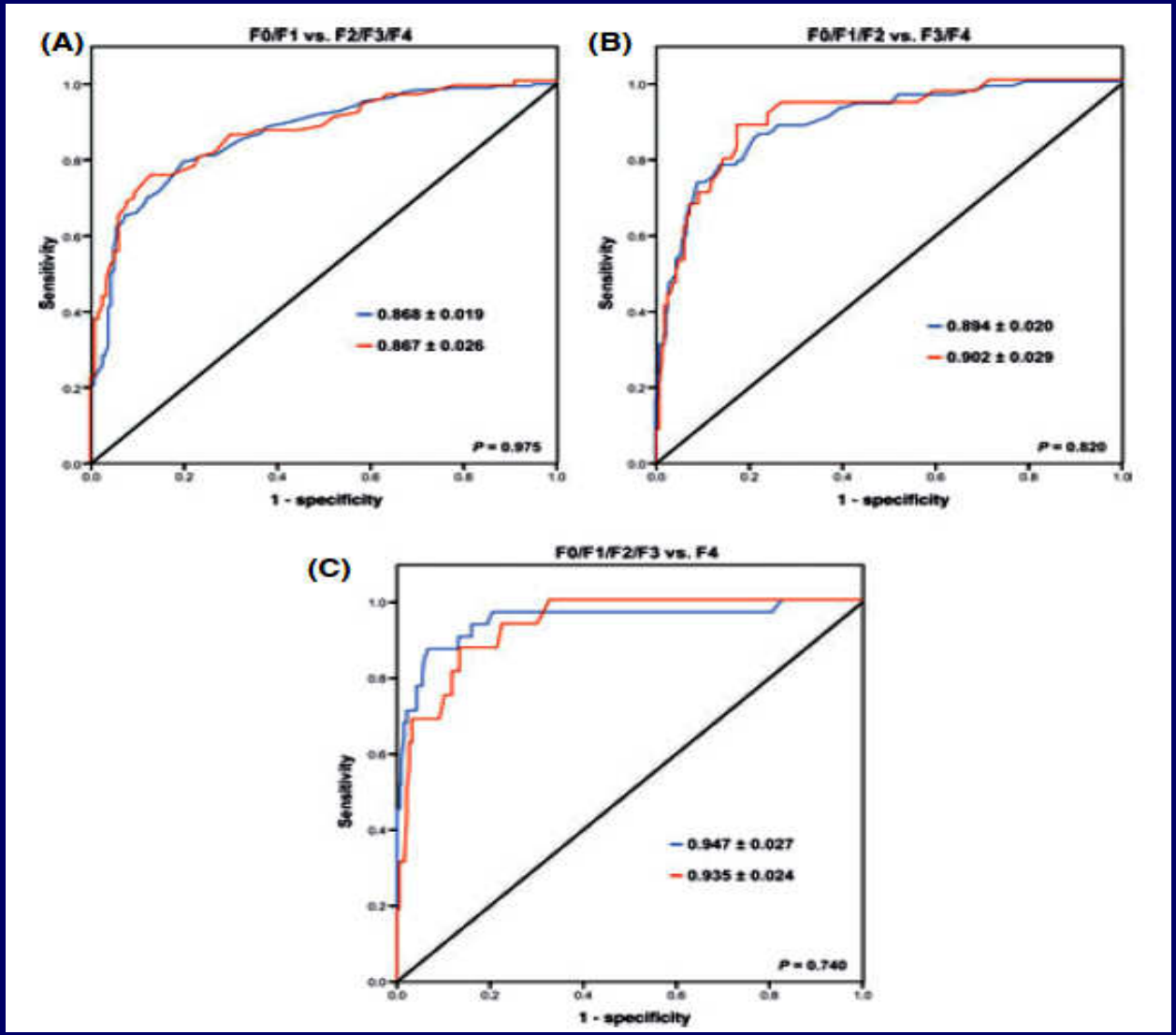



Kim et al. Liver Int 2010

A novel liver stiffness measurement-based prediction model for cirrhosis in hepatitis B patients

- …but ALT specific cutoff values did not significantly enhance the diagnostic performances in a study of 202 HBV-infected patients using FibroScan…

n = 202, HBV; n = 363, HCV




Cardoso et al. LI 2012

Direct comparison of diagnostic performance of TE in patients with chronic hepatitis B and chronic hepatitis C

# HBV

**Table 3.** Comparison of diagnostic accuracy of transient elastography in predicting significant fibrosis (METAVIR F2/F3/F4), advanced fibrosis (METAVIR F3/F4) and cirrhosis (METAVIR F4) in 186 HBV patients with distinct ALT levels, according to the cut-off values proposed by Marcellin *et al.* (11) and by Chan *et al.* (12)

| | ALT | Proposed cut-offs (kPa) | | PREV (%) | ACC (%) | SEN (%) | SPE (%) | PPV (%) | NPV (%) | LR (+) | LR (–) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Significant fibrosis | ≤1 ×ULN | Marcellin | 7.2 | 27 | 84 | 61 | 92 | 73 | 87 | 7.49 | 0.42 |
| | | Chan | 6.0 | | 72 | 78 | 69 | 48 | 89 | 2.54 | 0.32 |
| | 1–5 ×ULN | Marcellin | 7.2 | 48 | 80 | 74 | 86 | 83 | 78 | 5.34 | 0.31 |
| | | Chan | 7.5 | | 79 | 70 | 88 | 84 | 76 | 5.78 | 0.34 |
| Advanced fibrosis | ≤1 ×ULN | Marcellin | 8.1 | 10 | 93 | 86 | 93 | 60 | 98 | 12.86 | 0.15 |
| | | Chan | 9.0 | | 93 | 71 | 95 | 63 | 97 | 14.29 | 0.30 |
| | 1–5 ×ULN | Marcellin | 8.1 | 17 | 78 | 90 | 76 | 44 | 97 | 3.74 | 0.14 |
| | | Chan | 12.0 | | 88 | 53 | 96 | 71 | 91 | 12.11 | 0.50 |
| Cirrhosis | ≤1 ×ULN | Marcellin | 11.0 | 5 | 96 | 67 | 97 | 50 | 98 | 21.33 | 0.34 |
| | | Chan | 12.0 | | 97 | 67 | 98 | 67 | 98 | 42.67 | 0.34 |
| | 1–5 ×ULN | Marcellin | 11.0 | 10 | 87 | 73 | 88 | 40 | 97 | 6.06 | 0.31 |
| | | Chan | 13.4 | | 92 | 55 | 96 | 60 | 95 | 13.64 | 0.47 |

ACC, accuracy; LR(+), positive likelihood ratio; LR(–), negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; PREV, prevalence of the evaluated fibrosis staging; SEN, sensitivity; SPE, specificity; ×ULN, times the upper limit of normal.

Cardoso et al. LI 2012

Direct comparison of diagnostic performance of TE in patients with chronic hepatitis B and chronic hepatitis C

- Tapper et al. further delineated the positive necroinflammatory effects on LSM using FibroScan through linear regressions in 684 HCV patients with METAVIR F0, F1 and F2.
- Logistic regressions also showed that false positivity of liver fibrosis staging was associated with both histological and serum hepatic necroinflammatory activity…➡

n = 684, HCV

Table 2

| Table 2: Associations of Study Variables with Liver Stiffness | | | | | | |
|---|---|---|---|---|---|---|
| | Univariate Linear Regression | | | Multivariate Linear Regression | | |
| Variable | β | Standard Error | p value | β | Standard Error | p value |
| Grade of Inflammation | | | | | | |
| Grade 1 | 1.45 | 1.58 | 0.36 | | | |
| Grade 2 | 0.52 | 0.48 | 0.28 | | | |
| Grade 3 | 9.68 | 1.93 | 6.96E-07 | 9.07 | 1.85 | **1.15E-06** |
| ALT (x ULN) | 0.76 | 0.12 | **5.30E-10** | 0.69 | 0.12 | **1.85E-08** |
| Steatosis (yes/no) | 0.41 | 0.13 | 0.18 | | | |
| Age (per year) | 0.04 | 0.026 | 0.09 | | | |
| Gender | 0.072 | 0.24 | **0.003** | .. | .. | **ns** |
| BMI (kg/m$^2$) | 0.19 | 0.06 | **0.0009** | .. | .. | **ns** |
| Diagnosis of diabetes (yes/no) | 0.84 | 0.47 | 0.08 | | | |
| Diagnosis of HIV (yes/no) | 0.44 | 0.59 | 0.45 | | | |
| Alcohol Use (yes/no) | 0.34 | 0.26 | 0.19 | | | |

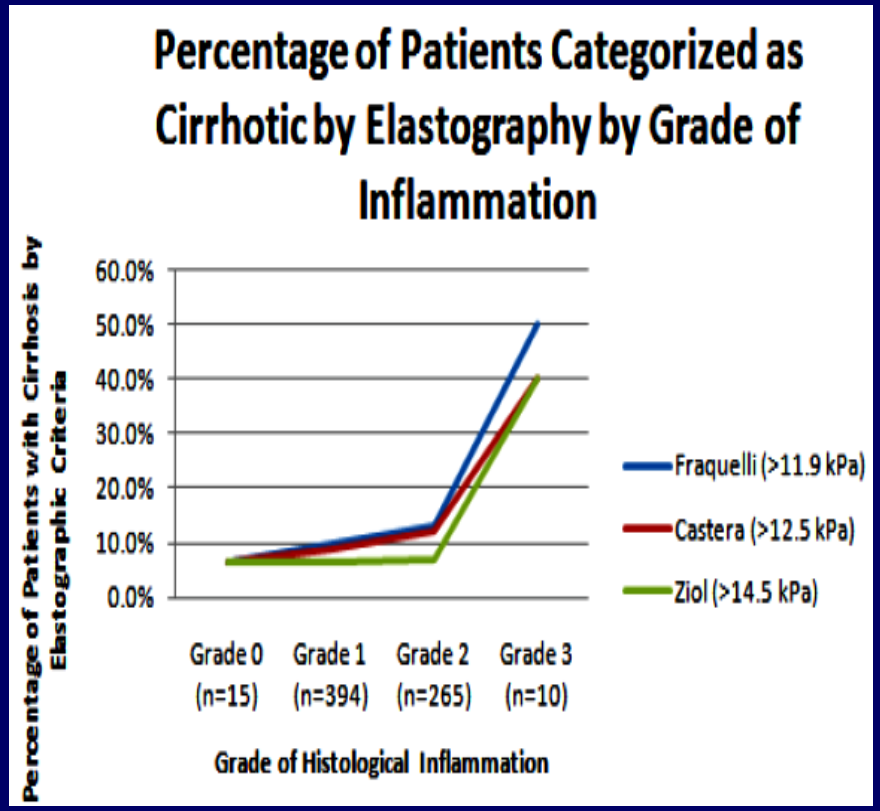
Tapper Clin Gastroenterol Hepatol 2012
Levels of Alanine Aminotransferase Confound Use of Transient Elastography to Diagnose Fibrosis in Patients with CHC

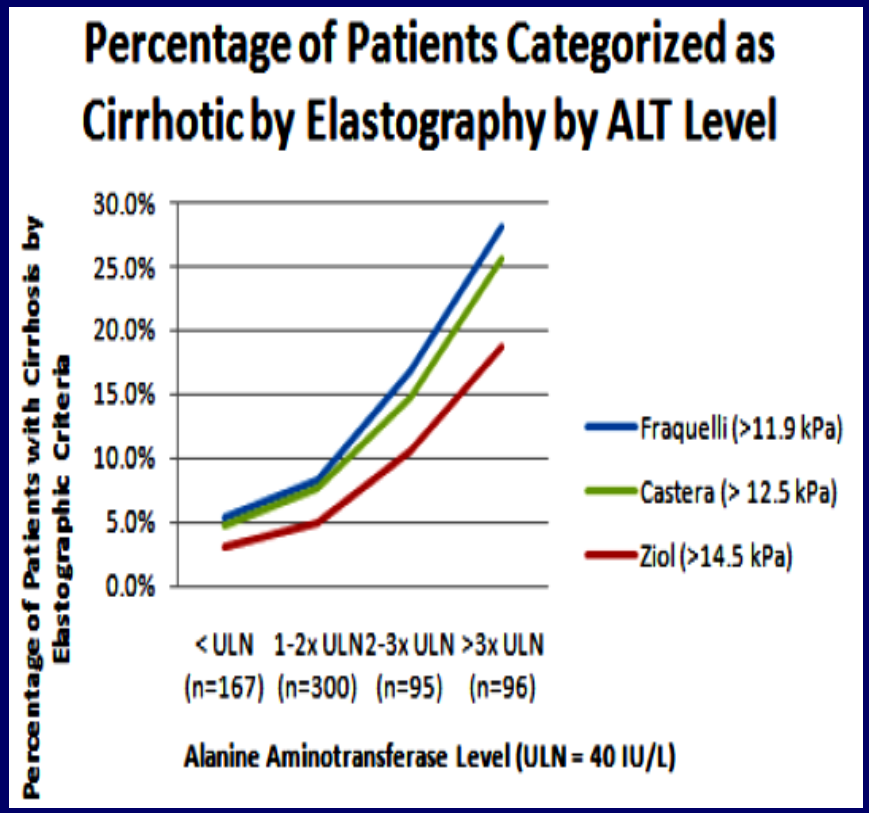
**Table 4**

Table 4: The Effect of Inflammation on the Odds of a Falsely Significant Liver Stiffness Measurement in Patients with F0-F1 Fibrosis

| | 9.5 kPa Cutoff for ≥ F3 Fibrosis (Castera) | 10.3 kPa Cutoff for ≥ F3 Fibrosis (Fraquelli) | 11.9 kPa Cutoff for Cirrhosis (Fraquelli) | 12.5 kPa Cutoff for Cirrhosis (Castera) | 14.5 kPa Cutoff for Cirrhosis (Ziol) |
|---|---|---|---|---|---|
| | Odds Ratio (95% CI) | Odds Ratio (95% CI) | Odds Ratio (95% CI) | Odds Ratio (95% CI) | Odds Ratio (95% CI) |
| ALT | | | | | |
| > ULN (40 IU/L) | **2.46 (1.24-4.88)** | **2.22 (1.08-6.24)** | 2.34 (0.95-5.75) | 2.34 (0.88-6.24) | 2.41 (0.69-8.34) |
| > 2x ULN (80 IU/L) | **5.64 (3.30-9.59)** | **3.25 (1.83-5.75)** | **4.27 (2.15-8.49)** | **3.76 (1.80-7.85)** | **4.82 (1.91-12.15)** |
| > 3x ULN(120 IU/L) | **3.90 (2.01-7.56)** | **2.02 (1.00-4.10)** | **2.42 (1.17-5.01)** | **3.49 (1.5-8.10)** | **3.62 (1.32-9.98)** |

Tapper Clin Gastroenterol Hepatol 2012
Levels of Alanine Aminotransferase Confound Use of Transient Elastography to Diagnose Fibrosis in Patients with CHC




Tapper Clin Gastroenterol Hepatol 2012
Levels of Alanine Aminotransferase Confound Use of Transient Elastography to Diagnose Fibrosis in Patients with CHC

- Yoon et al. used ARFI elastography to demonstrate a significant correlation (Pearson's r = 0.431, *P* < .05) between LSM values and serum ALT levels, and a marked positive effect of histological necroinflammatory activity on LSM.

- However, this study did not adjust for other relevant essential covariates…

n = 250, CLD

**Table 2** Histological information and LSM values obtained by use of ARFI elastography according to fibrosis stage and activity grade ($n = 250$)

| Fibrosis | | Activity | | ARFI elastography |
|---|---|---|---|---|
| Stage | Total | Grade | *n* | Velocity (m/s) |
| 0 | 45 (19) | 1 | 11 | 1.06 (0.87–1.85) |
| | | 2 | 17 | 1.08 (0.68–1.95) |
| | | 3 | 11 | 1.29 (0.84–2.11) |
| | | 4 | 6 | 1.60 (1.45–2.62) |
| 1 | 35 (14) | 1 | 5 | 1.10 (1.05–1.37) |
| | | 2 | 23 | 1.22 (0.76–4.65) |
| | | 3 | 6 | 1.30 (0.83–2.37) |
| | | 4 | 1 | 1.57 (0.93–2.45) |
| 2 | 70 (28) | 1 | 2 | 1.08 (0.80–1.35) |
| | | 2 | 27 | 1.32 (1.02–2.27) |
| | | 3 | 30 | 1.53 (0.87–3.10) |
| | | 4 | 11 | 1.94 (1.06–2.34) |
| 3 | 39 (15) | 1 | 3 | 1.23 (1.08–2.00) |
| | | 2 | 9 | 1.64 (1.12–1.92) |
| | | 3 | 19 | 1.89 (0.90–3.43) |
| | | 4 | 8 | 2.14 (1.25–2.91) |
| 4 | 61 (24) | 1 | 5 | 1.37 (1.18–2.65) |
| | | 2 | 41 | 1.65 (1.05–3.30) |
| | | 3 | 11 | 1.92 (0.94–2.63) |
| | | 4 | 4 | 2.21 (1.45–3.20) |

Variables are expressed as median (range) or *n* (%)

# Yoon Dig Dis Sci 2012
# Liver Stiffness Measurement Using Acoustic Radiation Force Impulse (ARFI) Elastography and Effect of Necroinflammation

**Table 3** Correlations between LSM values obtained by use of ARFI elastography and other clinical data ($n = 250$)

| Variable | LSM values obtained by use of ARFI elastography |
|---|---|
| Age (years) | 0.261* |
| Gender | −0.080 |
| Body mass index (kg/m$^2$) | 0.008 |
| Serum albumin (g/dL) | −0.458* |
| Total bilirubin (mg/dL) | 0.246* |
| Alanine aminotransferase (IU/L) | 0.431* |
| Prothrombin time (INR) | 0.233* |
| Platelet count ($10^3$/mm$^3$) | −0.142* |
| Fibrosis stage | 0.575* |
| Activity grade | 0.319* |
| APRI | 0.437* |

Indicated by R, *$P < 0.05$ by Pearson product-moment correlation

LSM, liver stiffness measurement; ARFI, acoustic radiation force impulse; FS, Fibroscan; INR, international normalized ratio; APRI, aspartate aminotransferase-to-platelet ratio index

Yoon Dig Dis Sci 2012

Liver Stiffness Measurement Using Acoustic Radiation Force Impulse (ARFI) Elastography and Effect of Necroinflammation

**Table 3 Three multiple linear regression models to identify independent significant factors that explain liver stiffness**

| Variable | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | B | SE | P | B | SE | P | B | SE | P |
| Age, year | -.003 | .004 | .512 | -.004 | .004 | .353 | -.004 | .004 | .366 |
| Male gender | -.193 | .084 | **.024** | -.194 | .083 | **.020** | -.124 | .085 | .147 |
| BMI, kg/m$^2$ | .032 | .013 | **.013** | .036 | .012 | **.005** | .026 | .012 | **.041** |
| INR | .972 | .572 | .092 | .890 | .564 | .117 | 1.146 | .573 | **.048** |
| Platelet, x10$^9$/L | -.003 | .001 | **.002** | -.003 | .001 | **.003** | -.002 | .001 | **.007** |
| METAVIR | | | | | | | | | |
| F2 | .089 | .113 | .430 | .049 | .113 | .666 | .123 | .114 | .284 |
| F3 | .739 | .154 | **<.001** | .670 | .155 | **<.001** | .670 | .161 | **<.001** |
| F4 | .989 | .168 | **<.001** | .954 | .165 | **<.001** | .892 | .171 | **<.001** |
| **ALT/ULN** | | | | | | | | | |
| **≧1<2x** | .307 | .110 | **.006** | | | | | | |
| **≧2<3x** | .429 | .122 | **.001** | | | | | | |
| **≧3** | .523 | .133 | **<.001** | | | | | | |
| **ActiTest A score** | | | | .717 | .163 | **<.001** | | | |
| **METAVIR A** | | | | | | | | | |
| **A1** | | | | | | | .189 | .100 | .061 |
| **A2-3** | | | | | | | .551 | .144 | **<.001** |
| $R^2$ | | .661 | | | .662 | | | .651 | |
| adjusted $R^2$ | | .629 | | | .636 | | | .620 | |

Variable references: female gender, METAVIR F1, ALT/ULN <1x, METAVIR A0; ALT, serum alanine aminotransferase; B, coefficient; INR, international normalized ratio of prothrombin time; SE, standard error of coefficient; ULN, upper limit of normal.

Chen et al. BMC GE 2012 Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in patients with chronic hepatitis C

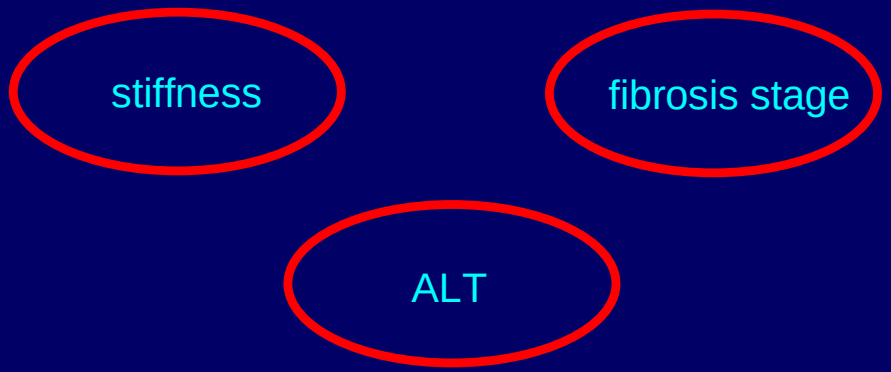
**Table 4 Factors associated with false positivity in patients with METAVIR F1, F2 and F3**

| Variable | Non FP n = 77 | FP n = 32 | OR(95% CI) | *P* value |
|---|---|---|---|---|
| Age, year | 50.8(1.4) | 53.4(2.0) | | .316 |
| Gender, male/female (n) | 35/42 | 16/16 | | .679 |
| BMI, kg/m$^2$ | 24.34(0.37) | 25.37(0.68) | | .155 |
| HCV genotype, 1/non-1 (n) | 38/39 | 15/17 | | .836 |
| HCV RNA, x 10$^6$, copies/mL | 7.14(1.12) | 10.61(3.12) | | .194 |
| ALT, IU/L | 83.01(9.40) | 133.88(15.02) | | .004 |
| ALT/ULN (n) | | | | |
| <1x | 24 | 2 | reference | |
| ≧1x <2x | 25 | 10 | 4.8(0.9-24.2) | .057 |
| ≧2x <3x | 16 | 5 | 3.8(0.6-21.7) | .140 |
| ≧3x | 12 | 15 | 15.0(2.9-76.6) | .001* |
| ActiTest A score (n) | | | | - |
| 0.00-0.35 | 31 | 2 | reference | |
| 0.36-0.75 | 24 | 13 | 8.4(1.7-40.8) | .008* |
| 0.76-1.00 | 22 | 17 | 11.9(2.5-57.2) | .002* |
| Bilirubin, umol/L | 15.76(0.56) | 19.30(1.12) | | .002 |
| Cr, umol/L | 70.82(2.82) | 74.14(4.55) | | .817 |
| INR | 1.00(0.01) | 1.05(0.02) | | .007 |
| Na, meq/L | 137.94(0.28) | 137.81(0.46) | | .527 |
| Platelet, x 10$^9$/L | 184.21(6.20) | 158.31(9.37) | | .025 |
| METAVIR F1/2/3 (n) | 38/32/7 | 8/8/16 | | <.001 |
| METAVIR A (n) | | | | |
| A0 | 28 | 3 | reference | |
| A1 | 45 | 15 | 3.1(0.8-11.7) | .094 |
| A2-3 | 4 | 14 | 32.7(6.4-166.5) | <.001* |
| Hepatic steatosis S0/1/2/3/4(n) | 10/28/35/3/1 | 5/9/17/1/0 | | .903 |
| Liver SWV, m/s | 1.34(0.03) | 2.40(0.11) | | <.001 |
| FibroTest, F score | 0.51(0.03) | 0.72(0.04) | | <.001 |

Chen et al. BMC GE 2012 Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in patients with chronic hepatitis C

# Conclusion

- Although necroinflammation exhibits positive effects on LS after adjusting for liver fibrosis stages,
- It exhibited negative effects on liver fibrosis staging after adjusting for LS
- Nonetheless, patients with higher ALT levels have been shown to be at increased risk of advanced liver fibrosis without adjusting for LS



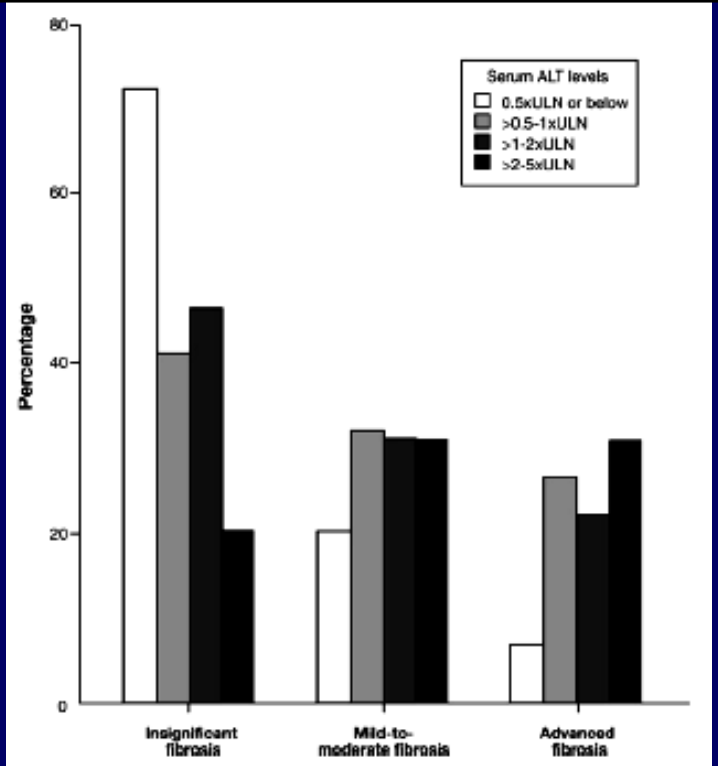



**Figure 2.** Bar charts on the prevalence of different severities of liver fibrosis in (*A*) different age groups and (*B*) different serum ALT levels.

**Table 2.** Risks of Advanced Fibrosis According to Different Serum Alanine Aminotransferase Levels Based on Our Cut-Off Levels (58 IU/L) and Gender-Specific Cut-Off Levels

| ALT levels | N (%)[a] | n/N (%)[b] | Odds ratio (95% confidence interval) | *P* value |
|---|---|---|---|---|
| ULN of 58 IU/L for both sexes | | | | |
| ≤0.5 × ULN | 73 (16.1%) | 5/73 (6.8%) | Referent | |
| >0.5–1 × ULN | 172 (38.0%) | 46/172 (26.7%) | 5.0 (1.9–13.1) | <.001 |
| >1–2 × ULN | 150 (33.1%) | 33/150 (22.0%) | 3.8 (1.4–10.3) | .005 |
| >2–5 × ULN | 58 (12.8%) | 31/58 (31.0%) | 6.1 (2.1–17.8) | <.001 |
| ULN of 30 IU/L for men and 19 IU/L for women | | | | |
| ≤1 × ULN | 80 (18%) | 8 (10%) | Referent | |
| >1–2 × ULN | 127 (28%) | 25 (20%) | 2.2 (0.9–5.2) | .06 |
| >2–5 × ULN | 196 (43%) | 50 (26%) | 3.1 (1.4–6.9) | .004 |
| >5 × ULN | 50 (11%) | 18 (36%) | 5.0 (2.0–12.8) | <.001 |

[a]Number (and percentage) of patients with that particular ALT level among the whole cohort.
[b]Number (and percentage) of patients suffering from advanced fibrosis among that particular ALT level.

Wong et al. CGH 2009 Clinical factors associated with liver stiffness in hepatitis B e antigen-positive chronic hepatitis B patients

- In contrast to results indicating positive necroinflammatory effects on liver stiffness, Harata et al. identified a negative correlation between serum ALT levels and liver stiffness in patients with cholestasis.
- Cholestasis is a condition in which the release of hydrostatic pressure with synchronous necroinflammatory activity can, paradoxically, reduce the values of LSM using FibroScan…➡

n = 29

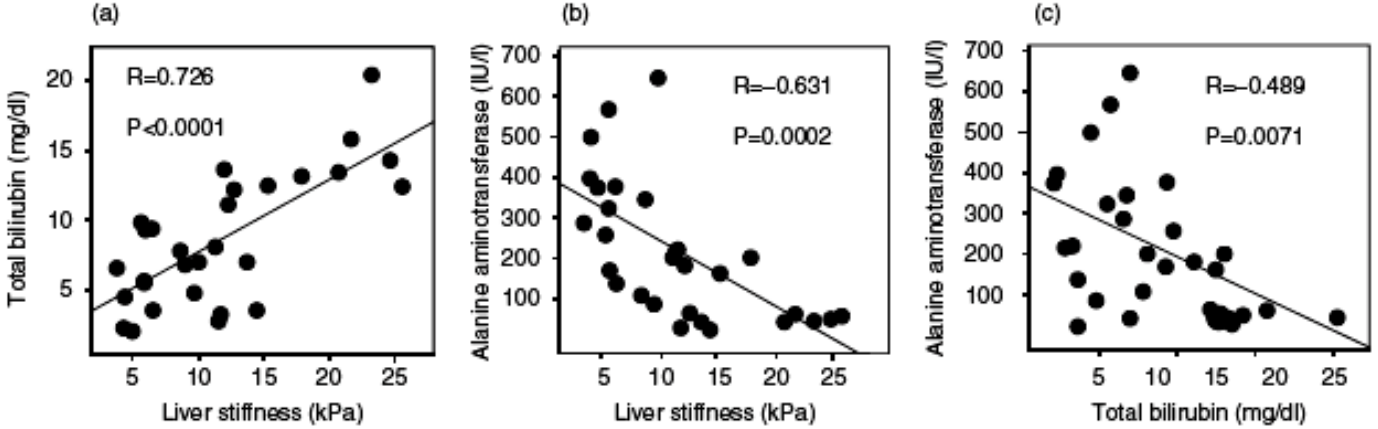



Figure 1 Correlation of liver stiffness with total bilirubin levels and alanine aminotransferase levels before biliary drainage. (a) Liver stiffness was positively correlated with total bilirubin levels ($r = 0.726$, $P < 0.0001$). (b) Liver stiffness was negatively correlated with alanine aminotransferase levels ($r = -0.631$, $P = 0.0002$). (c) Serum bilirubin levels were negatively correlated with alanine aminotransferase levels ($r = -0.489$, $P = 0.0071$).

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Table 2 Factors correlating with liver stiffness of the patients with extrahepatic cholestasis

| | Linear regression analysis | | Multiple regression analysis | |
|---|---|---|---|---|
| | *r* | *P* | β | *P* |
| Cause (benign diseases/carcinomas) | | $P = 0.0401$* | | NS |
| Sex (female/male) | | NS | | |
| Age (year) | | NS | | |
| Total bilirubin (mg/dL) | $r = 0.726$ | $P < 0.0001$ | $\beta = 0.774$ | $P = 0.0005$ |
| Direct bilirubin (mg/dL) | $r = 0.728$ | $P < 0.0001$† | | |
| AST (IU/L) | $r = -0.481$ | $P = 0.0082$ | | NS |
| ALT (IU/L) | $r = -0.631$ | $P = 0.0002$ | $\beta = -0.014$ | $P = 0.0138$ |
| ALP (IU/L) | | NS | | |
| γ-GTP (IU/L) | $r = -0.334$ | $P = 0.0764$ | | NS |
| WBC (/μL) | | NS | | |
| CRP (mg/dL) | | NS | | |
| Diameter of common bile duct (mm) | | NS | | |
| *R* | | | | 0.792 |
| Adjusted $R^2$ | | | | 0.599 |
| *F* | | | | 21.9 |
| *P* | | | | $P < 0.0001$ |

*Mean values of liver stiffness were compared between the patients with benign diseases and those with carcinomas by Student's *t*-test.
†Direct bilirubin levels were not included because of their close correlation with total bilirubin levels.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; γ-GTP, γ-glutamyl transpeptidase; NS, not significant; WBC, white blood cells.

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# Solutions anticipated for the near future

- We are currently developing a study design that will allow the analysis of the dynamic effects of necroinflammation on LSM over a short timeframe, during which changes in the fibrosis stage are not significant.
- Cutoff variability among previous studies on the LSM-based assessment of fibrosis may have resulted from the diverse etiologies of hepatitis, ethnicity, variable patient profiles, and prolonged intervals between liver biopsy and the acquisition of LSM. Any significant time lag between a biopsy and an ultrasound-based assessment of stiffness can affect LSM because of changes in fibrosis characteristics.
- Direct tissue and gene markers will also be employed.
- A larger sample will allow the randomization of training and validation cohort assignments, as well as the external validation of the necroinflammation-incorporated diagnostic approach.

# LSM

Submission under review: regarding the noninvasive diagnostic tool – ARFIE in CHB patients

Diagnostic index for advanced liver fibrosis in Asian chronic hepatitis B patients based on necroinflammation and liver stiffness measurement

- Validity
- Compared with competing tests
- Cutoffs
- Associated (host) factors
- Diagnostic index