Hepatic Fibrosis in HCV, Non Invasive and Economical Biochemical Markers, a Review!

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Abstract

Hepatitis is a medical condition defined by the inflammation of the liver and characterized by the presence of inflammatory cells in the tissue of the organ.By using Non- invasive biomarkers there is significant decrease in discomfort and risks and there can befrequent re-evaluation, objective interpretation and easy patient acceptance as compared to invasive markers in which there is higher cost along with intra and inter-observer variability.

Key words: Hepatitis, Liver Biopsy, Non- invasive Biomarkers & Invasive biomarkers.

INTRODUCTION

Hepatitis (*Hepar* meaning liver and*itis*means inflammation) is a medical condition defined by the inflammation of liver and characterized by the presence of inflammatory cells in the tissue of liver. Hepatitis often leads to jaundice characterized by yellow coloration of skin mucous and conjunctiva with poor appetite. Hepatitis is acute when it lasts less than six months and chronic when it lasts more than six months.[1]

Chronic hepatitis can lead to fibrosis (also known as scarring of liver) and cirrhosis (Chronic liver failure) which further leads to increased risk of developing Hepatocellular carcinoma(HCC).[2,3]

There are also some other factors that can lead to hepatitis which includes autoimmune diseases, alcohol overuse, medications like paracetamol and ingestion of some industrial toxic chemicals.

SYMPTOMS OF ACUTE HEPATITIS: Initial symptoms include joint and body ache, nausea, vomiting, headache, diarrhea, abdominal discomfort and loss of appetite along with yellow coloration of eyes and sclera.[4]

SYMPTOMS OF CHRONIC HEPATITIS: Chronic hepatitis may cause nonspecific symptoms including tiredness and weakness but physical examination may show enlargement of liver. Further symptoms includes scarring of liver leading to weight loss and accumulation of ascites. Further cirrhosis may lead to various complication like esophageal varices, hepatorenal syndrome and hepatic encephalopathy leading to confusion and coma.[5]

CAUSES OF VIRAL HEPATITIS: Viral Hepatitis is the most common cause of hepatitis worldwide and it includes five unrelated hepatotropic viruses which are Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D and Hepatitis E. Viral hepatitis is diagnosed through serological tests react to the antibodies formed by the immune system.[6]

OTHER CAUSES: Other common cause includes drug induced, alcoholic, fatty liver and metabolic disorders. Besides this there are some bacterial, fungal, mycobacterial and protozoan infections that can also cause hepatitis. Cholestasis due to hepatocellular dysfunction and obstruction of bile flow can also lead to liver damage and hepatitis. In metabolic disorders and toxic accumulation of dietary minerals as in hemochromatosis and in Wilson diseases can lead to inflammation and cirrhosis.[7,8]

INVASIVE DIAGNOSIS OF FIBROSIS: Liver biopsy remains the gold standard for evaluation of liver fibrosis in HCV infection and for prognostication and decision making regarding antiviral therapyand is important diagnostic tool in chronic liver disease, cirrhosis and hepatocellular carcinoma but it had some limitations and risks. Liver biopsy requires bed rest for atleast six hours and is associated with small and definite mortality. Complication s includes pain, bleeding, accidental needle puncture of the lung, intestine, gall bladder or kidney. Besides this there is higher cost along with intra and inter-observer variability.[9]

NON INVASIVE DIAGNOSIS OF LIVER FIBROSIS: Two types of Non-invasive markers are there which can be:

1. Direct Markers.
2. Indirect markers.

DIRECT MARKERS OF LIVER FIBROSIS: Multiple etiology in liver disease in chronic HCV infection, can lead to liver fibrosis through integrated signaling networks that regulate the deposition of

extracellular matrix. This includes activation of hepatic stellate cells and other extracellular matrix components.[10]

Markers of liver fibrosis are usually fragments of the liver matrix components produced by hepatic stellate cells during the process of ECM remodeling usually reflecting deposition and or removal of ECM. The most studied direct markers are:

1. Hyaluronic acid (HA)
2. YKL 40.
3. Laminin.
4. Fibronectin
5. Alpha 2 Microglobulin.
6. Procollagen type 1 carboxy terminal peptide(PICP)
7. Pro collagen type 3 amino terminal peptide(P3NP)
8. N terminal propeptide of Type 2 Collagen.
9. Metalloproteinases(MMPs)
10. Tissue inhibitors of matrix metallo proteinases(TIMPs)
11. Transforming Growth factor B1(TGF-B1).

Category	No	Hyaluronic acid (µg/L)	p value
Healthy controls	50	21± 10	
Fibrosis stage 0	21	38± 16	p<0.001
Fibrosis stage 1	38	61± 30	p<0.001
Fibrosis stage 3	26	273± 69	p<0.001
Fibrosis stage 4	15	583± 95	p<0.001

HYALURONIC ACID AS A MARKER OF LIVER FIBROSIS:Hepatic fibrosis is a complex process with increase in extracellular matrix components, cytokine release and tissue remodelling.The extracellular components comprises of Hyaluronic acid which is high molecular weight unbranched polysaccharide and is widely distributed in the extracellular spaces.The synthesis of Hyaluronic acid is increased in fibrogenesis and increased level in circulation is an indicator of fibrotic process. Circulating HA measurement may be helpful in differentiating non cirrhotic, cirrhotic and extent of fibrosis.

Hyaluronic acid levels were measured in different stages of Hepatic fibrosis and were compared with controls. Significant p value(<0.01) in different stages of fibrosis was observed when it was compared with health controls and serum levels of HA significantly increased with increased extent of fibrosis indicating HA as a good direct non invasive marker.[11]

NONINVASIVE INDIRECT MARKERS FOR LIVER FUNCTIONS IN CHRONIC HEPATITIS C INFECTION[12,13]

LIVER CHEMSITRY	CLINICAL IMPLICATION IN ABNORMALITY
ALT/AST	Hepatocellular Damage
ALP	Cholestasis
Total/Direct Bilirubin	Cholestasis
Bile acids	Cholestasis
LDH	Hepatocellular Damage
Albumin	Impaired Synthetic function
GGT	Cholestasis
Prothrombin Time	Impaired Synthetic Function

OTHER RATIOS AND INDIRECT MARKERS OF LIVER FIBROSIS:

1. AAR (AST:ALT Ratio)
2. APR I (AST-to platelet ratio index) (AST Level/Platelet count x100)
3. FIB-4 Ratio (Age x AST/Platelet count x ALT)

These three ratios are calculated from AST, ALT, Platelet Count and Patient Age. These ratios correlated with stages of fibrosis in patients with chronic HCV[14]

OTHER INDIRECT NON INVASIVE MARKERS

1. FIBROTEST SCORE

The fibro test score was originally proposed in 2001.It is one of the most validated models for predicting liver fibrosis in HCV infected patients. It is computed by accessing Patient's age, Sex, Serum haptoglobulin, α-2 macroglobulin, Apo-lipoprotein A-1, GGT and Total Bilirubin.[15]

A study conducted by Chou etalrevealed that Fibro test is better than APRI with significant fibrosis

2.FIBROSPECT- II Fibrospect panel includes, TIMP-1, α-2 macroglobulin and Hyaluronic acid levels.It was generated from a cohort of 696 HCV infected patients and exhibited significant fibrosis in the original study.[16]

3.HEPASCORE Itis a patented model that combines age, sex and 4 biomarkers(α-2 macroglobulin, HA, GGT, Total Bilirubin)It was devised in a cohort of chronic HCV patients and further validated in several studies.[17]

4.**ELF(ENHANCED LIVER FIBROSIS)ELF score provides a single value by an algorithm combining**

age as well as quantitative serum measurements of:TIMP 1,
P3NP, HA It was proposed in a cohort study including 496 HCV patients. ELF score is significantly influenced by gender(higher values in men) and age(higher scores in older persons) and this should be taken into account.[18]

5.FIBROMETER It includes Platelet count, Prothrombin index, AST, α-2 Macroglobulin, HA, BUN and age.[19]

DIFFERENT STUDIED MODELS COMBINING

Degree of Fibrosis	Stage	Mean AAR	Mean APRI	Mean FIB-4
No Fibrosis (F0)	0	1.04	1.08	1.50
Fibrous Port expansion (F1)	1,2	0.87	1.09	1.41
Few bridge & Septa (F2)	3	0.93	1.96	2.07
Numerous bridge & Septa (F3)	4	0.96	1.75	2.23
Cirrhosis (F4)	5,6	1.23	1.94	2.89

DIRECT & INDIRECT BIOMARKERS IN CHRONIC HCV[20]

SUMMARY AND CONCLUSIONS: In Nutshell we can conclude that Indirect Non-Invasive Markers &

SCORE NAME	MEDIAN SENSTIVITY	MEDIAN SPECIFITY
Fibrotest	92%	96 %
ELF	85%	70 %
Fibrometer	69%	81 %
Fibrospect II	80%	70 %
Hepascore	66%	79 %

Ratios are good in Prognostication of the Liver Fibrosis with good Sensitivity and Specificity. Therefore we can conclude that to decrease the risk of pain, accidental needle puncture, hospitalization, mortality, inter and intra observer variability we can shift to cheaper and economical markers and ratios.

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