# CHAPTER I

# INTRODUCTION

According to the American Association for the Study of Liver Disease (AASLD), nonalcoholic fatty liver disease (NAFLD) requires two entities: (1) evidence of hepatic steatosis, either by imaging or by histology, and (2) there are no causes for secondary hepatic fat accumulation such as alcohol consumption, steatogenic medication, or hereditary disorders. NAFLD is histologically further categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes. NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.[1]

NAFLD is now the commonest cause of chronic liver disease in many developed countries. Up to a third of the population have evidence of steatosis on imaging. Due to the metabolic risk factors, patients with NASH have an increased risk of cardiovascular death as well as liver related mortality. NASH can progress to cirrhosis, which puts patients at risk of liver-related complications.[2]

The features of NAFLD are closely related to cryptogenic cirrhosis. Patients with NAFLD are also at increased risk for HCC, but this risk is likely limited to those with advanced fibrosis and cirrhosis.[1]

Liver biopsy has been considered to be the gold standard for assessing the degree of liver fibrosis. Histology of the specimen allows clinicians to obtain diagnostic information not only on fibrosis but also on inflammation, necrosis, steatosis and hepatic deposits of iron or copper. However, several drawbacks of liver biopsy have been questioned to impair its accuracy and values in clinical practice. Liver biopsy samples are an extremely small (1/50000) part of the liver and therefore sampling error can occur even with optimal specimen. Moreover, despite the availability of widely validates standardized fibrosis scoring systems, accuracy of histological examination can be inherently compromised by a significant intraobserver and interobserver variability. Even an optimal biopsy specimen has a 25% rate of discordance for fibrosis staging which is further compounded by operator-related

expertise and specialization of the pathologist. Last but not least, liver biopsy is an invasive procedure-related morbidity (pain occurring in 20% and major complications such as intraperitoneal bleeding and hemobilia in 0.5%), with a mortality rate of 0.009-0.12%. Due to these limitations, consideration of liver biopsy as the "gold standard" has declined to "best available" standard, and has been challenged by the recent increasing availability and validation of noninvasive methods to assess liver fibrosis.[3]

The non-invasive methods to assess liver fibrosis can be divided in two main types: serum markers and imaging modalities. Serum markers are classified as direct (or class I) which represent extracellular matrix components (reflecting the pathophysiology of liver fibrogenesis), and indirect (or class II) which use routine laboratory data (reflecting the consequences of the liver damage). Direct and indirect markers may be used alone or, more commonly, in combination to produce composite scores.[3]

Table 1. Overview of non-invasive methods for the evaluation of liver fibrosis[3]

| a. Direct serum markers/panels | b. Indirect serum markers/panels | c. Patented serum panels | d. Imaging modalities |
|---|---|---|---|
| Hyaluronate [16] | AST/ALT ratio [28] | Fibrotest® [58] | Transient elastography (Fibroscan®) [84] |
| Laminin [17] | PGA [127] | Fibroindex® [66] | MR-elastography [86] |
| YKL-40 [18] | APRI [40] | Hepascore® [68] | Acoustic radiation force impulses (ARFI) [85] |
| Procollagen type I carboxy-terminal peptide (PICP) [19] | Forns index [43] | Fibrospect® [72] | Fibro-CT [87] |
| Procollagen type III amino-terminal peptide (PIIINP) [20] | FIB-4 [47] | Enhanced Liver Fibrosis score (ELF®) [76] | |
| Metalloproteinases (MMP)-1 and MMP-2 [21, 22] | Lok index [52] | Fibrometers® [71] | |
| Tissue inhibitors of the metalloproteinases (TIMPs) [21] | Fibrosis Probability Index (FPI) [36] | | |
| Transforming growth factor-β1 (TGF-β1) [23] | Goteborg University Cirrhosis Index (GUCI) [37] | | |
| MP3 [44] | Virahep-C model [38] | | |
| Microfibril-associated glycoprotein 4 (MFAP-4) [24] | SHASTA index [39] | | |
| | BAAT [134] | | |
| | NAFLD fibrosis score [136] | | |
| | BARD [139] | | |

*AST, aspartate transaminase; ALT, alanine transaminase; PGA, prothrombin time, gamma-glutamyl transpeptidase, apolipoprotein A1; APRI, aspartate transaminase to platelet ratio index; BAAT, body mass index, age, alanine transaminase, triglycerides; NAFLD, nonalcoholic fatty liver disease; MR, magnetic resonance; CT, computed tomography*

# CHAPTER II

# CLINICAL SCENARIO

## 2.1 Case Scenario

A 35 year-old woman came to the clinic complaining epigastric pain she has been suffering for 3 months prior admission. The pain is not radiating anywhere, and it is not related to meal time. At first, she felt the pain can be treated with omeprazole given by the doctors when she came to the clinic for her diabetes medication, but later she still feel the pain even though she had taken the medication. She had been on glibenclamide for diabetes which she had for 3 years. She also took statin for dyslipidemia. She has no other previous disease and no other medication.

On the physical examination, her vital is normal. Her weight is 60 kg and her height is 155 cm (BMI: 24,97). No icteric sclera. On abdominal examination, she had epigastric pain on palpation. Her liver and spleen is not palpable. No sign of cirrhosis.

She brought her last laboratory examination showed elevated transaminase (SGOT 88 SGPT 78), high blood glucose level (fasting glucose 155, 2 hour post prandial blood glucose 201), and dyslipidemia (triglyceride 223, total cholesterol 185, HDL 15, LDL 170). Her albumin level was 3.75 g/dl, total bilirubin 0.98 mg/dL, prothrombin time was 10,9 seconds (control 11,5 seconds), and APTT was 33,2 seconds (control 33,5 seconds). HBsAg and anti HCV was both negative. She then went on ultrasonography examination. From the examination, we found out that she had fatty liver.

She was diagnosed with non-alcoholic fatty liver disease, diabetes mellitus type 2, and dyslipidemia. We planned to give her vitamin E 1x400 IU, along with her diabetes and dyslipidemia medication. We educate the patient about the disease and the importance to control the metabolic syndrome.

To measure the fibrosis of her liver, we plan to do fibroscan. The patient planned to continue the medication in her hometown. We try to find best diagnostic study that can replace fibroscan so the patient can still monitor the fibrosis of her liver.

## 2.2 Clinical Question

“For nonalcoholic fatty liver disease, how is FIB 4 and NAFL score compare to fibroscan in measuring the fibrosis of the liver?”

# CHAPTER III

# METHODS

## 3.1 Searching the Evidence

Journal searching was conducted using Pubmed database and Cochrane on August 21st, 2015 using clinical queries broad filter for diagnostic articles, with a search command containing the words "((((NAFLD OR NASH OR NASH)) AND (fib 4 OR fib4)) AND (NAFL score OR NAFL index OR NAFLD score OR NAFLD index)) AND (fibroscan OR transient elastography)". There are 11 articles match these keywords in Pubmed and none was found in Cochrane. We searched only with full text availability and studies in adults. So we excluded 8 articles. The remaining 3 articles were decided to be used in the next process.

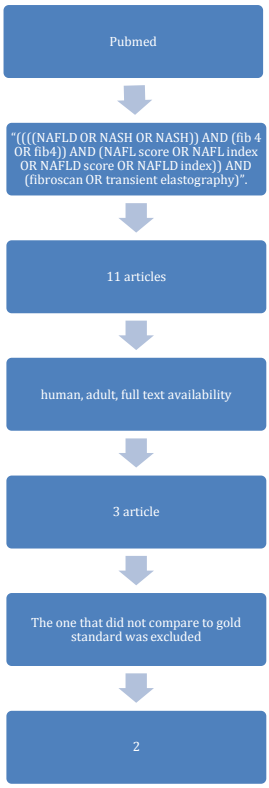


Figure 1. Flowchart of the evidence based research

## 3.2 Critical Appraisal

Appraisal was conducted using appraisal tool for diagnostic test taken from the Center of Evidence Based Medicine site.[4]

Table 2. Appraisal tool for diagnostic test[4]

| Appraisal Questions | Kumar et al | Wong et al |
|---|---|---|
| **1. Was the diagnostic test evaluated in a representative spectrum of patient (like those in whom it would be used in practice)?** | Yes | Yes |
| **2. Was the reference standard applied regardless of the index test result?** | Yes | Yes |
| **3. Was there an independent, blind comparison between the test index and an appropriate reference ('gold') standard of diagnosis?** | Yes | Yes |
| **4. Are test characteristics presented?** | Yes | Yes |
| **5. Were the methods for performing the test described in sufficient detail to permit replication?** | Yes | Yes |

After appraising those articles, we found that the 2 studies are good to discuss further.

## CHAPTER IV

## RESULT

In this evidence case report, we tried to answer about the performance of FIB 4 an NAFLD score compare to transient elastography (FibroScan®) in measuring the fibrosis for NAFLD patients.

Table 3. Characteristics of the studies[5,6]

| Characteristics | Kumar et al | Wong et al |
|---|---|---|
| **Aim of study** | Evaluate performance characteristics of liver stiffness measurement (LSM) by FibroScan in patients with different stages of NAFLD | Evaluate the accuracy of transient elastography for the diagnosis of fibrosis and cirrhosis in patients with NAFLD and to study factors associated with discordance between transient elastography and histology |
| **Patients and methods** | 307 subjects (120 NAFLD, 85 NAFLD related cirrhosis, and 102 healthy controls) in India underwent series of tests | 246 subjects with NAFLD in France and Hongkong underwent series of tests |
| **Results** | In NAFLD patients, LSM had significant correlation with fibrosis (r = 0,68, p<0.001), and increased progressively with increasing fibrosis (p<0,001). However, the difference between stage 1 and stage 2 fibrosis was not significant (p<0,07). The LSM in NAFLD without fibrosis and healthy controls was similar (p<0,37). The areas under receiver-operating characteristics (AUROC) curve of LSM for stages ≥1, ≥2, ≥3, and 4 were 0,82, 0,85, 0,94, and 0,96. For advanced fibrosis, the AUROC curve of LSM was 0,94, followed by FIB 4 (0,75), BARD score (0,68), NAFLD fibrosis score (0,66). | The AUROC of transient elastography for F3 or higher and F4 disease was 0,93 and 0,95, and was significantly higher than that of the aspartate aminotransferase-to-platelet ratioindex, FIB4, BARD, and NAFLD fibrosis scores (AUROC ranged from 0,62 to 0,81, p<0,05 for all comparisons). Liver stiffness was not affected by hepatic steatosis, necroinflammation, or BMI. By multivariate analysis, liver biopsy length less than 20 mm and F0-2 disease were associated with discordance. |
| **Conclusion** | LSM is a useful tool for evaluation of patient with NAFLD, and is the best among other noninvasive predictors of liver fibrosis | Transient elastography is accurate in most NAFLD patients. |

Table 4. Accuracy of transient elastography in Kumar study[5]

| Stage | AUROC (95% CI) | Cut-offs (KPa)[a] | Sn (%) | Sp (%) | PPV (%) | NPV (%) | LR+ | LR- | Post-test probability (%) | DA (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Stage 1 or more | 0.82 (0.75–0.89) | 6.1 | 78 | 68 | 87 | 53 | 2.51 | 0.31 | 87 | 76 |
| | | 4.3 | 93 | 22 | 76 | 53 | 1.19 | 0.31 | 76 | 74 |
| | | 7.2 | 58 | 91 | 92 | 43 | 4.63 | 0.48 | 92 | 66 |
| Stage 2 or more | 0.85 (0.78–0.92) | 7.0 | 77 | 78 | 75 | 81 | 3.66 | 0.28 | 75 | 78 |
| | | 5.8 | 90 | 48 | 59 | 86 | 1.76 | 0.19 | 59 | 67 |
| | | 8.2 | 61 | 90 | 82 | 73 | 5.76 | 0.43 | 82 | 76 |
| Stage 3 or more | 0.94 (0.89–0.98) | 9.0 | 85 | 88 | 68 | 95 | 7.16 | 0.16 | 68 | 87 |
| | | 7.8 | 96 | 78 | 43 | 98 | 4.43 | 0.04 | 57 | 82 |
| | | 11.2 | 71 | 93 | 57 | 91 | 10.9 | 0.30 | 76 | 88 |
| Stage 4 | 0.96 (0.92–1.0) | 11.8 | 90 | 88 | 41 | 98 | 7.61 | 0.11 | 41 | 88 |
| | | 10.6 | 100 | 82 | 33 | 100 | 5.50 | 0.0 | 33 | 83 |
| | | 19.4 | 70 | 98 | 78 | 97 | 38.1 | 0.30 | 77 | 95 |

*LSM* liver stiffness measurement, *NAFLD* nonalcoholic fatty liver disease, *AUROC* area under the receiver-operating characteristics curve, *Sn* sensitivity, *Sp* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *LR* likelihood ratio, *DA* diagnostic accuracy

[a] For each fibrosis stage, cutoffs with the highest combined sensitivity and specificity, sensitivity ≥90 %, and specificity ≥90 % are presented

Table 5. Accuracy of transient elastography in Wong study[6]

| Stage | AUROC | Cutoff (kPa) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | LR+ | LR− |
|---|---|---|---|---|---|---|---|---|
| ≥F2 | 0.84 (0.79-0.90) | 5.8 | 91.1 | 50.3 | 56.1 | 89.0 | 1.8 | 0.18 |
| | | 7.0 | 79.2 | 75.9 | 69.6 | 84.0 | 3.3 | 0.27 |
| | | 9.0 | 52.5 | 91.7 | 81.5 | 73.5 | 6.3 | 0.52 |
| ≥F3 | 0.93 (0.89-0.96) | 7.9 | 91.1 | 75.3 | 52.0 | 96.6 | 3.7 | 0.12 |
| | | 8.7 | 83.9 | 83.2 | 59.5 | 94.6 | 5.0 | 0.19 |
| | | 9.6 | 75.0 | 91.6 | 72.4 | 92.6 | 8.9 | 0.27 |
| F4 | 0.95 (0.91-0.99) | 10.3 | 92.0 | 87.8 | 46.0 | 99.0 | 7.5 | 0.091 |
| | | 10.3 | 92.0 | 87.8 | 46.0 | 99.0 | 7.5 | 0.091 |
| | | 11.5 | 76.0 | 91.0 | 48.7 | 97.1 | 8.4 | 0.26 |

For each fibrosis stage, cutoffs with sensitivity >90%, highest overall accuracy and specificity >90% were presented.
AUROC, area under the receiver-operating characteristics curve; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Table 6. Summary of Kumar study[5]

| Non-invasive markers | Fibrosis | | | *p* | | | |
|---|---|---|---|---|---|---|---|
| | Stage 0 (I) | Stage 1–2 (II) | Stage 3–4 (III) | Overall[a] | I–II | I–III | II–III |
| LSM, median (range) KPa | 5.2 (3.1–7.7) | 6.7 (3.5–25.7) | 16.8 (7.8–31.0) | <0.001 | <0.001 | <0.001 | <0.001 |
| AST/ALT ratio, median (range) | 0.75 (0.45–1.29) | 0.64 (0.41–1.27) | 0.89 (0.48–2.11) | <0.001 | 0.02 | 0.04 | <0.001 |
| APRI, median (range) | 0.47 (0.19–1.33) | 0.58 (0.19–3.59) | 0.74 (0.25–2.33) | 0.03 | 0.07 | 0.004 | 0.25 |
| BARD, median (range) | 0 (0–3) | 1 (0–4) | 2 (0–4) | 0.003 | 0.84 | 0.004 | 0.001 |
| FIB-4, median (range) | 0.96 (0.37–4.37) | 1.02 (0.19–4.25) | 1.77 (0.65–7.62) | 0.001 | 0.66 | 0.001 | <0.001 |
| NAFLD fibrosis score, median (range) | −2.2 (−8.8–1.5) | −2.2 (−6.9–1.1) | −1.6 (−4.8–6.0) | 0.009 | 0.73 | 0.04 | 0.005 |

[a] By Kruskal–Wallis test

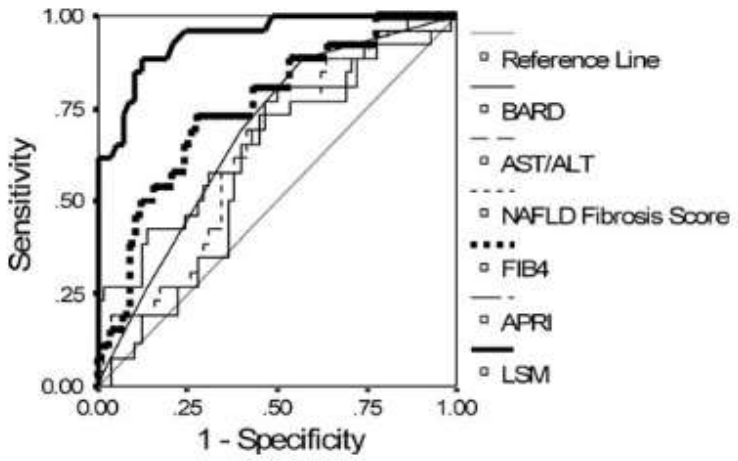


Figure 2. Diagnostic accuracy of the different noninvasive scoring systems in Kumar study[5]

Table 7. Summary of Wong study[6]

| | | ≥F3 | | | F4 | | |
|---|---|---|---|---|---|---|---|
| | N | AUROC (95% CI) | AUROC for Fibroscan (95% CI) | P | AUROC (95% CI) | AUROC for Fibroscan (95% CI) | P |
| AST/ALT | 245 | 0.66 (0.58-0.74) | 0.93 (0.89-0.96) | <0.0001 | 0.66 (0.55-0.77) | 0.95 (0.91-0.99) | <0.0001 |
| APRI | 245 | 0.74 (0.67-0.82) | 0.93 (0.89-0.96) | <0.0001 | 0.75 (0.64-0.85) | 0.95 (0.91-0.99) | <0.0001 |
| FIB-4 | 245 | 0.80 (0.74-0.87) | 0.93 (0.89-0.96) | 0.0004 | 0.81 (0.73-0.89) | 0.95 (0.91-0.99) | 0.001 |
| NAFLD fibrosis score | 228 | 0.75 (0.67-0.83) | 0.92 (0.89-0.96) | <0.0001 | 0.80 (0.69-0.92) | 0.95 (0.91-0.99) | 0.022 |
| BARD score | 244 | 0.69 (0.61-0.77) | 0.93 (0.89-0.96) | <0.0001 | 0.62 (0.50-0.75) | 0.95 (0.91-0.99) | <0.0001 |

*P* values refer to the comparison between transient elastography and other noninvasive tests.

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver-operating characteristics curve; CI, confidence interval.

Table 8. Comparative performance of noninvasive tests in Wong study[6]

| Noninvasive tests | Cutoffs | Se (%) | Sp (%) | PPV (%) | NPV (%) | +LR | −LR |
|---|---|---|---|---|---|---|---|
| Transient elastography | | | | | | | |
| (kPa)* | 7.9 | 77.3 | 68.8 | 44.0 | 90.5 | 2.5 | 0.33 |
| (failure n = 28) | 8.7 | 71.2 | 76.0 | 48.5 | 89.3 | 3.0 | 0.38 |
| | 9.6 | 63.6 | 83.7 | 55.3 | 87.9 | 3.9 | 0.43 |
| AST/ALT | 0.8 | 39.7 | 79.7 | 37.9 | 80.9 | 2.0 | 0.76 |
| | 1.0 | 20.6 | 90.1 | 39.4 | 78.4 | 2.1 | 0.88 |
| APRI | 0.5 | 65.1 | 72.3 | 42.3 | 86.9 | 2.4 | 0.48 |
| | 1.5 | 6.3 | 97.0 | 40.0 | 76.9 | 2.1 | 0.97 |
| FIB-4 | 1.30 | 65.1 | 80.2 | 50.6 | 88.0 | 3.3 | 0.44 |
| | 2.67 | 20.6 | 95.5 | 59.1 | 79.4 | 4.6 | 0.83 |
| NAFLD fibrosis score | −1.455 | 73.3 | 69.5 | 43.6 | 89.0 | 2.4 | 0.38 |
| | 0.676 | 18.3 | 96.3 | 61.1 | 78.6 | 4.9 | 0.85 |
| BARD score | 2 | 61.9 | 65.8 | 36.1 | 84.7 | 1.8 | 0.58 |

*In this "intention to treat" analysis, patients in whom ten valid liver stiffness measurements could not be acquired were included and counted as incorrect classification by transient elastography.

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

From these results, we can conclude that the accuracy of transient elastography to detect liver fibrosis was good. Both studies reached similar AUROC in each stage of fibrosis. In Wong study, the accuracy is better in detecting F2 or higher.

Regarding the comparative performance of noninvasive tests, we can see that transient elastography is superior to other noninvasive tests. In Kumar study, it appears that FIB4 is better than NAFLD fibrosis score. Similar to this result, Wong study also found that FIB4 has better AUROC than NAFLD fibrosis score in diagnosing fibrosis F3 and above (0.8 and 0.75, respectively), even though we can conclude all three noninvasive tests are good in diagnosing fibrosis stage because the values of AUROC are above 0,7.

# CHAPTER V

# DISCUSSION

The diagnosis of NAFLD requires that: (1) there is hepatic steatosis by imaging or histology, (2) there is no significant alcohol consumption, (3) there are no competing etiologies for hepatic steatosis, and (4) there are no co-existing causes for chronic liver disease. Common alternative causes of hepatic steatosis are significant alcohol consumption, hepatitis C, medications, parenteral nutrition, Wilson's disease, and severe malnutrition.[1]

Table 9. Common causes of secondary hepatic steatosis[1]

| |
|---|
| **Macrovesicular steatosis** |
| - Excessive alcohol consumption |
| - Hepatitis C (genotype 3) |
| - Wilson's disease |
| - Lipodystrophy |
| - Starvation |
| - Parenteral nutrition |
| - Abetalipoproteinemia |
| - Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids) |
| **Microvesicular steatosis** |
| - Reye's syndrome |
| - Medications (valproate, anti-retroviral medicines) |
| - Acute fatty liver of pregnancy |
| - HELLP syndrome |
| - Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease) |

NAFL is generally benign, whereas NASH can progress to cirrhosis, liver failure, and liver cancer. Recent guideline stated that liver biopsy is the most reliable approach for identifying the presence of steatohepatitis and fibrosis in patients with NAFLD, but it is generally acknowledged that biopsy is limited by cost, sampling error, and procedure-related morbidity and mortality. Serum aminotransferase levels and imaging tests such as ultrasound, CT-scan, magnetic resonance imaging do not reliably assess steatohepatitis and fibrosis in patients with NAFLD. Therefore, there has been significant interest in developing clinical prediction rules and non-invasive biomarkers for identifying steatohepatitis in patients with NAFLD.[1]

The FIB-4 score combines platelet count, ALT, AST, and age, and was initially developed for use in HCV/HIV co infection. In an analysis including a large cohort of HCV-infected patients, FIB-4 enabled good discrimination of both severe fibrosis

(AUROC 0,85) and cirrhosis (AUROC 0,91). This marker has been assessed in patients with chronic hepatitis B (CHB) with reported 71% sensitivity and 73% specificity for diagnosing fibrosis F2 and above. Moreover, it has been shown to be reliable in the setting of NAFLD, using a cut-off value of 1.3 the sensitivity and specificity for predicting advanced (F3-F4) fibrosis were 74-85% and 65-71% respectively, and 34% and 98% when a FIB-4 threshold of 2.67 was used.[3]

NAFLD fibrosis score (NFS) is comprised of six parameters such as diabetes/impaired fasting glucose, age, AST, ALT, platelets, BMI, and albumin. NFS has received the most extensive validation among other scoring systems and it has been recommended for clinical use in the recent practice guideline on the diagnosis and management of NAFLD.[7]

Table 10. Formula of noninvasive scoring system[7]

| | |
|---|---|
| **NAFLD fibrosis score** | −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m²) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio (AAR) − 0.013 × platelet count (×10⁹/ L) − 0.66 × albumin (g/dL). |
| **FIB4 index** | (Age [years] × AST [IU/ L])/(platelet count [×10⁹/L] ×√ALT[IU/L] ) |

Transient elastography, which measures liver stiffness non-invasively, has been successful in identifying advanced fibrosis in patients with hepatitis B and hepatitis C. Although a recent meta-analysis showed high sensitivity and specificity for identifying fibrosis in NAFLD, it has a high failure rate in individuals with a higher BMI.[1] Furthermore, it is not widely available throughout Indonesia.

From the above studies, we can conclude that transient elastography is superior to FIB4 or NAFLD fibrosis score. This result is similar to other review about non-invasive assessment of liver fibrosis. In Wong study, both FIB4 and NAFLD fibrosis score are good diagnostic tools, but in Kumar study, only transient elastography and FIB4 who have AUROC above 0,7. More study should be done to validate this facts in our population.

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