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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Use of Non-invasive Testing to Stage Liver Fibrosis in Patients with HIV

Bassem Matta[1] · **Tzu-Hao Lee**[2] · **Keyur Patel**[3,4]

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Abstract Patients with HIV have a proclivity to develop liver fibrosis, especially when associated with other conditions such as HCV, HBV, and NAFLD. Identifying HIV-infected patients with significant fibrosis or cirrhosis plays an important role in clinical and therapeutic decision-making. Liver biopsy is currently considered as the gold standard for fibrosis assessment but carries many shortcomings (cost, invasiveness, complications, false negative rate of 20 %). Multiple non-invasive methods of liver fibrosis assessment have been developed, but not all have been studied in HIV-infected individuals. Non-invasive liver fibrosis tools include both serologic-based testing scores (rely on direct and/or indirect markers) such as APRI, FIB4, FibroTest, FibroSpect II, HepaScore, or imaging-based methods such as vibration controlled liver elastography. There is validated data to support the use of non-invasive modalities of fibrosis assessment in HIV-HCV co-infected individuals for the exclusion of cirrhosis, but may be poorly reliable or not enough data exists for the assessment of other co-morbid disease processes.

Keywords Liver fibrosis · Biomarkers · Transient elastography · HIV-hepatitis C · HIV-hepatitis B · HIV non-alcoholic fatty liver disease

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✉ Keyur Patel
keyur.patel@uhn.ca

Bassem Matta
matta.bassem@gmail.com

Tzu-Hao Lee
tzuhao38@kfsyscc.org

[1] Department of Internal Medicine, Duke University Medical Center, Durham, NC, USA

[2] Division of General Internal Medicine, Koo Foundation Sun Yat-Sen Cancer Center, Taipei City, Taiwan

[3] Toronto Centre for Liver Disease, University Health Network Toronto, Toronto, ON, Canada

[4] University of Toronto, Toronto Centre for Liver Disease, Toronto General Hospital, Eaton North, 9th floor Room 232, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada

Introduction

Co-infection of human immunodeficiency virus (HIV) with hepatitis C virus (HCV) or hepatitis B virus (HBV) is commonly observed in clinical practice owing to the shared routes of transmission [1]. Estimates from epidemiological studies indicate that up to 30 % of HIV-infected individuals may also be chronic HCV carriers, while 10 % of HIV-positive individuals harbor HBV infection [1–3]. Furthermore, HIV-infected individuals have a special proclivity to developing non-alcoholic fatty liver disease (NAFLD) not only due to classic risk factors such as obesity, but also as a result of exposure to antiretrovirals (ART) for instance; nucleoside reverse-transcriptase inhibitors were associated with an odds ratio (OR) 1.12/year, (95 % confidence interval (CI) 1.03–1.22) [4]. HIV-infected individuals have received increased attention due to the development of rapid liver fibrosis progression leading to increased morbidity and mortality [5]. Approximately one quarter (15 to 30 %) of monoinfected-HCV patients develop cirrhosis after 30 years of infection; there is a 70 % greater risk of cirrhosis in HIV/HCV patients in the era of combined antretrovirals (cART) [6, 7]. The rate ratio of cirrhosis among co-infected individuals on ART was 2.1 (1.5–3.0) compared to 1.7 (1.1–2.8) in the group receiving

cART [7]. A large study that included 282 HIV-HCV co-infected patients with 435 paired liver biopsies revealed fibrosis progression by at least one METAVIR stage after 2.5 years of follow-up in 34 % of the study population [8]. A retrospective study of 135 co-infected individuals, with a median time of 3.3 years (2.0–5.2) between repeat biopsies, 44 % had fibrosis progression, with 16 % having a ≥2 METAVIR stage increase [9]. Early identification of patients with significant fibrosis, or cirrhosis, carries prognostic implications which might affect management such as screening for associated complications such as hepatocellular carcinoma (HCC), esophageal varices, or initiation of antiviral therapy. Moreover, in light of the recent development of chronic hepatitis C (CHC) interferon-free direct acting antiviral (DAA) regimens, which now achieve high rates of sustained virologic response (SVR) in all genotypes, current challenges revolve around resource allocation and universal availability of these expensive therapies [10–13]. Current guidelines suggest giving high priority to treating HIV-HCV co-infected population to prevent or reverse complications which might ensue from progressive liver damage [10, 14]. Pragmatically, however, there still seems to be issues surrounding access to such medications, and as such determination of (1) the presence of significant fibrosis (defined as METAVIR stage ≥2), or (2) liver cirrhosis is vital for resource allocation and treatment prioritization purposes, along with long-term management after achievement of SVR.

Historically liver fibrosis was assessed using liver biopsy, and this invasive procedure still remains the gold standard for assessment of liver injury, inflammation, and fibrosis. Unfortunately, liver biopsy carries many inherent disadvantages since it is associated with technical issues in obtaining adequate samples (for example 2 cm in length and/or includes 11 complete portal tracts), is subject to inter-observer variability in sample interpretation, and is an invasive procedure which is relatively expensive with the potential for complications (pain, bleeding, peritonitis, and bowel perforation) [15–17]. Moreover, due to the limited sampling of 1/50,000th of the organ's parenchyma, liver biopsy remains imperfect in diagnosing hepatic architectural distortion and collagen deposition. In fact, liver biopsies have been demonstrated to carry a diagnostic error rate of 20–32 % for fibrosis stage [18, 19].

Non-invasive modalities of liver fibrosis assessment have been developed in an attempt to circumvent some of the shortcomings of liver biopsy and allow for repeated testing. Such modalities include both serological-based indices and imaging-based assessments that have been adapted for estimating disease severity in HIV-HCV/HBV co-infected individuals or HIV-NAFLD patients.

Serum-Based Tests in HIV/HCV co-Infection

Over the past decade, we have witnessed the introduction of several surrogate blood biomarkers of liver fibrosis that were initially developed and validated in HCV monoinfection, but then adapted or modified for other chronic liver disease. These can be broadly categorized as (1) direct markers of extracellular matrix turnover such as the proprietary FibroSpect II (Prometheus, San Diego, CA), ELF panels or (2) indirect markers reflecting inflammatory changes at the extracellular matrix interface such as HCV FibroSure (LabCorp, Burlington, NC) also known as FibroTest (BioPredictive, Paris, FR), HepaScore (Quest Diagnostics, Madison, NJ), or FibroMeter (EchoSens, Paris FR). Other simple non-proprietary indirect markers include scores such as the aspartate transaminase (AST) to platelet ratio index (APRI) and FIB-4, which can be easily calculated based on routinely obtained testing.

Examples of direct and indirect serologic fibrosis markers:

- SHASTA index = −3.84 + 1.70 (1 if hyaluronic acid (HA) 41–85 ng/ml, 0 otherwise) + 3.28 (1 if HA >85 ng/ml, 0 otherwise) + 1.58 (albumin <3.5 g/dl, 0 otherwise) + 1.78 (1 if AST >60 IU/l, 0 otherwise) [20].
- FibroTest: patented formula combining α-2-macroglobulin, gamma glutamyl transferase (GGT), apolipoprotein A1, haptoglobin, total bilirubin, age, and gender [21].
- Forns index = 7.811–3.131 × ln (platelet count) + 0.781 × ln (GGT) + 3.467 × ln (age) −0.014 × (cholesterol) [22].
- APRI = AST (/ULN)/platelet (10^9/l) × 100 [23, 24].
- FIB-4: (age × AST)/platelet count (10^9/l) × alanine transaminase (ALT) [25].
- FibroSpect II: patented formula combining α-2-macroglobulin, HA and (TIMP metallopeptidase inhibitor 1) TIMP-1 [26].
- HepaScore: patented formula combining bilirubin, GGT, HA, α-2-macroglobulin, age, and gender [27].
- FibroMeter: patented formula combining platelet count, prothrombin index, AST, α-2-macroglobulin, HA, urea, and age [28].
- ELF panel: TIMP-1, amino-terminal propeptide of type III procollagen, and HA [29, 30].

An early study evaluated the utility of FibroTest in predicting significant fibrosis (≥F2 METAVIR) in 130 HIV-HCV co-infected patients (Table 1) [31]. A score >0.60 was associated with a sensitivity of 66 %, specificity 92 %, positive predictive value (PPV) 86 %, and negative predictive value (NPV) 77 % for detecting ≥F2 METAVIR fibrosis. Scores ≤0.20 had a sensitivity of 97 % and NPV of 93 % to exclude ≥F2 METAVIR fibrosis [31]. The index was also evaluated for its ability to detect cirrhosis (Table 1): a score

Table 1 Performance of non-invasive markers of liver fibrosis in HIV-HCV co-infection

Name (country)	Year	*N*	Index	Detection of	Cut offs	Sens	Spe	PPV	NPV	AUROC (95 % CI)
Myers (France) [31]	2003	130	FibroTest	METAVIR ≥ F2	≤0.20	97.0 %	36.0 %	55.0 %	93.0 %	0.856 (±0.035)
					>0.6	66.0 %	92.0 %	86.0 %	77.0 %	
				Cirrhosis	>0.5	100.0 %	65.0 %	30.0 %	100.0 %	0.869 ± 0.057
Kelleher (USA) [20]	2005	95	SHASTA	MHAI ≥ F3	<0.3	88.0 %	72.0 %	55.0 %	94.0 %	0.878
					>0.8	15.0 %	100.0 %	100.0 %	76.0 %	
			APRI	MHAI ≥ F3	N/A	N/A	N/A	N/A	N/A	0.71
Macias (Spain) [33]	2006	263	Forns	METAVIR ≥ F2	<4.2	78.0 %	38.0 %	64.0 %	56.0 %	0.77 (0.71–0.83)
					>6.9	43.0 %	96.0 %	94.0 %	55.0 %	
			APRI	METAVIR ≥ F2	<0.5	92.0 %	33.0 %	66.0 %	75.0 %	0.80 (0.75–0.86)
					>1.5	51.0 %	91.0 %	87.0 %	57.0 %	
			APRI	Cirrhosis	<1	78.0 %	57.0 %	24.0 %	93.0 %	0.79 (0.71–0.87)
					>2	53.0 %	89.0 %	46.0 %	91.0 %	
			Bonacini	Cirrhosis	<3	100.0 %	9.0 %	17.0 %	100.0 %	0.71 (0.63–0.79)
					>7	43.0 %	83.0 %	31.0 %	89.0 %	
			ALT/AST	Cirrhosis	>1	38.0 %	77.0 %	23.0 %	87.0 %	0.60 (0.50–0.69)
			Platelets	Cirrhosis	<150	63.0 %	37.0 %	33.0 %	92.0 %	0.79 (0.72–0.86)
Loko (France) [34]	2008	200	APRI	METAVIR ≥ F2	≤0.5	87.9 %	48.8 %	87.9 %	52.5 %	0.77 (0.70–0.85
					≥1.5	36.1 %	95.4 %	96.6 %	29.1 %	
			FIB-4	METAVIR ≥ F2	≤0.6	98.1 %	20.9 %	81.9 %	75.0 %	0.79 (0.72–0.86)
					≥1	83.1 %	53.5 %	86.7 %	46.9 %	
			Forns	METAVIR ≥ F2	<4.2	84.1 %	34.6 %	86.2 %	31.0 %	0.75 (0.66–0.84)
					>6.9	23.0 %	100.0 %	100.0 %	21.0 %	
			APRI	Cirrhosis	≤1	85.0 %	62.5 %	36.2 %	94.3 %	0.79 (0.72–0.86
					>2	47.5 %	84.4 %	43.2 %	86.5 %	
			FIB-4	Cirrhosis	≤1.45	82.5 %	63.7 %	36.3 %	93.6 %	0.80 (0.73–0.87)
					≥3.25	40.0 %	90.6 %	51.6 %	85.8 %	
			Platelets	Cirrhosis	<150	67.5 %	77.5 %	42.9 %	90.5 %	0.78 (0.69–0.87)
Macias (Spain) [36]	2010	120	APRI	METAVIR ≥ F2	<0.5	77.0 %	44.0 %	70.0 %	54.0 %	0.66 (0.56–0.76)
					>0.5	29.0 %	91.0 %	85.0 %	44.0 %	
			Forns	METAVIR ≥ F2	<4.2	87.0 %	27.0 %	66.0 %	55.0 %	0.66 (0.56–0.77)
					>6.9	28.0 %	89.0 %	81.0 %	43.0 %	
Vergara (Spain) [51]	2007	169	VCTE	METAVIR ≥ F2	≥7.2 kPa	88.0 %	66.0 %	75.0 %	88.0 %	0.83 (0.75–0.90)
				Cirrhosis	≥14.6 kPa	91.0 %	88.0 %	83.0 %	94.0 %	0.94 (0.89–0.98)
Cacoub (France) [35]	2008	272	FibroMeter	METAVIR ≥ F2	<0.5; ≥0.5	N/A	N/A	N/A	N/A	0.70 (0.64–0.76)
			HepaScore	METAVIR ≥ F2	<0.5; ≥0.5	N/A	N/A	N/A	N/A	0.69 (0.63–0.74)
			FibroTest	METAVIR ≥ F2	<0.48	N/A	N/A	N/A	N/A	0.64 (0.58–0.70)
			FIB-4	METAVIR ≥ F2	≤1.45; ≥3.25	N/A	N/A	N/A	N/A	0.65 (0.59–0.71)
			SHASTA	METAVIR ≥ F2	<0.3; >0.8	N/A	N/A	N/A	N/A	0.64 (0.58–0.70)
			APRI	METAVIR ≥ F2	≤0.5; ≥1.5	N/A	N/A	N/A	N/A	0.65 (0.59–0.71)
			Forns	METAVIR ≥ F2	<4.29; >6.9	N/A	N/A	N/A	N/A	0.69 (0.53–0.65)
			FibroMeter	Cirrhosis	<0.5; ≥0.5	N/A	N/A	N/A	N/A	0.84 (0.78–0.88)
			HepaScore	Cirrhosis	<0.5; ≥0.5	N/A	N/A	N/A	N/A	0.83 (0.78–0.88)
			FibroTest	Cirrhosis	<0.48	N/A	N/A	N/A	N/A	0.81 (0.76–0.85)
			FIB-4	Cirrhosis	≤1.45; ≥3.25	N/A	N/A	N/A	N/A	0.72 (0.67–0.78)
			SHASTA	Cirrhosis	<0.3; >0.8	N/A	N/A	N/A	N/A	0.72 (0.67–0.78)
			APRI	Cirrhosis	≤0.5; ≥1.5	N/A	N/A	N/A	N/A	0.70 (0.64–0.75)
			Forns	Cirrhosis	<4.29; >6.9	N/A	N/A	N/A	N/A	0.79 (0.74–0.84)
Cales (France) [37]	2010	444	APRI	METAVIR ≥ F2	>0.7	62.2 %	77.6 %	84.1 %	51.7 %	0.716 (±0.041)
			FIB-4	METAVIR ≥ F2	>1.28	72.1 %	67.2 %	80.8 %	55.7 %	0.722 (±0.042)
			FibroTest	METAVIR ≥ F2	>0.65	61.3 %	82.8 %	87.2 %	52.7 %	0.778 (±0.038)
			FibroMeter	METAVIR ≥ F2	>0.48	75.7 %	72.4 %	84.0 %	60.9 %	0.783 (±0.037)
			HepaScore	METAVIR ≥ F2	>0.31	90.1 %	58.6 %	80.6 %	75.6 %	0.779 (±0.038)
			FibroMeter HICV	METAVIR ≥ F2	>0.54	84.7 %	69.0 %	83.9 %	70.2 %	0.828 (±0.034)
			HICV	METAVIR ≥ F2	>0.54	83.8 %	72.4 %	85.3 %	70.0 %	0.822 (±0.035)
Lin (NA) [23]	2011	6529	APRI	METAVIR ≥ F2	<0.5	74.0 %	49.0 %	55.0 %	69.0 %	N/A
					>1.5	37.0 %	93.0 %	82.0 %	63.0 %	N/A
					≥0.7	77.0 %	72.0 %	70.0 %	79.0 %	0.77
		4458	APRI	Cirrhosis	1	76.0 %	72.0 %	55.0 %	69.0 %	0.83
					2	46.0 %	91.0 %	82.0 %	63.0 %	
Kliemann (Brazil) [38]	2015	92	AST/ALT	METAVIR ≥ F2	<1	63.5 %	55.0 %	64.7 %	53.7 %	N/A
			APRI	METAVIR ≥ F2	≥1	22.0 %	76.5 %	42.9 %	54.9 %	N/A
					<0.5	21.2 %	82.5 %	61.1 %	44.6 %	N/A
					>1.5	47.6 %	80.3 %	41.7 %	86.4 %	N/A
			FIB–4	METAVIR ≥ F2	<1.45	59.6 %	65.0 %	68.9 %	55.3 %	N/A
					>3.25	42.9 %	54.9 %	21.9 %	76.5 %	N/A

Table 1 (continued)

Name (country)	Year	*N*	Index	Detection of	Cut offs	Sens	Spe	PPV	NPV	AUROC (95 % CI)
			FCI	METAVIR ≥ F2	<0.13	48.1 %	45.0 %	53.2 %	40.0 %	N/A
					>1.25	9.5 %	97.2 %	50.0 %	78.4 %	N/A
De Ledinghen (France) [50]	2006	72	VCTE	METAVIR ≥ F2	≥4.5 kPa	93.2 %	17.9 %	N/A	N/A	0.72 (0.60–0.84)
				Cirrhosis	≥11.8 kPa	100.0 %	92.7 %	81.0 %	100.0 %	0.97 (0.94–1.0)
					≥14.5 kPa	N/A	N/A	N/A	N/A	N/A
		64	Platelets	Cirrhosis	<140	N/A	N/A	N/A	N/A	0.80 (0.64–0.95)
		46	AST/ALT	Cirrhosis	>1	N/A	N/A	N/A	N/A	0.45 (0.20–0.70)
		47	APRI	Cirrhosis	>2	N/A	N/A	N/A	N/A	0.76 (0.59–0.92)
		46	FIB-4	Cirrhosis	≥3.25	N/A	N/A	N/A	N/A	0.73 (0.57–0.89)
Kirk (USA) [52]	2009	192	VCTE	METAVIR ≥ F2	≥9.3 kPa	85.9 %	75.2 %	67.0 %	90.1 %	0.81 (0.75–0.86)
				Cirrhosis	≥12.3 kPa	75.0 %	86.1 %	64.3 %	91.2 %	0.81 (0.74–0.87)
Sanchez, Conde (Spain) [53]	2010	100	VCTE	METAVIR ≥ F2	>7 kPa	76.7 %	75.4 %	70.2 %	81.1 %	N/A
				Cirrhosis	≥14 kPa	100.0 %	93.5 %	57.1 %	100.0 %	0.99 (0.97–1.00)
Castera (France) [55]	2014	116	VCTE	METAVIR ≥ F2	≥7.1 kPa	85.4 %	76.5 %	71.9 %	88.1 %	0.87 (0.81–0.94)
			FibroTest		>0.48	89.6 %	61.8 %	62.3 %	89.4 %	0.85 (0.89–0.92)
			APRI		≤0.5	81.3 %	41.2 %	49.4 %	75.7 %	0.71 (0.61–0.81)
					>1.5	35.4 %	91.2 %	73.9 %	66.7 %	
			VCTE	Cirrhosis	≥12.5 kPa	76.9 %	86.4 %	41.7 %	96.7 %	0.92 (0.86–0.98)
			FibroTest		≥0.75	61.5 %	73.8 %	22.9 %	93.8 %	0.78 (0.66–0.89)
			APRI		≤1.0	76.9 %	72.8 %	26.3 %	96.2 %	0.73 (0.58–0.88)
					>2	30.80 %	88.30 %	25.00 %	26.00 %	
Schmid (Switzerland) [30]	2015	99	VCTE	METAVIR ≥ F2	≥7.0 kPa	75.7 %	79.0 %	68.3 %	84.5 %	0.85 (0.78–0.93)
		104	APRI		≥1.5	36.8 %	92.4 %	73.7 %	71.8 %	0.76 (0.66–0.86)
		103	FIB4		≥1.45	73.0 %	59.1 %	50.0 %	79.6 %	0.77 (0.68–0.87)
		101	Fibrotest		≥0.48	86.5 %	48.4 %	49.2 %	86.1 %	0.75 (0.65–0.85)
		102	Hepascore		≥0.5	75.0 %	43.9 %	42.2 %	76.3 %	0.68 (0.57–0.80)
		102	ELF		≥9.8	40.0 %	92.5 %	73.7 %	74.7 %	0.77 (0.67–0.86)
		99	VCTE	Cirrhosis	≥12.5 kPa	85.7 %	92.9 %	66.7 %	97.5 %	0.97 (0.94–1.0)
		104	APRI		>2	42.9 %	92.2 %	46.2 %	91.2 %	0.89 (0.82–0.96)
		103	FIB4		>3.25	57.1 %	93.3 %	57.1 %	93.3 %	0.91 (0.84–0.97)
		101	Fibrotest		≥0.75	85.7 %	72.4 %	33.3 %	96.9 %	0.84 (0.75–0.92)
		102	Hepascore		≥0.84	78.6 %	71.6 %	30.6 %	95.5 %	0.82 (0.69–0.95)
		102	ELF		≥11.3	28.6 %	98.9 %	80.0 %	89.7 %	0.82 (0.69–0.95)

N number of patients, *Sens* sensitivity, *MHAI* Ishak modified histological activity index, *Spec* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *AUROC* area under the receiver operating curve, *AST* aspartate transaminase, *ALT* alanine transaminase, *N/A* not applicable, *ELF* enhanced liver fibrosis score

≥0.5 had 100 % sensitivity, 65 % specificity with a PPV 30 % while a score <0.5 had 100 % NPV. In this study cohort, FibroTest could have prevented 55 % of biopsies for a diagnosis of stage F2–F4 [31].

The SHASTA index was one of the first scores developed to estimate fibrosis specifically in HIV-HCV co-infected individuals. This score comprises three variables: (1) hyaluronic acid >86 ng/ml with OR 27 (95 % CI 5.11–138.7) for ≥F3 fibrosis by Ishak modified histologic activity index (MHAI) score, (2) albumin <3.5 g/dl with OR 4.85 (95 % CI 1.24–19.0), and (3) AST >60 IU/l with OR 5.91 (95 % CI 1.62–21.5) [20] (Table 1). The predictive performance using SHASTA for Ishak 3–6 was dependent on low and high index thresholds: a score <0.3 had a sensitivity of 88 % and specificity of 72 %, while a score >0.8 carried 15 % sensitivity and 100 % specificity [20]. Using the SHASTA index, the authors could correctly identify 42 % of patients in whom biopsy might be avoided for Ishak 3–6. Notably, the test outperformed APRI in diagnostic accuracy, with one possible explanation being that antiretroviral therapy could have affected AST levels [25, 32]. FIB-4 is a simple index which was specifically developed in 832 co-infected patients enrolled in the AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT). This index is based on easily available clinic parameters such as age, AST, ALT, and platelets, and in the initial co-infection study noted, an area under the receiver operating curve (AUROC) of 0.765 for Ishak score ≥4; FIB-4 < 1.45 was associated with a sensitivity 70 %, and NPV 90 % to exclude advanced fibrosis, while a score >3.25 had a specificity of 97 %, and a PPV of 65 % [25]. Unfortunately, index values between 1.45 and 3.25 are classified as being indeterminate with poor predictive values for advanced fibrosis, and accounts for around 30–65 % of patients [20, 25, 31].

Macias et al. evaluated and compared multiple commonly used fibrosis indices: APRI and Forns had AUROCs of 0.80 and 0.77, respectively, which could allow avoidance of liver biopsies in up to 34 % of patients (Table 1) [33]. Importantly, stratification by CD4 count (≤500 and >500) did not affect the performance of the tests. When Forns index and APRI are

applied sequentially (Forns is applied to indeterminates by APRI), the test showed the following characteristics: sensitivity 25 %, specificity 98 %, PPV 91 %, and NPV 64 %, which would allow avoidance of a liver biopsy in up to 41 % of patients [33]. A later published cross-sectional study reported AUROCs of Forns at 0.75, and APRI at 0.77 for METAVIR ≥ F2 [34]. Using Forns and APRI, the authors found that patients could be spared a liver biopsy for ≥F2 in 25–39 % of patients. A large retrospective study compared multiple non-invasive scores to liver biopsy, and showed that FibroMeter, HepaScore, and FibroTest outperformed APRI, FIB-4, and Forns index [35]. Adjustment for the heterogeneous distribution of fibrosis stages through DANA (difference advanced-non-advanced fibrosis stage analysis), yielded much higher AUROCs for different indices: FibroMeter = 0.86, HepaScore = 0.84, FibroTest = 0.78, FIB-4 = 0.77, SHASTA = 0.75, APRI = 0.74, Forns index = 0.73 [35]. Notably, combination testing did not further improve diagnostic accuracy [35].

Macias et al. evaluated 519 HIV-HCV co-infected individuals and noted improved predictive performance for indices with liver biopsy length of ≥15 mm [36]. Combining APRI and the Forns index in that study yielded a better AUROC for significant fibrosis at 0.69 (0.69–0.78) [36] (Table 1). CD4 count, HIV RNA, and alcohol use did not significantly affect the performance of either test [36]. Another study examined two new indices FibroMeter HICV (which performed marginally better than FibroMeter but did not reach significance), and HICV test which had AUROCs which were significantly higher than APRI, FIB-4, and FibroTest (Table 1) [37]. FibroMeter HICV was adequately able to classify all patients' fibrosis stages into four categories (≤F1, F1 ± 1, ≥F1, ≥F2) allowing complete avoidance of liver biopsy for this classification [37]. Notably, two landmark meta-analyses (initially in 2007, updated in 2011) have investigated APRI both as a maker for HCV monoinfection as well as HIV/HCV co-infection [23, 24]. Forty studies with 8739 patients (1848 of which were HIV-HCV co-infected) were considered in the analysis; APRI had an AUROC of 0.77 (0.75 for co-infected patients) for significant fibrosis and 0.83 for cirrhosis (0.79 for co-infected patients). Two different thresholds were used: 0.7 for significant fibrosis (77 % sensitive, 72 % specific) and 1.0 for cirrhosis (76 % sensitive and 72 % specific) [23]. More recently, fibrosis-cirrhosis index (FCI) was introduced after achieving promising results in HCV-monoinfected individuals. This index (based on alkaline phosphatase, bilirubin, albumin, and platelet count) demonstrated an AUROC for significant fibrosis of 0.932; however, this index does not seem to perform as well in HIV-HCV co-infected patients (Table 1) [38, 39].

Overall, it appears that serum-based markers of liver fibrosis are less accurate for significant fibrosis in HIV-HCV co-infected patients than monoinfected patients. Most serologic tests seem be more accurate in detection of cirrhosis versus significant fibrosis, and similar to the HCV-monoinfected population. When assessing the accuracy of a specific blood test to detect significant fibrosis in co-infected individuals, multiple factors should be taken into account such as HIV-related thrombocytopenia, highly active antiretroviral therapy (HAART)-related hepatotoxicity, and the higher prevalence of advanced fibrosis in HIV-HCV-infected individuals [40–42]. However, it is important to note that in two large studies comparing patients HAART versus no therapy, there were no significant differences in fibrosis indices between these groups [33, 34]. Other potential considerations in co-infected patients include GGT (used in the Forns index and FibroTest) elevation in patients on nevirapine. However, when evaluated in prior studies, there were no significant differences between patients on nevirapine versus patients on alternate therapy, and this is not a commonly used antiretroviral [35, 43]. Moreover, atazanavir increases total and in-direct bilirubin due to uridine glucoronyl transferase inhibition, which is a component of FibroTest and HepaScore. As such, results from patients on such medications should have other non-invasive indices used [35]. Other physiologic or non-liver-related etiology for variation in serum biomarkers should also be considered. Due to the limitations of "biochemical"-based indices of fibrosis, multiple imaging modalities have been introduced to the field to try to provide complementary "physical" measures of fibrosis.

Imaging-Based Tests in HIV/HCV co-Infection

Multiple imaging-based modalities of assessment of liver fibrosis have been proposed and validated in HCV-monoinfected individuals. These include vibration-controlled liver elastography (VTCE) [44], acoustic radiation force impulse (ARFI) [45, 46], and magnetic resonance (MR) elastography [47]. Of the three, only VTCE alternatively referred to as FibroScan © (Echosens, Paris, FR) has been validated for use in HIV-HCV co-infected patients [48]. The VCTE device consists of two separate components: a 50 Hz low frequency vibrator that produces elastic shear waves that propagate through liver parenchyma and is combined with an ultrasound probe that measures the shear wave propagation to generate a liver "stiffness" measure (LSM) that is proportional to the degree of fibrosis [44, 49]. This technique is simple to learn, reproducible, has well-defined quality criteria, and provides a point-of-care result. VCTE provides an important clinical tool for assessment of liver disease severity and now forms an integral part of routine clinical practice in many countries. Based on previous validation studies, it was determined that in patients with chronic HCV monoinfection a LSM > 9.5 kPa was indicative of at least F3 stage fibrosis with an AUROC of 0.83 (95 % CI 0.76–0.88), while

LSM > 12.5 kPa had an AUROC of 0.95 (95 % CI 0.91–0.98) for presence of cirrhosis [49].

VCTE was found to be better than APRI, AST/ALT ratio, platelet count, and FIB-4 in diagnostic accuracy for cirrhosis determination, with an impressive AUROC of 0.97. However, performance for determining significant fibrosis was modest (AUROC = 0.72) [50]. Vergara et al. studied 169 co-infected individuals and found improved AUROCs for detecting significant fibrosis at a cutoff of 7.2 kPa (Table 1) [51]. Another study of 192 HCV patients (including 139 with HIV co-infection) revealed a better performance of VCTE in HCV-monoinfected individuals compared to HIV-HCV patients: AUROC 0.94 (0.89–1.00) versus 0.84 (0.77–0.9), respectively, for significant fibrosis, and AUROC 0.92 (0.85–0.99) versus 0.85 (0.77–0.93), respectively, for cirrhosis. Using liver elastography in HCV monoinfected individuals yielded more frequent correct classification of significant fibrosis compared to co-infected patients (87 vs. 76 %), whereas cirrhosis identification was equivalent between both groups (83 %) [52]. Underperformance of VCTE in cirrhosis detection was attributed to the relatively small portion of patients with cirrhosis (25 %) among the study population [52]. Comparative studies indicate that VCTE appears to perform better than other non-invasive serologic markers (Table 1) [50, 53]. In fact, one study revealed VCTE AUROCs as being significantly better than other serologic markers in assessing severe fibrosis (METAVIR F ≥ 3): AUROC FIB-4 0.69, AUROC APRI 0.77, and Forns 0.75, while AUROCs for VCTE were 0.92–0.93 for advance fibrosis. However, this study included only 15 co-infected patients with advanced disease [53]. In addition, VCTE has been applied in HIV-HCV co-infected individuals in an attempt to determine the presence of esophageal varices with encouraging results [54]. The combination of VCTE and FibroTest (Castera) was compared to the combination of APRI and FibroTest (SAFE) in a French study that included 116 HIV-HCV patients. VCTE and FibroTest had a similar diagnostic accuracy for F2-F4 and VCTE performed better for cirrhosis. Combination algorithms did not improve diagnostic performance for F2-4 or cirrhosis in this study [55]. Confounding factors for VCTE failure or poor reliability of LSM include operator inexperience, young age, narrow intercostal spaces, ascites (since shear wave does not propagate in fluid), and obesity thus the introduction of an XL probe which, however, has lower fibrosis thresholds than standard probes and has not been broadly validated [44]. Factors associated with erroneously elevated results include inflammation (up to three times the normal value), transaminase elevation, cholestasis, hepatic congestion, and food intake [44].

HIV/HBV co-Infection

Over the past decade, non-invasive fibrosis markers used in HCV monoinfection have been applied to HBV-infected patients with encouraging success. Nonetheless, there are few studies investigating non-invasive tests in HBV-monoinfected or HBV-HIV-co-infected individuals compared to HCV [56–58].

A landmark study by Bottero et al. comparing the performance of 11 biomarkers among HIV/HBV co-infected patients, namely FibroTest, Zeng, HepaScore, FibroMeter, SHASTA, APRI, FIB-4, Forns, AST/ALT ratio, hyaluronic acid, and Hui scores, revealed that FibroTest had the best performance with AUROCs consistently higher than 0.75 regardless of the predicted fibrosis stage [59]. Zeng score, HepaScore, and FibroMeter seem to have good performance for the diagnosis of significant fibrosis (AUROCs 0.7–0.8), advanced (METAVIR F3-F4) fibrosis (AUROCs 0.8–0.9), and cirrhosis (METAVIR F4) (AUROCs 0.9–1) [59] (Table 2). Cutoffs used for each stage of fibrosis were also close to data previously published for HCV-monoinfected patients [27, 28, 60]. Despite better relative performance compared to other indices, FibroTest, HepaScore, FibroMeter, and Zeng score were in agreement with liver biopsy findings for only 50 % of cases. Attempts at improving non-invasive testing performances by combining two serologic tests did not increase the overall diagnostic accuracy [59].

Following validation for HCV monoinfection, VCTE has also been associated with encouraging results in HBV monoinfection [61, 62]. To the best of our knowledge, only one study evaluated the performance of VCTE in HIV-HBV co-infected patients where the authors reported AUROCs in the range of 0.85 to 0.93 at different stages of fibrosis (Table 2) [63]. Overall test performance with the use of a sequential combination algorithm of VCTE and FibroTest correctly identified most F0–F1 patients (NPV = 93 %), and F ≥ 2 fibrosis (PPV = 100 %) [63]. In this study, VCTE and FT concordance was observed in 67 % of cases, 97 % of which could have avoided undergoing liver biopsy [63].

HIV and NAFLD

Non-alcoholic fatty liver disease seems to be prominent (15–60 %) in HIV-infected individuals and is thought to be related to a greater incidence of metabolic syndrome, insulin resistance, in addition to HIV-associated factors (antiretroviral therapy and lipodystrophy) [4, 64–68].

The NAFLD fibrosis score (NAFLD-FS) is currently the most studied and validated liver fibrosis index for patients with NAFLD [69–71]. Morse et al. demonstrated that individuals (NAFLD + HIV) with a higher grading of liver fibrosis by biopsy (Ishak stage ≥ 2) had significantly higher FIB-4 and NAFLD-FS than the group with mild fibrosis [72].

The main challenges of using VCTE in NAFLD patients are the high failure rate (no valid acquisition) and the unreliable results (does not meet manufacturer's recommendations) [58, 73–76]. The newly developed XL probe does carry a

Table 2 Performance of non-invasive serologic and imaging-based markers of liver fibrosis in HIV-HBV co-infection

Name (Country)	Year	*N*	Index	Detection of	Cut offs	Sens	Spec	PPV	NPV	AUROC (95 % CI)
Bottero (France) [59]	2009	108	Fibrotest	METAVIR ≥ F2	>0.43	70 %	72 %	80 %	61 %	0.77 (0.68–0.86)
				Cirrhosis	>0.74	75 %	85 %	50 %	94 %	0.87 (0.79–0.94)
			Fibrometer	METAVIR ≥ F2	>0.46	73 %	68 %	78 %	62 %	0.74 (0.65–0.84)
				Cirrhosis	>0.83	81 %	85 %	52 %	96 %	0.89 (0.82–0.96)
			Hepascore	METAVIR ≥ F2	>0.48	67 %	68 %	77 %	57 %	0.74 (0.64–0.83)
				Cirrhosis	>0.90	80 %	89 %	60 %	96 %	0.92 (0.86–0.97)
			Zeng score	METAVIR ≥ F2	>17.2	74 %	66 %	77 %	62 %	0.75 (0.65–0.84)
				Cirrhosis	>21.0	75 %	87 %	54 %	94 %	0.91 (0.84–0.97)
			FIB-4	METAVIR ≥ F2	N/A	N/A	N/A	N/A	N/A	0.74 (0.64–0.83)
				Cirrhosis	N/A	N/A	N/A	N/A	N/A	0.80 (0.67–0.93)
			Forns	METAVIR ≥ F2	N/A	N/A	N/A	N/A	N/A	0.72 (0.62–0.82)
				Cirrhosis	N/A	N/A	N/A	N/A	N/A	0.81 (0.67–0.94)
			APRI	METAVIR ≥ F2	N/A	N/A	N/A	N/A	N/A	0.73 (0.63–0.82)
				Cirrhosis	N/A	N/A	N/A	N/A	N/A	0.76 (0.64–0.89)
			Hyaluronic acid	METAVIR ≥ F2	N/A	N/A	N/A	N/A	N/A	0.66 (0.55–0.76)
				Cirrhosis	N/A	N/A	N/A	N/A	N/A	0.85 (0.75–0.95)
			SHASTA	METAVIR ≥ F2	N/A	N/A	N/A	N/A	N/A	0.65 (0.55–0.75)
				Cirrhosis	N/A	N/A	N/A	N/A	N/A	0.75 (0.59–0.90)
			Hui	METAVIR ≥ F2	N/A	N/A	N/A	N/A	N/A	0.67 (0.56–0.77)
				Cirrhosis	N/A	N/A	N/A	N/A	N/A	0.67 (0.51–0.83)
			AST/ALT	METAVIR ≥ F2	N/A	N/A	N/A	N/A	N/A	0.48 (0.36–0.59)
				Cirrhosis	N/A	N/A	N/A	N/A	N/A	0.51 (0.35–0.68)
Miaihes (France) [63]	2011	59	VCTE	METAVIR ≥ F2	>5.9 kPa	81 %	87 %	91 %	74 %	0.85 (0.75–0.95)
				Cirrhosis	>9.4 kPa	92 %	94 %	79 %	98 %	0.96 (0.92–1.00)
			Fibrotest	METAVIR ≥ F2	>0.38	77 %	86 %	89 %	72 %	0.86 (0.75–0.96)
				Cirrhosis	>0.58	100 %	81 %	56 %	100 %	0.93 (0.85–0.99)

Sens sensitivity, *Spec* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *AUROC* area under the receiver operating curve, *N/A* not applicable or not available

lower failure rate for the patients with higher BMI, but the unreliable result does not decrease significantly [73]. However, VCTE does have a high negative predictive value for cirrhosis and severe fibrosis and could be used as a first line screening method for NAFLD patients without the need for liver biopsy [48]. At this stage, no study has specifically evaluated the clinical utility of VCTE in NAFLD-HIV individuals. This may warrant further investigation given the higher prevalence of NAFLD in HIV-positive patients compared to the general population [64].

Non-Invasive Markers Prognostic Value

Several studies have examined the correlation between VCTE and hepatic venous pressure gradient (HVPG) [77, 78]. A meta-analysis which included 3644 patients revealed AUROCs of 0.93 for detection of significant portal hypertension (sensitivity = 90 %; specificity = 79 %) and 0.84 for esophageal varices (sensitivity = 87 %; specificity = 53 %) [79]. Notably, however, this correlation does not seem to remain significant with portal values >12 mmHg, likely due to contribution of extra hepatic factors to portal hypertension in advanced liver cirrhosis [80]. Other studies have evaluated spleen stiffness in combination with VCTE for determination of HVPG with impressive results (R^2 of the model used was 0.82) [81]. Furthermore, VCTE has been found to correlate with the risk of HCC development in the presence of HCV and HBV infections [82, 83]. In fact, a prospective study including 866 patients with chronic HCV demonstrated an increasing hazard ratio (HR) comparing individuals with LSM ≤10 kPa, to others with higher LSMs: HR 16.7 (95 % CI 3.71–75.2; $P < 0.001$) for LSM 10.1–15 kPa; HR 20.9 (95 % CI 4.43–98.8; $P < 0.001$) for LSM 15.1–20 kPa, HR 25.6 (95 % CI 5.21–126.1; $P < 0.001$) for LSM 20.1–25 kPa, and 45.5 (95 % CI 9.75–212.3; $P < 0.001$) for LSM >25 kPa [82]. Moreover, VCTE proved to be a valuable tool to assess the likelihood of liver disease-related decompensation: when compared to HVPG, VCTE's AUROC was 0.837 [0.754–

0.920] compared to 0.815 [0.727–0.903] in a 100 patients with chronic liver disease followed over 2 years [84]. Unfortunately, no study to date has evaluated VCTE or other non-invasive tests for such purposes in an HIV-mono or co-infected cohort exclusively.

Conclusion

Non-invasive fibrosis tests have become popular and gained general acceptance with health care providers in the last decade, particularly with the increased availability of reproducible, simple, and relatively rapid methods of liver fibrosis assessment. These tests have mainly been validated in CHC-infected individuals with encouraging and reproducible results in HIV-HCV co-infection. Both serum and imaging-based methods seem to perform well for cross-sectional diagnosis of cirrhosis, but appear less reliable for significant fibrosis (F2-F4) in HIV-HCV co-infected patients. At present, there are no non-invasive tests of fibrosis that are completely reliable for assessment of liver disease severity, particularly when the gold standard liver biopsy is associated with inherent diagnostic limitations. Thus, non-invasive test results should be considered in conjunction with available clinical, laboratory, and other imaging data. Notably, no current data exists about accuracy of non-invasive modalities in assessing fibrosis progression, or for determination of fibrosis regression in HIV-HCV-co-infected individuals after HCV clearance. Furthermore, HBV and NAFLD in HIV infection have not garnered the same level of attention as HIV-HCV co-infection, and there are few studies of non-invasive tests in these populations. As liver biopsy is performed infrequently in HIV monoinfection, there are no specific non-invasive liver fibrosis staging methods that have been developed for these patients, and assessment of fibrosis remains dependent on non-invasive tests validated in HIV co-infection. Future studies should combine genetic and clinical risk assessments with emerging ‘omics and imaging methodology, and evaluate these in relation to quantitative immunohistochemical measures of fibrogenesis. This may provide refined and improved non-invasive methods for liver fibrosis assessment in this population that remains at significant risk of liver disease progression and development of cirrhosis.

Compliance with Ethical Standards

Conflict of Interest Bassem Matta, Tzu-Hao Lee, and Keyur Patel declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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