

# **Training workshop on screening, diagnosis and treatment of hepatitis B and C**

## **Session 9**

### Non-invasive markers of chronic liver disease or liver fibrosis

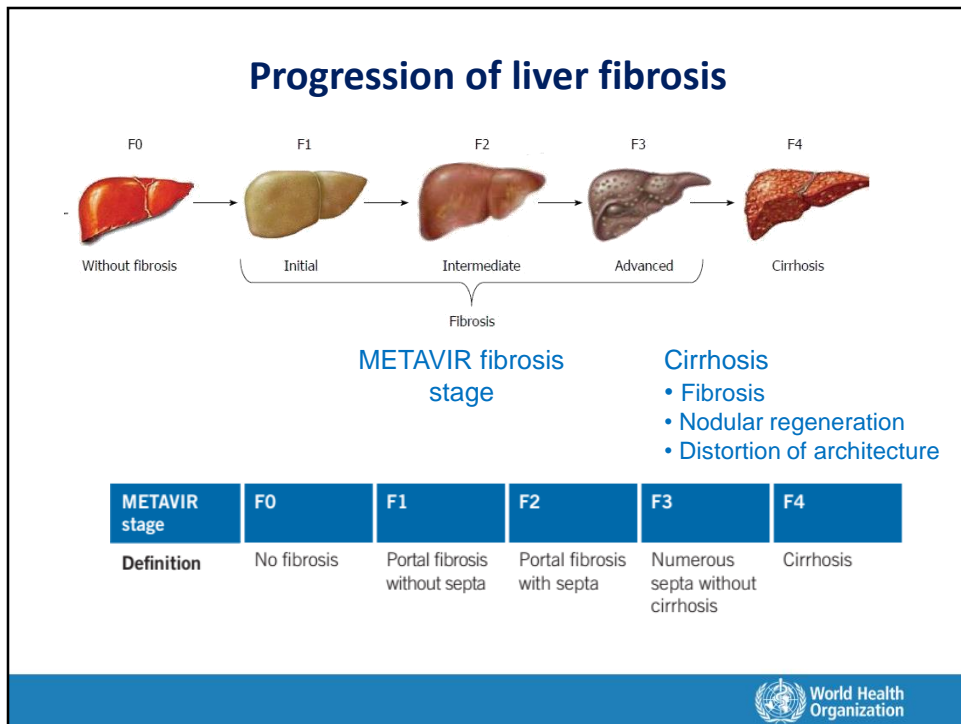
## Learning objectives

At the end of this session, participants should:

- understand the importance of assessing liver fibrosis while managing patients with viral hepatitis
- know about common non-invasive tests used to assess liver fibrosis, and understand their performance characteristics
- be able to calculate and interpret non-invasive tests such as APRI.



In this session we will learn about the importance of liver fibrosis, simple scores for fibrosis assessment and interpretation of these fibrosis scores.

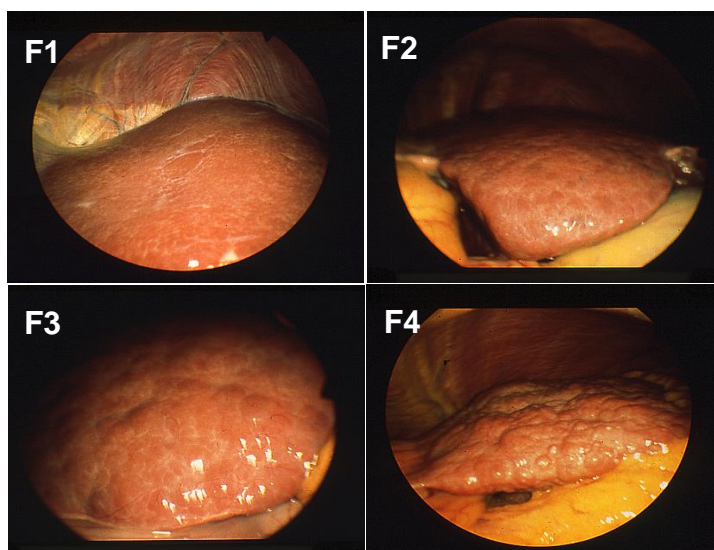


The spectrum of liver disease ranges from minimal fibrosis to cirrhosis.

Without any antiviral therapy, chronic hepatitis gradually progresses to cirrhosis in 20–30 years.

The METAVIR fibrosis staging system is a scoring system for assessing liver fibrosis based on pathological findings.

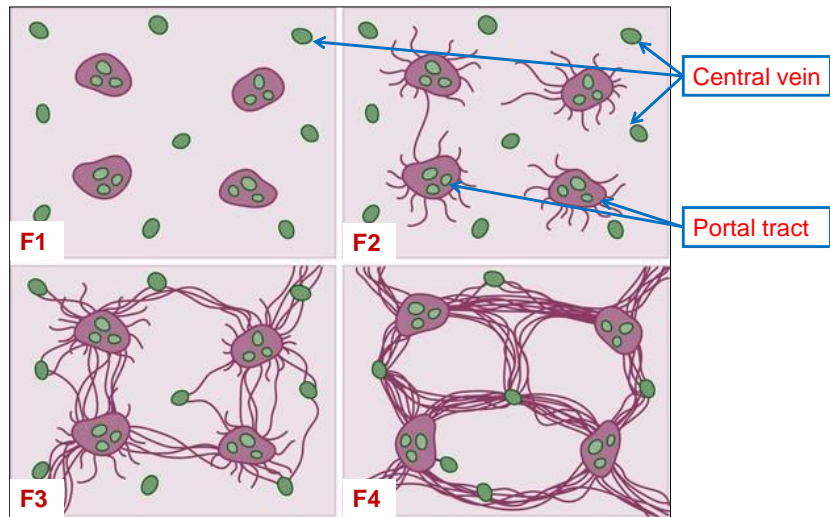
## Assessing the degree of liver fibrosis



This slide shows the cirrhotic liver in a laparoscopic view.

The liver surface becomes irregular and nodular as the stage of fibrosis advances from F1 to F4.

## Prolonged liver injury leads to scarring (fibrosis)



Progressive laying down of scar tissue around the central vein and portal tracts

Fibrosis starts around the portal area and nodules develop.

F1 indicates fibrosis in the portal area.

F2 indicates portal fibrosis with fibrous septa.

F3 indicates numerous septa without cirrhotic nodules.

F4 indicates cirrhosis, nodule formation or findings suggestive of nodule formation.

## Progression of liver fibrosis

- The stages of liver fibrosis are often thought of as discrete states that occur one after the other



- However, in real life, fibrosis is actually a continuous and not a step-wise process (akin to the colour spectrum)



The stages of liver fibrosis are often thought of as discrete states that occur one after the other.

However, in real life, fibrosis is actually a continuous and not a step-wise process (akin to the colour spectrum).

## What is cirrhosis?

An advanced stage of chronic liver disease characterized by

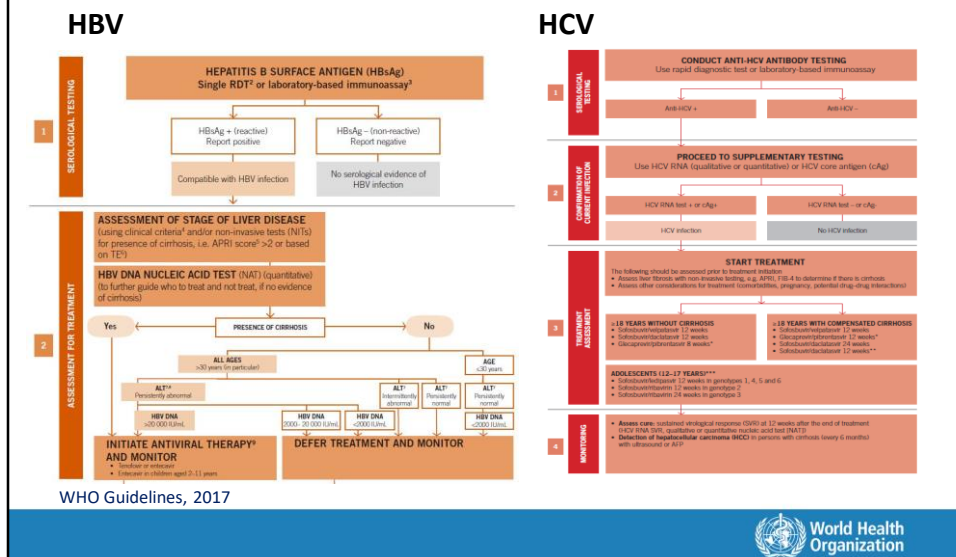
- extensive hepatic fibrosis
- alteration of liver architecture
- disrupted hepatic circulation
- liver nodularity.

Cirrhosis is the most advanced stage of liver fibrosis, which is characterized by extensive fibrosis, altered liver microarchitecture, altered hepatic blood circulation and liver nodularity.



# Assessment of liver fibrosis

Assessment of liver fibrosis or detection of cirrhosis plays an important role in management of hepatitis

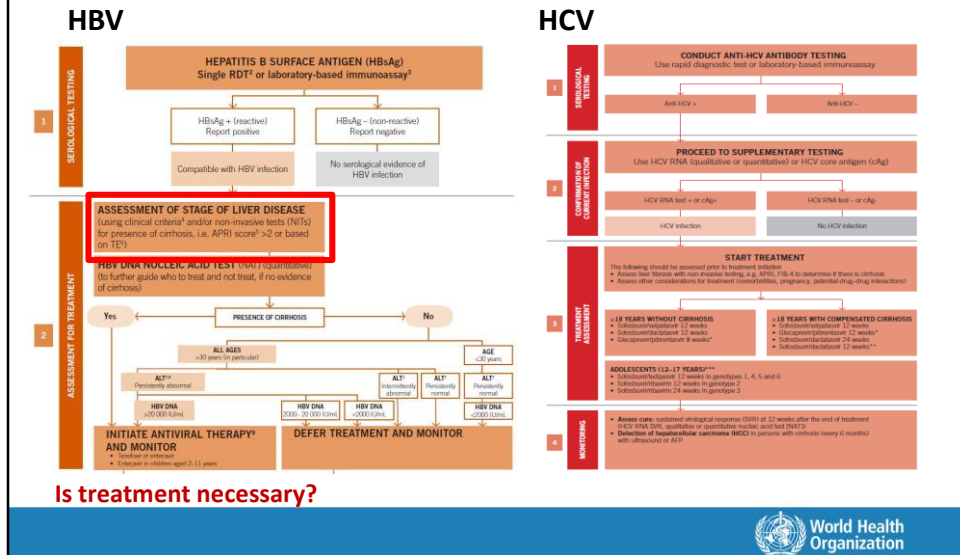


For HBV, if cirrhosis is present, initiation of antiviral treatment is recommended.

For HCV, treatment duration changes depending on the assessment of liver fibrosis.

# Assessment of liver fibrosis

Assessment of liver fibrosis or detection of cirrhosis plays an important role in management of hepatitis

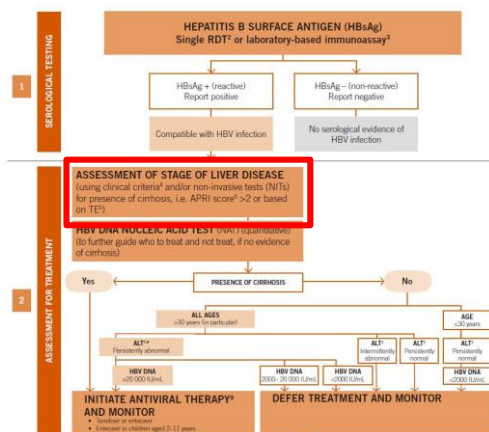


Is treatment necessary?

# Assessment of liver fibrosis

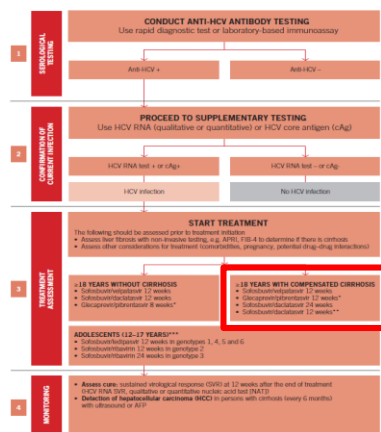
Assessment of liver fibrosis or detection of cirrhosis plays an important role in management of hepatitis

## HBV



Is treatment necessary?

## HCV



Choice of treatment regimen



World Health Organization

## Effect of liver fibrosis on patient care

Presence of significant liver fibrosis ( $\geq F2$ ) or cirrhosis (F4) in patients with viral hepatitis influences:

- need for treatment (HBV)
- treatment regimen (HCV)
- treatment response rate
- risk of hepatocellular carcinoma after successful treatment (e.g. HCV treatment)
- need for follow up after successful treatment of HCV.

WHO Guidelines, 2017



The staging of liver fibrosis influence the decision about starting treatment, selection of drugs, duration of treatment and need for follow up.

## Tests to assess liver fibrosis

- Invasive tests
  - Liver biopsy                      Gold standard
- Non-invasive tests

Liver biopsy is the gold standard to assess liver fibrosis and cirrhosis.

Several non-invasive tests based on blood or serum indices or ultrasound principles are now available and increasingly used for evaluating liver fibrosis.

## Problems with liver biopsy

- An invasive procedure needing hospitalization (in most settings)
- Requires expertise:
  - to perform biopsy
  - to interpret the biopsy
- Carries a definite risk of serious complications (albeit small)
- Patients are unwilling to undergo the procedure
- Sampling error
- Discontinuous scale (F0–F4) with very few grades
- Interobserver variation
- Repeated measurements difficult

**Need simpler, non-invasive, observer-independent and repeatable tests**



Though liver biopsy is the gold standard for assessment of liver fibrosis, it has several issues such as the highly invasive nature of the investigation with the inherent risks of complication and death, need for expertise in performing it, sampling error because of patchy distribution of fibrosis, etc.

Furthermore, biopsy is a costly investigation that requires hospitalization.

## Non-invasive assessment

- Clinical features
- Indirect tests
  - Haemogram, especially platelet count
  - Biochemical tests: ALT, AST, albumin
  - Composite measures
    - FIB-4, APRI, FibroTest
- Imaging
  - Ultrasound
- Specialized tests
  - Endoscopy for varices
  - Elastography



The presence of cirrhosis can be identified by a combination of clinical findings (oedema, ascites, variceal bleed, hepatic encephalopathy), haemogram (which may show pancytopenia; the platelets are the first to show a reduction in number), liver function tests (low serum albumin and composite scores such as APRI, FIB-4), ultrasound abdomen (nodular and shrunken liver, dilated portal vein, splenomegaly, etc.), and endoscopy (for oesophageal and gastric varices).

If available, liver stiffness measurement (transient elastography) could also help in diagnosing cirrhosis.

## Non-invasive assessment

- Clinical features
- Indirect tests
  - Haemogram, especially platelet count
  - Biochemical tests: ALT, AST, albumin
  - **Composite measures**
    - **FIB-4, APRI, FibroTest**
- Imaging
  - **Ultrasound**
- Specialized tests
  - Endoscopy for varices
  - **Elastography**



## **Advantages of non-invasive tests for fibrosis**

- Easy to perform
- Free from complications
- Widespread availability
- Can be done in the outpatient setting
- Cheap
- Do not require specialized training
- Homogeneity because of automated measurements of their component variables
- Tools for automated computation of score available (phone apps)
- Easy to repeat at frequent intervals



Non-invasive tests of liver fibrosis are preferred over liver biopsy because of several advantages.

They are easy to perform and can be repeated, carry no risk of complication, cost less and do not need hospitalization.

Furthermore, no or limited expertise is needed to perform them.

## Abdominal ultrasonography

- Most widely used and available
- Can differentiate cirrhosis from no cirrhosis
- Identifies the features of portal hypertension, an indirect marker of cirrhosis
- However, it cannot reliably differentiate between stages F0 to F3
- Even for cirrhosis, the sensitivity/specificity low
- Operator/machine dependent



Ultrasonography (USG) of the abdomen is a widely available diagnostic test that could be efficiently used to diagnose cirrhosis. A carefully performed USG can identify the features of portal hypertension and cirrhosis. However, it cannot differentiate between the various grades of fibrosis.

## Abdominal ultrasound: markers of cirrhosis

- Small, shrunken liver
- Nodular surface with irregular margins
- Coarse echotexture
- Features of portal hypertension
  - Enlarged spleen (>11 cm)
  - Dilated portal vein (diameter >12 mm)
  - Presence of venous collaterals
- Presence of complications
  - Ascites

We need to train our radiologists/ultrasonographers to look for and mention on the report for the features of portal hypertension such as a small shrunken liver with a nodular surface and irregular margins, dilated portal vein, splenomegaly, ascites, etc.

## Commonly used non-invasive tests

	Components	Requirements	Cost
APRI	AST, platelets	Simple serum and haematology test	+
FIB-4	Age, AST, ALT, platelets		
FibroTest	GGT, haptoglobin, bilirubin, apoprotein A1, $\alpha$ 2-macroglobulin	Specialized tests at designated laboratories	++
FibroScan <sup>®</sup>	Transient elastography	Dedicated equipment	+++

AST	aspartate aminotransferase
ALT	alanine aminotransferase
GGT	gamma glutamyl transpeptidase
APRI	aspartate aminotransferase-to-platelet ratio index
FIB-4	fibrosis-4 score

There are three common tests for assessing liver fibrosis – APRI (AST-to-platelet ratio index), FiB-4 (fibrosis-4 score) and FibroTest.

As shown in this table, FibroTest needs several specific tests such as haptoglobin, A1apoprotein and alpha2-macroglobulin at designated laboratories and the test is commercially patented.

Considering the ease of calculation and accessibility, APRI is recommended as the non-invasive test of choice.

## Non-invasive test (NIT) techniques

**ARFI: Acoustic radiation force impulse**



**Shear wave elastography**



Incorporated into new ultrasound imaging machine  
Needs more operator training and expertise than FibroScan

**FibroTouch diagnostic system**



WHO Guidelines, 2015



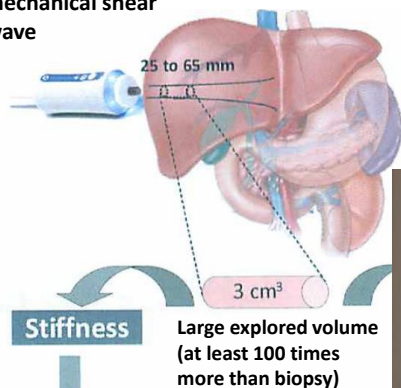
There are several other elastography techniques for assessing liver fibrosis, such as acoustic radiation force impulse (ARFI) and shear wave elastography

These two are incorporated into some of the new high-end ultrasound imaging machines.

FibroTouch has been developed in China.

## Transient elastography (example: FibroScan)

Transducer sends a mechanical shear wave



Monitor display of FibroScan



FibroScan sends a mechanical shear wave from a specific transducer and measures the velocity of the wave in a relatively large volume of liver, which is at least 100 times more than biopsy.

From the velocity of the wave, the liver stiffness is calculated and shown on the monitor display. The unit of measurement is kilopascal (kPa).

## Transient elastography (example: FibroScan)



- **Median**
  - Calculated from 10 valid measurements
  - Is used as the final result
- **Interquartile range (IQR)**
  - Spread of the middle half of observations
  - Should be small
- **IQR/median**
  - Ratio of IQR to median
  - Indicates variability in different readings
  - High values mean large variation
  - If >30%, implies no reliability

In transient elastography measurements on FibroScan, 10 measurements are taken and the median of 10 effective results is accepted as the final result.

A high IQR per median indicates variation in the result. If the value of the IQR is more than 30%, the reliability of the result is questionable.

## Transient elastography

- Advantages
  - Easy, non-invasive
  - Can be done in outpatient or community settings
  - Takes <10 min to perform
  - Health-care staff can be easily trained
- Limiting factors
  - High cost of equipment
  - Equipment needs regular maintenance/calibration by trained personnel
  - No universal cut-off values for specific stages of fibrosis
  - Difficult to measure in very obese persons



Transient elastography measurement has a few advantages and disadvantages over liver biopsy. The advantages are ease and speed of performance, and its non-invasive nature. The disadvantages are the high cost of the instrument, need for regular maintenance and inability to measure in obese people.



## Factors that can affect a liver stiffness reading

- Fasting or fed state
- Any inflammation of the liver (e.g. acute hepatitis)
- Biliary obstruction
- Fluid overload such as end-stage renal disease, heart disease

Liver stiffness, as measured with transient elastography, is affected by several factors such as diet, inflammation, congestion, etc.

If using FibroScan, the scan should be done after 8 hours of fasting.

## Transient elastography e.g. FibroScan

- For liver stiffness measured by transient elastography, several different cut-offs have been proposed in different studies and disease conditions.
- A commonly used cut-off for cirrhosis: >12.5 kPa.

Though various studies have described several different cut-offs for defining cirrhosis, most of these cut-offs define cirrhosis as a value above 11–14 kPa.

## AST-to-platelet ratio index (APRI)

$$\text{APRI} = \frac{\frac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count (10}^9\text{/L)}} \times 100$$

- AST upper limit of normal: Use 40 IU/L if none specified
- Platelet count: expressed in terms of X1000/microLitre

APRI online calculator:

<https://www.hepatitisc.uw.edu/page/clinical-calculators/apri>



APRI means AST-to-platelet ratio index.

We can estimate liver chronicity by the AST and platelet count.

AST is divided by the AST value that is the upper limit of normal for that laboratory.

Then the result is multiplied by 100.

This is then divided by the platelet count.

## AST-to-platelet ratio index (APRI)

$$\text{APRI} = \frac{\frac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count (10}^9\text{/L)}} \times 100$$

### Example

- AST (SGOT) 90 IU/L (normal 32-45)
- Platelet count 80,000 /microLitre

$$\begin{aligned} \text{• APRI} &= \frac{(90/45) \times 100}{80} \\ &= \frac{2 \times 100}{80} = \frac{200}{80} = 2.5 \end{aligned}$$

This is an example of an APRI calculation.

## FIB-4

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}}$$

- AST/ALT upper limit of normal: use 40 IU/L if none specified
- Platelet count: expressed in terms of X1000/microLitre
- Calculation needs a calculator, a phone app or an online tool  
example FIB-4 calculator:

<https://www.hepatitisc.uw.edu/page/clinical-calculators/apri>



As shown in the slide, the FIB-4 score is relatively complicated and needs a calculator.

## Cut-offs for significant fibrosis or cirrhosis

	APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)
Significant fibrosis (METAVIR $\geq$ F2)	0.5	1.5	1.45	3.25
Cirrhosis (METAVIR F4)	1.0	2.0	–	–

For APRI and FIB-4 indices, WHO recommends two cut-off levels to define cirrhosis: (i) A lower cut-off value, which has a high sensitivity (means it detects true positives) to detect cirrhosis if it is present and (ii) an upper cut-off value, which is more specific for diagnosing cirrhosis.

Values above the high cut-off indicate a high probability of having cirrhosis; any value below the low cut-off value indicates a very low probability of having cirrhosis.

## Cut-offs for significant fibrosis or cirrhosis

	APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)
Significant fibrosis (METAVIR $\geq$ F2)	0.5	1.5	1.45	3.25
Cirrhosis (METAVIR F4)	1.0	2.0	–	–

- Use of a single cut-off for APRI and FIB-4 results in suboptimal sensitivity and specificity.
- Hence, there are two cut-off points.
- A high cut-off has high specificity (few false-positive results): used to diagnose fibrosis  $\geq$  a particular stage (e.g.  $\geq$ F2).
- A low cut-off has high sensitivity (few false-negative results): used to rule out the presence of a particular stage of fibrosis.

## Performance of APRI and FIB-4

	APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)
Significant fibrosis (METAVIR $\geq$ F2)	0.5	1.5	1.45	3.25
Cirrhosis (METAVIR F4)	1.0	2.0	–	–

		APRI (low cut-off)	APRI (high cut-off)	FIB-4 (low cut-off)	FIB-4 (high cut-off)	Transient elastography
Significant fibrosis (METAVIR $\geq$ F2)	Sensitivity (95% CI)	82 (77–86)	39 (32–47)	89 (79–95)	59 (43–73)	79 (74–84)
	Specificity (95% CI)	57 (49–65)	92 (89–94)	42 (25–61)	74 (56–87)	83 (77–88)
Cirrhosis (METAVIR F4)	Sensitivity (95% CI)	77 (73–81)	48 (41–56)	–	–	89 (84–92)
	Specificity (95% CI)	78 (74–81)	94 (91–95)	–	–	91 (89–93)

This slide shows the sensitivity and specificity of APRI and FIB-4.

If we use a high cut-off, the specificity is more than 90%.

If we use a low cut-off, the sensitivity is more than 82%



## Summary

- It is important to assess the presence of significant liver fibrosis or cirrhosis in a patient with HBV or HCV infection.
- Liver fibrosis influences the treatment, response to treatment and prognosis.
- Liver biopsy is the gold standard for assessing fibrosis, but has several limitations.
- Hence, liver fibrosis is often assessed using simple and easily available non-invasive methods, which are fairly reliable.
- APRI is the most widely used, easy-to-calculate and validated non-invasive test for fibrosis assessment in outpatient and community settings.



Assessment of liver fibrosis is of paramount importance in the management of patients with either HBV or HCV infection because it determines the treatment and response to treatment and prognosis.

Fibrosis is best assessed by liver biopsy though non-invasive methods are preferred and APRI is the most commonly used non-invasive method.

### **Case study 1**

A 60-year-old male with HCV infection

Laboratory data as follows:

- PLT  $88 \times 10^9/L$
- AST 58 U/L

**Q. What is the stage of liver disease?  
(liver cirrhosis or not)**

Case study 1

A 60-year-old male with HCV infection

Laboratory data as follows;

PLT  $88 \times 10^9/L$

AST 58 U/L

Question.

What is the stage of liver disease?

(Liver cirrhosis or not liver cirrhosis)

### **Case study 1**

A 60-year-old male with HCV infection

Laboratory data as follows:

- PLT  $88 \times 10^9/L$
- AST 58 U/L

**Q. What is the stage of liver disease?  
(liver cirrhosis or not)**

For calculation of APRI, the ULN of AST is needed.

Answer:

For calculation of APRI, the ULN of AST is needed.

### **Case study 1**

A 60-year-old male with HCV infection

Laboratory data as follows:

- PLT  $88 \times 10^9/L$
- AST 58 U/L (ULN 30 U/L)

**Q. What is the stage of liver disease?  
(liver cirrhosis or not liver cirrhosis)**

Upper limit of normal is 30 U/L.

Now, you can calculate the APRI.

### **Case study 1**

A 60-year-old male with HCV infection

Laboratory data as follows:

- PLT  $88 \times 10^9/L$
- AST 58 U/L (ULN 30 U/L)

**Q. What is the stage of liver disease?  
(liver cirrhosis or not)**

$$\begin{aligned} \text{APRI} &= [(58/30) \times 100] / 88 \\ &= 193 / 88 \\ &= 2.20 > \text{cut-off index } 2.0 \quad \textbf{liver cirrhosis} \end{aligned}$$



Thus,

APRI is 2.20, more than the cut-off index for cirrhosis, 2.0.

So, the final diagnosis is liver cirrhosis.

### **Case study 2**

A 55-year-old male with HBV infection

Laboratory data as follows:

- PLT  $134 \times 10^9/L$
- AST 42 U/L (ULN 32 U/L)

**Q. What is the stage of liver disease?  
(liver cirrhosis or not)**

### **Case study 2**

A 55-year-old male with HBV infection

Laboratory data as follows:

- PLT  $134 \times 10^9/L$
- AST 42 U/L (ULN 32)

**Q. What is the stage of liver disease?  
(liver cirrhosis or not)**

$$\begin{aligned} \text{APRI} &= [(42/32) \times 100] / 134 \\ &= 131 / 134 \\ &= 0.98 < \text{cut-off index } 2.0 \quad \text{not liver cirrhosis} \end{aligned}$$



Thus, the APRI is 0.98.

It is less than the cut-off index for cirrhosis, which is 2.0.

So, the final diagnosis is not cirrhosis.

### **Case study 2**

A 55-year-old male with HBV infection

Laboratory data as follows:

- PLT  $134 \times 10^9/L$
- AST 42 U/L (ULN 32 U/L)

**Q. What is the stage of liver disease?  
(liver cirrhosis or not)**

$$\begin{aligned} \text{APRI} &= [(42/32) \times 100] / 134 \\ &= 131 / 134 \\ &= 0.98 < \text{cut-off index } 1.5 \end{aligned}$$

**No significant fibrosis**



Thus, APRI is 0.98.

It is less than the cut-off index for significant fibrosis, more than F2, 1.5.

So, the final diagnosis is no significant fibrosis.