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REVIEW

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Novel biomarkers assist in detection of liver fibrosis in HCV patients

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Abstract

Background: Accurate staging in individuals infected with hepatitis C is imperative to understand their long-term risk for liver-related complications. Liver biopsy has a traditional role to determine the levels of liver fibrosis specifically in hepatitis C virus patients. However, the development of non-invasive options has reduced the utilization of biopsy in this population.

Main body of the abstract: Detecting fibrosis levels through blood samples is already an acceptable alternative to biopsy; however, the optimal non-invasive panel has yet to be defined. Our study indicated hyaluronic acid, collagen oligomeric matrix protein, collagen type IV, and liver fibrosis scoring systems to distinguish fibrosis patients from the non-fibrosis group.

Short conclusion: The combination of these novel biomarkers, H. A, CO-IV, and Comp tests, could be used to accurately stage individuals with hepatitis C.

Keywords: Noninvasive markers, Viral hepatitis, Chronic liver diseases, Biopsy, Fibrosis scoring systems

Background

Health consequences secondary to hepatitis C (HCV) are well recognized. As liver-related morbidity and mortality are strongly linked to the degree of hepatic fibrosis, defining the degree of fibrosis in those infected with HCV is important for the timing of therapy, screening for complications, and post cure monitoring. Although the pathogenesis of HCV-infected fibrosis is poorly understood, liver fibrosis may be a response of repair when the liver is injured or inflamed. Furthermore, the accurate detection of liver fibrosis is recommended in all clinical guidelines to help guide appropriate patient management [AASLD/IDSA, EASL] [1, 2]. Liver biopsy which is implemented by histological examination remains the gold standard for the evaluation of liver fibrosis when non-invasive studies are discordant or there is a concern for a second disease [AASLD/IDSA, EASL] [1, 2]. Although biopsy has an effective role in the evaluation of fibrosis stages, it is often regarded as a faulty standard due to its several complications which are enclosing the stay of 1–5% of patients at the hospital and causing mortality effective percentages of cases. The inaccuracy of sample drawing leads to advanced stages of liver disease such as cirrhosis in approximately 20% of patients. Actually, the increment exploitation of biopsy to determine the progression of liver disease or to measure the effect of treatment is considered hurtful due to its complications and patient's unawareness [3]. The study of the consequences of biopsy in several areas has resulted that disruption between pathologists as well as a long stay of cases at hospital and increase of treatment cost [4]. Hence, looking for non-invasive alternatives to detect the levels of liver fibrosis is inevitable to be assessable in observation of treatment response and awareness of any harmful frequent of liver disease progression. Despite transient elastography (fibroscan) has been used as a noninvasive tool to detect fibrosis in chronic liver diseases, TE determine the shear wave speed across the liver which reflects liver stiffness

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and not the actual amount of fibrosis in the liver. Thereafter, conditions that increase the stiffness of the liver independent of fibrosis will increase the value of the liver stiffness measurement (LSM), and then the false result of high estimation of liver fibrosis will be released [5]. Magnetic resonance imaging (MRI) can only differentiate between non-fibrotic and cirrhotic patients and cannot be an effective tool in intermediate stages of fibrosis [6]. However, the recognized potential advantages of combined morphological and functional analysis of the liver, the inclusion of hepatobiliary contrast agents in international guidelines, besides the Japan Society of Hepatology, is still pending particularly in serological tests.

Main text

Detecting fibrosis levels by serological markers

Serum biomarkers that are under studying would be regarded as an attractive, profitable alternative to liver biopsy for both patients and clinicians in the cases of liver fibrosis as the following:

Collagen Oligomeric Matrix Protein (COMP) is an extracellular matrix (ECM) protein primarily present in cartilage and encoded by the COMP gene. It is considered a potential biomarker that interacts with collagen and is suggested to have a role in regulating fibril assembly as well as a structural role for maintaining the mature collagen network.

Hyaluronic Acid (HA) is known as a glycosaminoglycan which is a vital substance of extracellular matrix is found in the highest concentration in a fluid such as joint and eyes [7]. HA has shown promise as an effective biomarker of hepatic fibrogenesis secondary to chronic viral disease [8].

The extrinsic pathway is influenced by signals which originate from the death receptors found on the cell surface. The activation of these receptors is made by ligands, such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and FasL (CD95L), and the apoptosis is mediated by Fas/CD95 and its ligand FasL, which is one of the most well-defined apoptotic signaling pathways [9]. In normal physiological conditions, hepatocytes express Fas/CD95 receptor in low levels but under a pathological condition in which inflammatory cytokines and oxidative stress are secreted, the expression of Fas/CD95 receptor is upregulated to enhance cellular apoptosis by the Fas/CD95 system [10]. HGF is a mitogenic cytokine that is produced by mesenchymal stem cells of various organs such as the liver. It is implicated in the regeneration of hepatic tissue and is considered a prognosis factor in liver diseases as HCC [11].

Serum hepatocyte growth factor (HGF) has various levels in liver diseases, but it has exhibited a negative correlation with albumin concentration and prothrombin time in cirrhotic patients. In addition, individuals with hepatitis C virus had higher levels of serum HGF than those with hepatitis A or B viruses [12]. In HCC, the mRNA levels of HGF and the MET receptor are markedly increased compared with those in normal liver. A high serum HGF concentration is associated with a poor prognosis for overall survival after hepatic resection, and the serum level of HGF represents the degree of the carcinogenic state in the livers of patients with C-viral chronic hepatitis and cirrhosis [13].

Endostatin is an anti-angiogenesis factor. It is mainly produced after the degradation of collagen XVIII [14]. The inhibitory mechanisms of endostatin include restriction of endothelial proliferation, migration, and also induction of apoptosis of endothelial cell [15]. It was reported that the endostaton/collagen XVIII transcripts were found in hepatocytes of fibrotic livers [16]. Recently, it was demonstrated that endostatin serum level was positively correlated with disease severity in HCV patients, and it was included in the differentiate function named Angio-Index for accurate diagnosis of hepatic fibrosis [17].

Some specific study has reported that the combination comprises: Fas/CD95, HGF, endostatin, albumin, and platelet count which have reported FHEPA test. The diagnostic power of FHEPA test was assessed by ROC curve analyses giving an AUC of 0.99 for differentiating patients with significant liver fibrosis (F2–F4), AUC of 0.877 for differentiating advanced fibrosis (F3–F4), and AUC of 0.847 for discriminate patients with cirrhotic liver (F4) [18].

Collagen type IV (CO-IV) is a substance of ECM that also with promise as a biomarker for liver fibrosis [19]. CO IV has been studied across several etiologies of chronic liver diseases [20]. There are other markers that have been applied in studies of fibrosis including the SHASTA index that is based on serum hyaluronic acid, AST, and albumin. This index can be calculated by the following formula: SHASTA index = 3.84 + 1.7 (if 4 < HA<85 ng/mL, otherwise 3.28) + 1.58 (if albumin <3.5 mg/dl, otherwise 0) + 1.78 (if AST > 60 IU/L, otherwise 0) [21]. The FIB-4 scoring system uses a combination of patient age, platelet count, AST, and ALT. APRI (AST/platelet ratio) and the NAFLD fibrosis score is a validated, noninvasive tool for identifying patients who have NAFLD (non-alcoholic fatty liver disease) has advanced to liver fibrosis. It is relatively easy to use a panel that includes age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT. It relies on readily available clinical information and routinely measured laboratory data [22]. The NAFLD fibrosis score is recommended by the American Association for the Study of Liver Diseases (AASLD), American College of

Gastroenterology (ACG), and the American Gastroenterological Association (AGA) [23].

Effectiveness of recent biomarkers

As presented in Tables 1 and 2 [24] through our research, the cutoff value of CO-IV >181 ng/ml is diagnostic efficient which helps to characterize liver disease early from late stages of fibrosis (cirrhosis and HCC) with sensitivities 76.92 and specificity of 94.29. These results are relatively close to many researchers' reports with various cutoffs in other areas that made several searches on CO-IV but in different liver pathogenic disease-induced fibrosis implicate scoring system and HCV patients [25]. COMP serum levels have shown a similar effect as APRI and FIB4 score in detecting cirrhosis in HCV patients, suggesting COMP as an essential non-invasive and feasible biomarker in the estimation of liver fibrosis stages. As a result of the current study, indirect fibrosis scoring systems tests such as SHASTA, APRI, Fibrosis-4, and NAFLD are effective in insulation advanced fibrosis with efficient precision for excluding or determining moderate forms of fibrosis. SHASTA is considered as a perfect fibrosis scoring system and it is fully dependent on a precise measuring of hyaluronic acid, albumin, and alanine amino transferase.

Comparison between liver biopsy and serum markers

The serum markers of fibrosis have many advantages such as attractive, non-invasive, and affordable alternatives, while the liver biopsy is a complicated process.

Table 3 shows a comparison between liver biopsy and serum markers according to their advantages and disadvantages in the diagnosis of liver fibrosis stages [26].

Conclusion

Liver biopsy is still an important tool in the evaluation and management of a liver disease. However, it is invasive and could cause significant complications. Needle liver biopsy cannot be considered an ideal test. On the other side, serological biomarkers are noninvasive, reliable, safe, and feasible. According to the reports of the current study, some serum markers have been found better than biopsy in excluding advanced fibrosis from mild fibrosis patients. In addition, some markers have a low accuracy, and they need further researches. Scoring systems alone are likely not sufficiently sensitive to discriminate against significant diseases. Hence, the combination of

Table 1 Presentation of sensitivity and specificity and accuracy of serum biomarkers levels and fibrosis scoring systems to discriminate liver fibrosis from control curve in HCV patients

	AUC	*p*	95% CI		Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
			LL	UL						
H.A	0.998*	<0.001*	0.994	1.00	>46	96.72	98.67	98.3	97.4	97.79
CO IV (μg/L)	0.863*	<0.001*	0.795	0.932	>98.1	77.05	100.0	100.0	84.3	89.71
COMP (μg/mL)	0.977*	<0.001*	0.953	1.002	>15	91.80	100.0	100.0	93.7	96.32
APRI	0.733*	<0.001*	0.625	0.842	>0.25	72.13	97.33	95.7	81.1	86.03
SHASTA	0.990*	<0.001*	0.980	1.001	>-2.14	91.80	88.0	86.2	93.0	89.71
NAFLD	1.000*	<0.001*	1.000	1.000	>-1.645	100.0	100.0	100.0	100.0	100.0
FIB-4	0.974*	<0.001*	0.949	1.000	>0.9	91.80	100.0	100.0	93.7	96.32

Table 2 Presentation of sensitivity and specificity and accuracy of serum biomarkers levels and fibrosis scoring systems to differentiate advanced from early stages of liver fibrosis in HCV patients

	AUC	*p*	95% CI		Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
			LL	UL						
H.A	0.957*	<0.001*	0.910	1.00	>161	96.15	85.71	83.3	96.8	90.16
CO IV (μg/L)	0.901*	<0.001*	0.824	0.978	>181	76.92	94.29	90.9	84.6	86.89
COMP (μg/mL)	0.676*	0.019*	0.537	0.816	>27	57.69	74.29	62.5	70.3	67.21
APRI	0.762*	0.001*	0.637	0.886	>1.41	61.54	82.86	72.7	74.4	73.77
SHASTA	0.757*	0.001*	0.637	0.877	>1.22	100.0	51.43	60.5	100.0	72.13
NAFLD	0.901*	<0.001*	0.816	0.986	>1.55	84.62	94.29	91.7	89.2	90.16
FIB-4	0.927*	<0.001*	0.858	0.996	>1.85	96.15	82.86	80.6	96.7	88.52

Table 3 Comparison between liver biopsy and serum markers

Factor	Liver biopsy	Serum markers
Cost	Expensive	Laboratory cost
Risks	Significant	Minimal
Contraindications	Multiple: bleeding diathesis, morbid obesity, ascites, extrahepatic biliary obstruction	Conditions with a high rate of false positivity
Accuracy	80%	60–80%
System requirements	Operator, pathology laboratory, pathologist	Clinical laboratory, phlebotomy, materials.
Specimen adequacy	Length of the liver fragment at least 15 mm with 6–8 portal tracts	Blood sample
False positives	Interobserver variability	Sepsis, nonhepatic inflammation, hemolysis, trombocitopenia
False negatives	Sampling variability	Varies per test
Time for results	24–72 h minimum	1–2 h minimum

serological markers and scoring indexes are being perfect predictors to evaluate all stages of fibrosis. However, further researches are needed to prove reliable and Noninvasive markers of liver fibrosis until liver biopsy will be fully replaced.

Abbreviations

ECM: Extracellular matrix; COMP: Cartilage oligomeric matrix protein; AST: Aspartate amino transferase; ALT: Alanine amino transferase; APRI: AST to platelet ratio index; FIB-4: Fibrosis-4 score; PLT: Platelets; ACG: American College of Gastroenterology; AGA: American Gastroenterological Association; HCV: Hepatitis C virus; HSC: Hepatic stellate cells; HA: Hyaluronic acid; CO-IV: Collagen type four; LSM: Liver stiffness measurement; NAFLD: Non-alcoholic fatty liver disease; AASLD/EASL: American Association for the Study of Liver Diseases/European Association for the Study of the Liver; IDSA: Infectious Diseases Society of America; HCC: Hepatocellular carcinoma; HGF: Hepatocyte growth factor; MET: Met proto-oncogene (hepatocyte growth factor receptor); TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; CD95: Fas cell surface death receptor.

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Authors' contributions

The authors completed the study protocol and were the main organizer of data collection drafting and revising the manuscript perfectly. T.A. Addissouky has written the article and guarantees the paper carefully. All authors contributed to the discussion and reviewed the manuscript as well as helped in designing the study and protocol and engaged in a critical discussion of the draft manuscript. All authors have affirmed on the final copy of the manuscript. Moreover, all authors have read and approved the manuscript.

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Availability of data and materials

All data are available and sharing is available as well as publication.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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