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Liver fibrosis from viral hepatitis: advances in non-invasive diagnosis

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ABSTRACT

The stages of liver fibrosis can reflect the severity of chronic viral hepatitis and the probability of liver cancer. Biopsy is still regarded as the reference for staging fibrosis, but the invasive method is not suitable for first-line screening. In recent years, noninvasive methods for detecting virus-driven liver fibrosis have been developed rapidly, which mainly include biological (serum biomarkers indexes) and physical (imaging assessment of liver stiffness) strategies. In this review, we introduce these noninvasive methods, enumerate their diagnosis performances and discuss the role of ferroptosis. At last, we propose directions for future researches.

KEYWORDS

Noninvasive; Liver fibrosis; Diagnostic tests; Serum biomarkers; Imaging techniques

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1. Introduction

Chronic viral hepatitis, including chronic hepatitis B (CHB) and C (CHC), has become a major public health problem worldwide [1, 2]. Both viruses infect liver cells, replicate within them and activate hepatic stellate cells, leading to inflammatory cascades, production of excessive collagen and fibrosis [3, 4]. Liver fibrosis is the accumulation of excessive parenchymal collagen and it becomes as the intermediate stage of liver cirrhosis which contributes to a high rate of morbidity, mortality and high cost of medical resources [5, 6]. As the condition of early-stage liver fibrosis is insidious without apparent symptoms, it is common that many patients face intractable liver injury due to the rapid progress of fibrosis when they are diagnosed with advanced fibrosis or cirrhosis which has limited reversal leeway [7, 8]. Moreover, early-stage fibrosis is reversible and patients who treated with early fibrosis have significantly higher survival rates compared with those untreated [9]. Therefore, it is necessary to conduct early diagnosis and management for patients with liver fibrosis.

Liver biopsy is currently recommended as the reference method for evaluating the severity of liver diseases (e.g. hepatic fibrosis and cirrhosis) because it can accurately find some valuable information regarding staging, prognosis and management [10, 11]. However, this method has several limitations. Interobserver variation really exists in liver biopsy and it can potentially limit the diagnostic accuracy [12, 13]. And more notably, liver biopsy is an invasive method and it can cause intraprocedural pain and some postprocedural complications such as abdominal pain, hemobilia, septicemia, mesenteric thrombosis, ascites and arteriovenous fistula [14-18]. Although these complications remain rare, patients' determination of accepting biopsy has been substantially affected.

Due to limitations of liver biopsy, noninvasive methods for staging virus-driven liver fibrosis have advanced and the use of liver biopsy has reduced. We review noninvasive diagnostic methods for liver fibrosis and discuss novel research idea about fibrosis-related markers.

2. Histologic stage of liver fibrosis

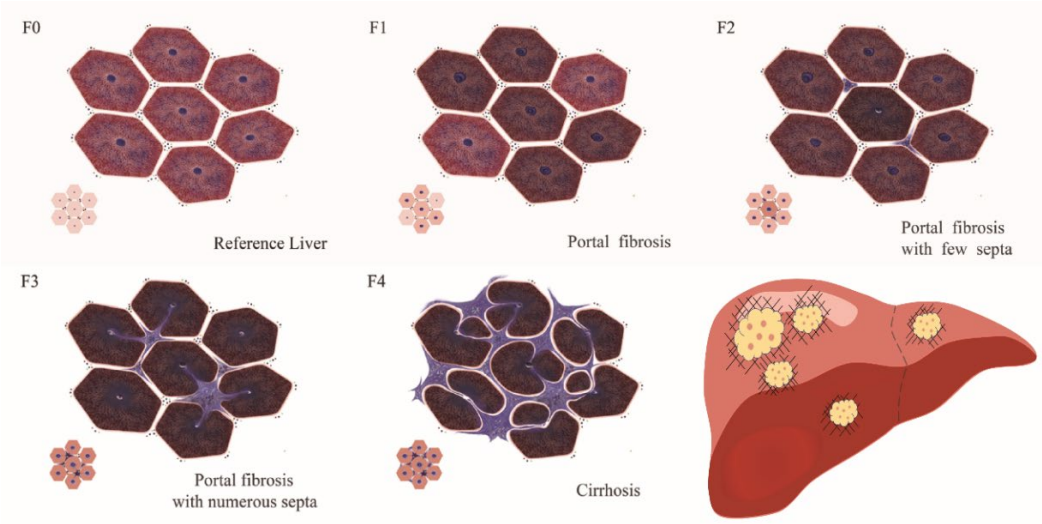

Figure 1. Diagrammatic representation of the five stages (0-4) of the Metavir score system. Normal liver (stage 0) has little fibrous tissue in the portal areas and the walls of central veins. Chronic viral hepatitis leads to fibrous expansion of portal tracts and eventually of all portal tracts (stage 1). Fibrous septa extend to form bridges between adjacent vascular structures (stage 2), progressing to numerous bridges or septa (stage 3). Eventually, parenchymal nodules completely surrounded by fibrosis may form while some areas still maintain lobular architecture, indicating an early-stage or incomplete cirrhosis, and it can be considered as an established cirrhosis when the tissue is entirely composed of nodules (stage 4). Serious fibrosis indicates a high incidence of liver cancer.

The Metavir system was specially designed for chronic hepatitis C [19], but it is also applied for hepatitis B. As shown in **Figure 1**, stage 1 represents portal fibrosis without septa. Stage 2 and 3 are defined when rare septa and

numerous septa are present, respectively. Stage 4 represents cirrhosis. We recommend assigning stage 2 only when there is bridging fibrosis, which is consistent with most clinical studies considering stage 2 as clinically significant fibrosis. We cite the Metavir system mainly because most clinical studies staged liver fibrosis according to the Metavir system. In addition, the Metavir system was initially designed for chronic viral hepatitis B and C which are our concerned etiologies in this review.

3. Noninvasive methods of liver fibrosis assessment

Liver fibrosis can be noninvasively assessed through two approaches including a "biological" approach (quantifying serum biomarkers) or a "physical" approach (measuring liver stiffness with the use of image technology). These two approaches can perform their unique functions according to different rationales.

3.1. Serum biomarkers of liver fibrosis

There are numerous serum biomarkers evaluated for their speciality to indicate fibrosis, particularly in CHC patients [20-23]. In general, the traditional proposed biomarkers are divided into direct and indirect markers. Direct markers such as glycoproteins (hyaluronic acid (HA), laminin and YKL-40), collagens (type III procollagen aminoterminal peptide (PIIINP) and type IV collagen), collagenases and their inhibitors (matrix metalloproteases and tissue inhibitor of metalloproteinase 1 (TIMP-1)), indicate the deposition or removal of fibrotic tissue in the liver. Indirect markers are variables associated with liver function. These factors include the prothrombin time, platelet count, haptoglobin, α2-macroglobulin (A2M), apolipoprotein A1, bilirubin, glutamyltranspeptidase (T), APRI score (AST/platelet ratio) and aspartate aminotransferase to alanine aminotransferase ratio (AST/ALT). In addition, combinations of direct and indirect markers data have been used in diagnosis. For instance, markers (A2M, α2-globulin, γ-globulin, apolipoprotein A1, T and total bilirubin) in t he FibroTest as the first proposed algorithm were combined with age and gender [24]. Other blood test scores have been proposed (**Table 1**)[25-42]. These published models have been used as diagnostic methods on the basis of routine laboratory tests. olgi protein 73 (P73), Mac -2 binding protein glycan isomer (M2BPi), Wisteria floribunda agglutinin -positive Mac-2 binding protein (WF), microfbrillar-associated protein 4 (MFAP4), Sialic-acid-binding immunoglobulin-like lectin-7 (Siglec-7) level, soluble Axl (sAxl), osteopontin, serum iron markers (especially ferritin and transferrin) and angiotensin converting enzyme (ACE) were found as potential biomarkers in recent years [42-50]. The applications of these new-found serum biomarkers for diagnosis of liver fibrosis need more practice and further research.

Using serum biomarkers to assess liver fibrosis has practical advantages including their high applicability (>95%) [51, 52], their great interlaboratory reproducibility [53, 54], and their widespread availability [55]. However, they lack specificity to the liver and their results are influenced by concurrent systemic conditions. Furthermore, the clearance of these biomarkers is dependent on renal and hepatic function [56]. For instance, when using Fibrotest or Hepascore, the hyperbilirubinemia in patients with ilbert's syndrome or hemolysis can lead to false-positive results [57]. Similarly, acute hepatitis can result in false-positive results in several blood indexes such as APRI, FPI, Fibrometers, Lok index, UCI, Virahep -c model, Fibroindex and FIB-4, because all need to measure levels of aminotransferases in their formulas.

Table 1. Blood Indexes for Assessment of Liver Fibrosis or Cirrhosis in Paitents with Chronic Viral Hepatitis

Index	Items, *n*	Age	Platelet Count	AST Level	ALT Level	Other Components
FibroTest	7	√				A2M, α_2-globulin, γ-globulin, apolipoprotein A1, T, total bilirubin and sex
Forns index	4	√	√			T and cholesterol
APRI	2		√	√		
FibroSpectII	3					A2M, HA and TIMP-1
ELF	4	√				HA, MMP-3 and TIMP-1
FPI	5	√		√		Past alcohol use, insulin resistance and cholesterol
Hepascore	6	√				Bilirubin, T, HA, A2M and gender
Fibrometers	7	√	√	√		Prothrombin index, A2M, HA, urea and gender
Lok index	4		√	√	√	INR
UCI	3		√	√		Prothrombin-INR
Virahep-c model	5	√	√	√		Race and alkaline phosphatase
Fibroindex	3		√	√		γ-globulin
FIB-4	4	√	√	√	√	
MP3	2					PIIINP and MMP-1
HALT-C model	3		√			TIMP-1 and HA
FIB-5	5		√	√	√	Albumin and alkaline phosphatase
Hui score	4		√			BMI, bilirubin, and albumin
Zeng score	4	√				A2M, T and HA
P73 algorithm	1					P73

Notes: ALT = alanine aminotransferase; APRI = AST-platelet ratio index; AST = aspartate aminotransferase; A2M =α2-macroglobulin; BMI = body mass index; ELF = enhanced liver fibrosis; FPI = fibrosis probability index; T = γ-glutamyltransferase; P73 = olgi protein 73; UCI = oteborg University cirrhosis index; HA = hyaluronic acid; HALT-C = Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis; INR = international normalized ratio; MMP-1 = matrix metalloproteinase-1; MMP-3 = matrix metalloproteinase-3; PIIINP = type III procollagen aminoterminal peptide; TIMP-1 = tissue metalloproteinase inhibitor 1.
The last three blood indexes are used in patients with hepatitis B and the others are suitable for patients with hepatitis C.

3.2. Morphologic and imaging methods

3.2.1. Transient elastography

Liver fibrosis can be staged with the use of one-dimensional (1-D) transient elastography (TE) [58]. TE is a technique based on ultrasound (US) (5 MHz) and low-frequency (50 Hz) elastic waves, whose propagation velocity through the liver is directly related to liver tissue stiffness. The measurement results are expressed in kilopascals (kPa) which range between 2.4 and 75.4 kPa [59]. The normal value of liver stiffness is around 4.5 kPa [60, 61].

Advantages of TE include a short procedure time (< 5 min), immediate results and convenience. It can be easily performed after a little amount of training [62]. Nevertheless, accurate TE results require median value on the basis of at least 10 validated measurements, a high measurement success rate (≥60%), and an interquartile range (IQR) less than 30% of the median (M) liver stiffness measurements (LSM) value (IQR/M ≤30%) [63-65]. TE analysis has excellent intra- and interobserver agreement [66, 67], but its low applicability compared with serum biomarkers becomes the major limitation of TE [68]. It was reported the occurrence of LSM failure is 3.1%, which resulted from

obesity (especially increased waist circumference) and limited operator experience [69]. Currently, the applicability of TE can be increased in obesity with the use of a new probe named XL probe, which can overcome the limitations for overweight or obese patients [70, 71]. Since velocity of the elastic waves attenuate when propagating through liquids, it is impossible to obtain TE results from patients with ascites [72]. Space-occupying tissue abnormalities, including edema, inflammation, cholestasis and congestion, can interfere with TE results [73]. The influence of steatosis remains controversial [74-77].

3.2.2. Ultrasound- and magnetic resonance-based methods

Technological advances have allowed liver fibrosis staging using various elasticity-based imaging techniques, including ultrasound-based techniques (acoustic radiation force impulse imaging (ARFI) or 2-D ShearWave elastography (2D-SWE)) and magnetic resonance elastography (MRE) [78, 79].

ARFI involves mechanical excitation of liver tissue using short-duration (~262 μsec) acoustic pulses which propagate shear waves and generate localized, μ-scale displacements in liver tissue [80]. The major advantage of ARFI is higher applicability than TE [81]. ARFI values are not expressed in kPa and have a narrower range (0.5-4.4 m/sec), which limits the definition of clinically relevant cut-off values.

2D-SWE, as a novel elastographic technique, is performed with Aixplorer ultrasound system, where shear waves are created in tissue from the radiation force generated by focused ultrasonic beams and a very high frame rate ultrasound imaging sequence has the ability to catch the transient propagation of resulting shear waves with a high range of values (2-150 kPa) [82]. The applicability of 2D-SWE is high: it requires approximately 7 min per examination and steatosis or disease activity has almost no influence on to the results [83, 84]. Like ARFI, its definition of clinically relevant cut-off values is limited.

3-D MRE images the propagation characteristics of the shear wave in the liver with a modified phase-contrast method [85], that can be implemented on a conventional magnetic resonance imaging (MRI) system. Elasticity is quantified by MRE (expressed in kPa) with the use of a formula that calculates the shear modules [86]. A cut-off value of 3 kPa in MRE is used to distinguish patients with normal liver parenchyma from those with fibrosis [87, 88]. MRE has obvious advantages including assessment of almost the entire liver and 3-D evaluation of the displacements induced by the mechanical waves [89]. In addition, MRE is not affected by obesity, ascites and space-occupying tissue abnormalities, indicating that it has good applicability. However, the hepatic MRI signal can be so low when performed in patients with moderate to severe iron overload because of hemochromatosis or hemosiderosis, which results from signal-to-noise limitations [90]. In current routine practice, MRE remains very costly and time-consuming.

3.3. Computed tomography

Computed tomography (CT), as a frequently used diagnostic method in modern medicine, is inferior to above-mentioned methods (laboratory testing and elasticity-based imaging techniques) in the noninvasive diagnosis of liver fibrosis [91]. Several quantitative indexes can contribute to diagnosis of liver fibrosis. The three major hepatic vein diameters and the caudate-right-lobe radio (ld/crl-r) is a powerful method even in precirrhotic stage of the disease. It was reported that ld/crl-r ≤ 23.9 could be performed with a sensitivity of 0.83 and a specificity of 0.76 to detect F1-F3 liver fibrosis. Another discovered index is liver-to-spleen volumetric ratio with high sensitivity and high specificity for staging liver fibrosis [92, 93]. Perfusion CT is a noninvasive functional imaging method that can reveal the hemodynamic state of tissue and organs. Researchers agree that portal venous perfusion or total liver perfusion is negatively corelated with the severity of liver fibrosis and cirrhosis which is positively corelated with hepatic arterial perfusion, hepatic perfusion index (HPI), the peak time and the mean transit time [94, 95]. It is very easy to carry out CT scanning (almost 5 min per examination) even in local small hospitals which becomes as the

major advantage of CT. However, CT lacks enough diagnostic accuracy due to the limited image findings for the significant and advanced fibrosis [96, 97].

4. Diagnostic performance

4.1. Serum biomarkers

Table 2. Diagnostic Performance of Serum Biomarkers of Significant liver Fibrosis (F ≥2) or Cirrhosis (F4) in Patients with Viral Hepatitis.

Index	Etiologies	Year	Patients (n)	F≥2 (%)	F4 (%)	Cut-offs	AUROC	Se (%)	Sp (%)	CC (%)
FibroTest	HCV	2001	339	80		>0.48	0.87	75	85	
Forns index	HCV	2002	476	26		<4.2 >6.9	0.81	30-94	51-95	
APRI	HCV	2003	270	50		≤0.5 >1.5	0.80	41-91	47-95	
					17	<1.0 ≥2.0	0.89	57-89	75-93	
FibroSpectII	HCV	2004	696	52		>0.36	0.83	77	73	
ELF	Mixed	2004	1021/496[a]	40		0.102	0.78	87	51	
					12	NA	0.89	NA	NA	NA
FPI	HCV	2005	302	48		≤0.2 ≥0.8	0.77	42-85	48-98	20
Hepascore	HCV	2005	211	57		≥0.5	0.82	63	89	92
					16	>0.84	0.89	71	89	NA
Fibrometers	Mixed	2005	598/503[b]	56		NA	0.89	80	84	82
Lok index	HCV	2005	1141		38	<0.2 ≥0.5	0.81	40-98	53-99	52
UCI	HCV	2005	179		12	>0.1	0.85	80	70	NA
Virahep-c model	HCV	2006	398	37		≤0.22 >0.55	0.83	51-90	54-90	52
Fibroindex	HCV	2007	360	50		≤1.25 ≥2.25	0.83	30-40	97	35
FIB-4	HCV	2007	847		17[c]	<1.45 >3.25	0.85	38-74	81-98	68
MP3	HCV	2004	194	45		<0.3 >0.4	0.82	35-65	85-96	NA
HALT-C model	HCV	2008	512		38	<0.2 ≥0.5	0.81	47-88	45-92	48
FIB-5	HCV	2017	604	35		≥7.505	0.71	18	94	86
Hui score	HBV	2005	235	25		≤0.15 >0.5	0.79	37-88	50-88	49
Zeng score	HBV	2005	372	58		<3.0 >8.7	0.77	40-98	28-90	35
P73 algorithm	HBV	2017	133	54		>63	0.76	68	75	71

Notes: AUROC = area under ROC curve; CC = correctly classified: true positive and true negative; HBV = chronic hepatitis B; HCV = chronic hepatitis C; NA = not available; Se = sensitivity; Sp = specificity.

[a]Number of HCV patients.

[b]Number of patients with viral hepatitis.

[c]F3-F4 patients.

Computed the diagnostic performances of serum biomarkers of liver fibrosis are summarized in **Table 2**. Overall, serum biomarkers are less accurate in detecting significant fibrosis than single cirrhosis. The most widely used and clinically validated are the APRI (a free non-patented index) and the FibroTest (a patented index that is not widely available). A systematic review including 172 studies conducted in patients with HCV reported that median AUROCs of 0.77 and 0.84 for APRI and of 0.79 and 0.86 for FibroTest, for significant fibrosis and cirrhosis, respectively [98]. A meta-analysis that analyzed data from 4248 patients with HBV (2494 for significant fibrosis and 1754 for cirrhosis) who received the FibroTest and liver biopsies found that the mean standardized AUROC of significant fibrosis and cirrhosis was 0.84 and 0.87, respectively [99]. Another meta-analysis of APRI in 8739 HCV patients found that the summary AUROC of significant fibrosis, severe fibrosis, and cirrhosis were 0.77, 0.80, and 0.83, respectively [100]. In a large comparative study (n=9377 patients infected with HBV) [101], the summary AUROC values were of 0.74 and 0.73 for APRI and of 0.82 and 0.84 for FIB-4, for significant fibrosis and cirrhosis, respectively. A recent study [102] compared the diagnostic performance of 10 biomarkers of liver fibrosis including patented tests (ELF, Hepascore, FibroSpectII, Fibrometer V2 and Fibrometer V3) and nonpatented but popular tests (AST:ALT ratio, APRI, Forns index, FIB4 and HA) among 80 CHC patients. Results of this study showed that the best performing biomarkers were the virus-specific indexes, Fibrometer V2 and Fibrometer V3 overall and the best performing indexes were ELF and Hepascore with regard to biomarkers used in all etiologies of liver diseases. Although nonpatented tests (APRI, the Forns index and FIB4) could have inferior diagnostic performance compared with those patented indexes, they do not lead to any cost with high cost-effectiveness.

4.2. Morphologic and imaging methods

4.2.1. Transient elastography

The ability of TE to quantify virus-driven liver fibrosis has been confirmed in many studies [103-114]. TE more accurately detects cirrhosis (AUROC, 0.85-0.97; correct classification (CC), 82%-94%) than significant fibrosis (AUROC, 0.75-0.90; CC 57%-90%) (**Table 3**). There seems no difference of proposed cut-off values between patients with HCV (Cut-off values, 5.2-7.4 kPa) and patients with HBV (Cut-off values, 5.2-7.8 kPa). However, cut-off values for cirrhosis in HCV groups (11.9-14.5 kPa) were higher than these in HBV groups (9.0-12.9 kPa). A meta-analysis [115] showed, several researchers have proposed the optimal cut-off value of 7.65 kPa and 13.01 kPa for significant fibrosis and cirrhosis, respectively.

Meta-analyses have confirmed TE behave better for cirrhosis than significant fibrosis [115-118]. In a meta-analysis of 22 studies including 4430 patients, sensitivity and specificity values were 0.72 and 0.82, respectively, for patients with significant fibrosis and 0.84 and 0.95, respectively, for patients with cirrhosis [117]. A recent meta-analysis that analyzed data from 10504 patients found that the AUROC was 0.931 and pooled estimates for the sensitivity of TE for detecting liver cirrhosis was 0.81 and the specificity was 0.88, which indicated that TE had good performance for diagnosis of cirrhosis [118]. However, a meta-analysis of data from individual patients is still lacking.

Table 3. Diagnostic Performance of Transient Elastography for Significant Fibrosis (F ≥2) or Cirrhosis (F4) in Patients with Viral Hepatitis.

Authors	Etiologies	Year	Patients (n)	F≥2 (%)	F4 (%)	Cut-offs (kPa)	AUROC	Se (%)	Sp (%)	CC (%)
Castera et al	HCV	2005	183	74		7.1	0.83	67	89	73
					25	12.5	0.95	87	91	90
Lupsor et al	HCV	2008	324	65		7.4	0.86	76	84	79
					21	11.9	0.94	87	91	90
Kirk et al	HCV[a]	2009	192	37		9.3	0.87	86	75	79
					25	12.3	0.87	75	86	83
Degos et al	HCV	2010	913	62		5.2	0.75	90	32	57
					14	12.9	0.90	72	89	87
Cardoso et al	HCV	2012	363	54		7.1	0.87	68	89	78
					8.5	12.5	0.95	84	94	93
Zarski et al	HCV	2012	382	47		5.2	0.82	97	35	64
					14	12.9	0.93	77	90	88
Seo et al	HCV	2015	349	64		6.8	0.82	67	86	67
					6.3	14.5	0.91	82	89	82
Elsharkawy et al	HCV	2017	652	46		7.1	0.90	86	86	85
					12	12.2	0.96	92	99	91
Foucher er al	Mixed	2006	354	69		7.2	0.80	64	85	71
					27	17.6	0.96	77	97	92
Coco et al	Mixed	2007	228	62		8.3	0.93	85	91	87
					50[b]	14.0	0.96	78	98	88
Oliveri et al	HBV	2008	188	26		7.5	0.97	94	88	90
					20[b]	11.8	0.97	86	96	94
Degos et al	HBV	2010	284	42		5.2	0.78	89	38	59
					10	12.9	0.85	52	93	89
Cardoso et al	HBV	2012	202	42		7.2	0.87	74	88	82
					8	11.0	0.94	75	90	89
oyal et al	HBV	2013	357	23		6.0	0.84	82	67	NA
					6	9.0	0.93	81	90	NA
Seo et al	HBV	2015	567	72		7.8	0.77	71	74	72
					21	11.6	0.90	85	85	85
Zeng et al	HBV	2017	235	46		7.3	0.85	79	81	80
					13	11.2	0.91	94	83	85

Notes: AUROC = area under ROC curve; CC = correctly classified: true positive and true negative; HBV = chronic hepatitis B; HCV = chronic hepatitis C; NA = not available; Se = sensitivity; Sp = specificity.

[a]Part of patients infected with human immunodeficiency virus (HIV) in the meantime.

[b]More than half of patients with clinical cirrhosis.

4.2.2. Ultrasound-based methods

Performances of ultrasound-based techniques including ARFI and 2D-SWE are shown in **Table 4**. Like TE, ARFI and 2D-SWE more accurately detect cirrhosis (AUROC values: 0.79-0.97 and 0.93-0.98, for ARFI and 2D-SWE, respectively) than significant fibrosis (AUROC values: 0.73-0.86 and 0.76-0.97, for ARFI and 2D-SWE, respectively). A large study [119] including 349 patient data which evaluated ARFI for staging of CHB and CHC reported similar sensitivity and specificity of 0.7-0.8 for significant fibrosis and cirrhosis. And in terms of 2D-SWE, the largest study [120] including 437 patient data for staging of chronic hepatitis B, reported sensitivity and specificity for significant

fibrosis of 0.78 and 0.85 and for cirrhosis of 0.92 and 0.84, respectively.

Table 4. Diagnostic Performance of ultrasound-based techniques for Significant Fibrosis (F ≥2) or Cirrhosis (F4) in Patients with Viral Hepatitis

Authors	Methods	Etiologies	Year	Patients (n)	F≥2 (%)	F4 (%)	Cut-offs (kPa)	AUROC	Se (%)	Sp (%)	CC (%)
Friedrichrust et al	ARFI	Mixed	2009	81	67		5.6	0.82	69	93	77
						27	9.2	0.91	82	92	89
Cassinotto et al	ARFI	Mixed	2013	321	58		5.7	0.77	71	78	74
						23	7.8	0.84	82	74	76
Friedrich-Rust et al	ARFI	HBV	2013	88	25		5.8	0.73	50	90	38
						3.4	NA	0.97	NA	NA	NA
Cassinotto et al	ARFI	Mixed	2014	349	61		5.7	0.81	72	81	75
						27	7.8	0.90	81	77	78
Li et al	ARFI	HCV	2014	128	68		7.0	0.78	58	90	NA
						13	9.6	0.79	79	75	NA
Zhang et al	ARFI	HBV	2015	180	72		6.4	0.76	59	88	67
						18	9.2	0.83	73	84	82
Li et al	ARFI	HBV	2017	126	60		7.6	0.86	68	88	NA
						16	11.1	0.95	85	92	NA
Zeng et al	2D-SWE	HBV	2014	104	55		7.2	0.91	85	81	83
						16	11.7	0.97	88	88	60
Zheng et al	2D-SWE	Mixed	2015	167	59		5.7	0.86	86	74	81
						20	11.6	0.93	91	80	82
Wu et al	2D-SWE	HBV	2016	437	47		8.2	0.90	78	85	82
						14	11.3	0.93	92	84	85
Zhuang et al	2D-SWE	HBV	2016	155	85		7.6	0.97	92	88	91
						48	10.4	0.98	92	95	94
Paul et al	2D-SWE	Mixed	2017	237	49		6.0	0.76	67	70	74
						2.5	9.7	0.93	83	91	91
Zeng et al	2D-SWE	HBV	2017	235	46		7.1	0.88	89	76	82
						13	11.3	0.93	94	87	88
Abe et al	2D-SWE	HCV	2018	233	64		7.3	0.92	85	86	85
						30	11.2	0.95	91	91	91
Serra et al	2D-SWE	Mixed	2018	174	36		8.1	0.86	75	86	83
						10	11.0	0.94	88	89	89

Notes: ARFI = acoustic radiation force impulse; AUROC = area under ROC curve; CC = correctly classified: true positive and true negative; HBV = chronic hepatitis B; HCV = chronic hepatitis C; NA = not available; Se = sensitivity; Sp = specificity; 2D-SWE = two-dimensional shear-wave elastography.

Several meta-analyses have proved the better performance of ARFI or 2D-SWE for cirrhosis than for significant fibrosis [121-123]. A pooled meta-analysis analyzing data from 518 patients (83.2% with viral hepatitis) showed AUROCs were 0.87 for significant fibrosis and 0.93 for cirrhosis [121]. Cut-off values suggested in this meta-analysis were 1.34 m/s (5.39 kPa) for significant fibrosis and 1.80 m/s (9.72 kPa) for cirrhosis. Moreover, guidelines used 1.35 m/s (5.47 kPa) and 1.87 m/s (10.49 kPa) as cut-off values [124]. In addition, alanine transaminase (ALT) levels can influence ARFI measurements. A comparative study [125] suggested the optimal cut-off values for ARFI were 1.63 m/s (7.97 kPa) for significant fibrosis and 2.00 m/s (12 kPa) for cirrhosis in patients with elevated ALT levels. The cut-off values decreased to 1.24 m/s (4.61 kPa) and 1.41 m/s (5.96 kPa) in patients with normal ALT levels. The latest meta-analysis of 2D-SWE [123] that analyzed data from 1134 patients reported the overall accuracy were

69.7% and 82.9% for significant fibrosis and liver cirrhosis, respectively. This meta-analysis found the cut-off values of 2D-SWE are different due to etiologies. Cut-off values of 2D-SWE were 7.095 kPa and 13.3 kPa, respectively, for significant fibrosis and cirrhosis in CHC and 6.95 kPa and 10.90 kPa, respectively, for significant fibrosis and cirrhosis in CHB.

4.2.3. 3-D magnetic resonance elastography

In recent years, not so many studies have evaluated 3-D MRE for staging liver fibrosis and performances of MRE are summarized in **Table 5**[126-129]. These studies reported similar accuracy of MRE for significant fibrosis and cirrhosis. In a meta-analysis [130] of 13 studies including 989 patients, sensitivity and specificity were 0.87 and 0.92, respectively, for significant fibrosis and 0.91 and 0.92, respectively, for cirrhosis. A systematic review [131] that analyzed data from 687 patients found the high AUROC of 0.88 and 0.92 for significant fibrosis and cirrhosis, respectively.

Three studies have compared MRE and TE in patients with chronic liver diseases [87, 127, 132]. Two studies [87, 127] suggested that MRE might be more accurate than TE for diagnosing significant fibrosis whereas another study [132] reported similar results. A comparative study [133] reported that MRE is more accurate than ARFI with particularly for early-stage liver fibrosis.

Table 5. Diagnostic Performance of MRE for Significant Fibrosis (F ≥2) or Cirrhosis (F4) in Patients with Viral Hepatitis.

Authors	Etiologies	Year	Patients (n)	F≥2 (%)	F4 (%)	Cut-offs (kPa)	AUROC	Se (%)	Sp (%)	CC (%)
Venkatesh et al	HBV	2014	63	62		3.2	0.99	97	100	98
					33	4.3	0.98	100	95	97
Ichikawa et al	Mixed	2015	113	76		2.3	0.98	99	52	88
						2.7		94	96	95
					38	3.7	0.97	98	80	87
						5.3		74	99	89
Shi et al	Mixed	2016	179	50		3.1	0.96	96	85	91
					23	4.2	0.98	97	89	92
Hennedige et al	HBV	2017	63	62		3.2	0.99	97	100	98
					33	4.3	0.98	100	95	97

Notes: AUROC = area under ROC curve; CC = correctly classified: true positive and true negative; HBV = chronic hepatitis B; HCV = chronic hepatitis C; MRE = magnetic resonance elastography; NA = not available; Se = sensitivity; Sp = specificity.

4.2.4. Computed tomography for staging liver fibrosis

CT lacks enough diagnostic accuracy and several single indicators of it require a formula to build relationships. As previously mentioned, an ld/crl-r <24 showed a sensitivity of 0.83 and a specificity of 0.76 for precirrhotic liver fibrosis and liver cirrhosis could be detected with a sensitivity of 0.88 and a specificity of 0.82 if ld/crl-r <20. Another study using perfusion CT reported that a mean transit time threshold of 13.4 seconds allowed discrimination between minimal (F1) and intermediate (F2 or F3) fibrosis with a sensitivity of 0.71 and a specificity of 0.65. A study [134] using deep learning techniques based on CT images showed the AUROC values for diagnosing significant fibrosis and cirrhosis were 0.74 and 0.73, respectively, indicating that liver fibrosis can be staged by using deep learning with moderate performance. Wang et.al used radiomics on non-contrast CT images to successfully

predict HBV-driven liver cirrhosis [96] and then provided an updated image biomarker based on radiomics at contrast-enhanced CT for significant and advanced fibrosis and cirrhosis [97].

5. Prospects

5.1. Novel blood biomarkers of fibrosis

A new generation of functional genomic biomarkers are emerging tools for evaluating the dynamic nature of fibrogenesis. However, it is difficult to validate these complex and relatively expensive methodologies, thus limiting their clinical practice. The sustained development of molecular pathology techniques in established rodent models (e.g. targeted bioimaging to evaluate fibrogenic pathways of progression and reversibility) is a promising approach to identify novel biomarkers of liver fibrosis. For instance, integrin αvβ6 and the PDF receptor, which are upregulated on activated cholangiocytes and hepatic stellate cells (HSC), respectively, are attractive targets for small molecular imaging ligands, which could help quantitation of fibrogenesis across the whole liver [135]. Recent advances and decreasing costs of high-throughput genotyping technologies have resulted in an increasing number of genome-wide association studies (WAS) to evaluate disease progression [136]. For instance, the Cirrhosis Risk Score (CRS) using an algorithm based on seven single-nucleotide polymorphisms (SNP) is corelated with disease progression in CHC patients with mild liver fibrosis [137].

Current genomic and proteomic research provides a number of candidate serum biomarkers [138-140]. For instance, Cheung et al. found hepatitis C-related fibrosis progression was related to galectin-3-binding protein (3BP) [141]. Lu et al. identified peroxi redoxin 2 as a potential biomarker of HBV related liver fibrosis [142]. However, independent validation of these candidate biomarkers is lacking and reproducibility is still a major concern [143].

MicroRNAs (miRNA) are small noncoding RNAs that regulate posttranscriptional gene expression and are associated with a diverse range of pathophysiologic processes. Several miRNAs have been proposed as potential markers of fibrosis since miRNAs appear to regulate the fibrogenic cascade at multiple levels [144]. For instance, many studies have demonstrated how miRNAs interact with Hh signaling in liver fibrosis, which could be useful biomarkers and novel therapeutic agents of personalized medicine for fibrosis [145]. A study analyzing miRNA profiles in a total of 495 CHB patients, cirrhosis patients and healthy donors, reported that some circulating miRNAs have promising diagnostic performance in discriminating CHB from cirrhosis with a sensitivity of 0.85 and specificity of 0.70[146]. The identification of biomarkers based on miRNA transcripts that are detectable in blood or urine represents novel approaches to noninvasively diagnosing liver fibrosis and cirrhosis.

5.2. Future imaging techniques

ARFI and SWE representing ultrasound-based elastography techniques are the most advanced and promising. Their use is becoming more frequent and common in clinical practice. MRE has its unique advantage of analyzing a substantially larger liver volume in order to precisely analyze the viscoelastic properties of the liver through a full 3D assessment of the wave displacement. However, whether MRE has better performances than TE remains controversial because studies comparing MRE with TE have shown conflictive results. Additionally, MRE procedure is too cumbersome and not standardized enough for widespread use in routine clinical practice. In the future, image analysis techniques such as radiomics can be applied to CT images so as to dig deeper for more information [96, 97]. Indirect features such as liver-to-spleen volumetric ratio and blood vessel diameter ratio can become as auxiliary references, which require algorithm models to be built to establish relationship among effective features.

5.3. New strategies for staging liver fibrosis

Strategies that integrate more than two serum indices with or without LSM have been proposed to increase diagnostic accuracy for CHC [147-151]. Traditional models such as above-mentioned blood indexes generally use statistical methods to make fitting formulas which can not include all serum biomarkers, let alone parameters from imaging methods. Artificial neural network algorithm such as deep convolutional neural network used in these two studies [152] can combine almost all parameters to analyze and cluster for staging liver fibrosis, although these parameters are not related with each other. Future diagnostic strategies can import machine learning algorithms and comprehensively consider multifaceted diagnostic features (**Figure 2**)[153].

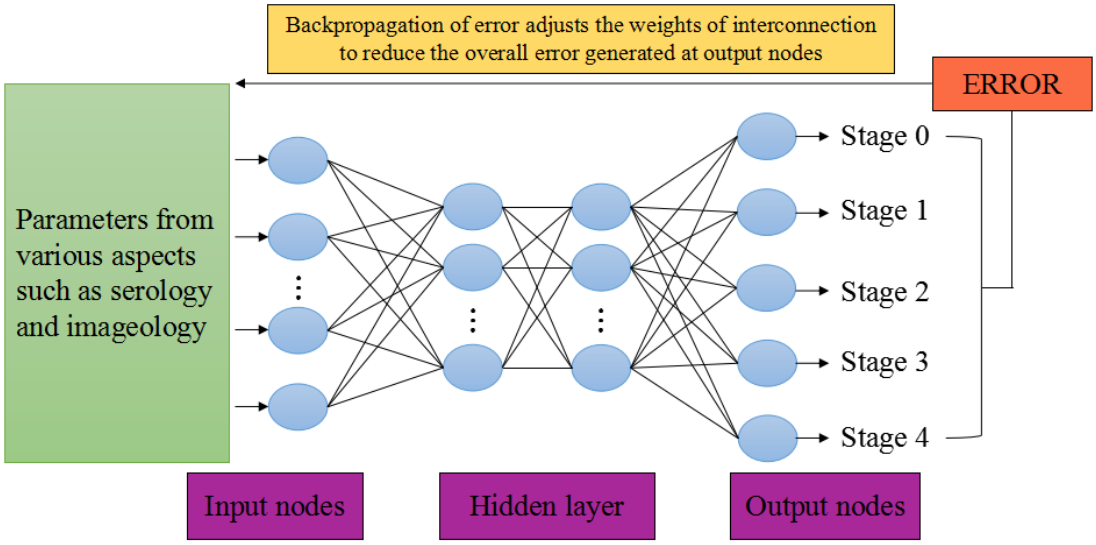

Figure 2. Schematic representation of the artificial neural network (ANN) envisaged to predict liver fibrosis stage. Parameters from various aspects such as serology (serum biomarkers) and imageology (elastography values and imaging features) can be input into the ANN model and clustering results (fibrosis stages) can be output with calculation of hidden layers. The number of hidden layers depends on several relational expression involving the number of input nodes or output nodes. When errors of clustering results happen, models will adjust the weights of interconnection to reduce the overall error generated at output nodes with the negative feedback mechanism in the model.

5.4. Strategies derived from ferroptosis

Ferroptosis provides new directions for diagnosis and treatment in patients with liver fibrosis. Li et al. proved the status of the ferroptosis pathway significantly corelated with the clinical outcomes and intratumor heterogeneity of breast cancer [154]. Xing et al. developed and validated a nomogram integrating ferroptosis- and immune-related biomarker for predicting diagnosis and prognosis in kidney renal clear cell carcinoma [155]. Therefore, selection of ferroptosis-related genes using machine learning techniques in patients with liver fibrosis might offer the opportunity of exploring novel biomarkers. It remains uncertain whether ferroptosis promotes or prohibits fibrosis, and thus many experimental studies are required.

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Conflict of interest

All the authors claim that the manuscript is completely original. The authors also declare no conflict of interest.

Author contributions

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