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Assessment of liver disease (non-invasive methods)

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Abstract

Purpose of review—The purpose of this review is to highlight new findings published in 2010-11 related to noninvasive fibrosis assessment in HIV/HCV co-infected patients. Overall, in 2010-11, 15 papers were published, of which two were excluded because they were published in languages other than English.

Recent findings—11 papers focused on serum marker panels. Papers sought to either 1) validate established panels in HIV/HCV co-infected patients often by comparing multiple serum marker panels in the same population; 2) establish new marker panels using combinations of markers used in previously validated panels; and 3) develop new marker panels using novel methodology. Overall, all panels performed within similar ranges of diagnostic accuracy as measured by the area under the receiver operating characteristic curve (AUROC) but the Fibrometer panel and its derivations achieved the highest performance. Four studies focused on transient elastography (TE). Two papers confirmed its accuracy for identifying fibrosis and cirrhosis and two papers confirmed that misclassification rates are higher in the presence of elevated triglycerides and steatosis.

Summary—Overall, performance of TE appeared superior to the majority of serum marker panels for the detection of significant fibrosis and cirrhosis in HIV/HCV co-infected patients. Challenges of widespread application of TE remain high misclassification in some subgroups, lack of standardized cutpoints and lack of widespread availability. Panels that were newly developed in 2010-11 specifically for HIV/HCV appeared to perform better than existing panels such as APRI and FIB-4; however additional external validation will be needed to confirm their accuracy.

Keywords

hepatitis C virus; liver fibrosis; HIV; elastography; serum markers

Introduction

Accurate assessment of fibrosis stage in persons infected with chronic hepatitis C virus (HCV) is important for management, understanding progression risk and determination of treatment urgency. Fibrosis assessment is particularly important in HIV/HCV co-infected patients because of the more rapid disease progression that has consistently been observed [1-4], diminished responses to therapy [5,6] and the need to consider antiretroviral therapy in conjunction with hepatitis C treatment decisions.

Liver biopsy is the standard of care for ascertainment of fibrosis. However, biopsy is invasive, expensive, associated with severe complications and highly subject to measurement error [7,8]. These limitations have driven a proliferation of non-invasive strategies or ‘surrogates’ for liver fibrosis. Non invasive strategies have numerous

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advantages including that they are less costly and have higher patient acceptability thus making them more amenable to repeat measurement across more frequent intervals then biopsy. Broadly, noninvasive strategies can be grouped into two categories: serum marker panels and imaging techniques. However, the degree to which these non-invasive strategies are currently used in clinical practice for HIV/HCV coinfected patients varies considerably by country and continent, with widespread use in some European countries and limited use in the Unites States.

The purpose of this review is to highlight new findings published in 2010-11 related to noninvasive fibrosis assessment in HIV/HCV co-infected patients. Overall, we found 32 papers related to noninvasive strategies in HIV/HCV co-infected patients of which 15 were published in 2010-11. We excluded two papers published in languages other than English.

Serum Markers

Reports on serum marker panels focused on either 1) validating established panels through comparison multiple serum marker panels in the same population; 2) establishing new panels using combinations of markers used in previously validated panels; or 3) applying new methodology. A key challenge of marker panels applied to HIV/HCV co-infection is that the majority were developed specifically for HCV mono-infected patients and then subsequently applied to co-infected patients sometimes making performance sub-optimal. Table 1 illustrates the performance of all marker panels across the various studies conducted in 2010-11. Serum marker panels included a combination of direct, indirect and both direct and indirect markers. Whereas direct markers of fibrosis actually reflect serum extracellular matrix (ECM) turnover, indirect markers reflect functional alterations in hepatic function and do not directly measure hepatic ECM metabolism. Accuracy of marker panels was generally measured by the area under the receiver operating characteristic curve (AUROC), which reflects overall performance of the serum marker panel relative to the gold standard (biopsy) taking into account sensitivity and specificity across the full range of cutpoints. The minimum possible value of the AUROC is 0.5; a perfect test would have a score of 0.1 but scores >0.8 are generally considered very good.

Individual Serum Markers

Hyaluronic acid (HA), a direct fibrosis marker, has been found to predict fibrosis and cirrhosis in HCV mono-infected patients alone and in combination with other markers but has not been widely evaluated alone in co-infection [15,19]. In 2010-2011, HA was the only marker evaluated alone in terms of performance relative to the biopsy and marker panels. Resino et al evaluated the performance of HA compared to HGM-1, HGM-2, Forns, APRI and FIB-4 among 201 HIV/HCV co-infected patients [9]. The AUROC values for significant fibrosis (>F2), advanced fibrosis (>F3) and cirrhosis were 0.68, 0.77 and 0.86 respectively; these were comparable to performance of other indices. The only improvement over other panels was with respect to cirrhosis; using a low and a high cutoff, biopsy could be avoided in 52% of patients for diagnosis of cirrhosis. The advantage of using HA is that it only requires one test and is not likely affected by other factors associated with HIV, which can impact some of the markers included in the more simple non-invasive indexes. However, HA is not commonly measured in hospitals versus the other indexes, which include markers that are routinely available in clinical practice. Overall, this study failed to demonstrate superiority of HA compared to these other markers.

Previously validated serum marker panels

Several studies applied previously validated marker panels to co-infected patients and drew comparisons accross marker panels. All included APRI as one of the comparators. APRI has

the advantage of using readily available laboratory tests and a simple calculation. However, a recent meta-analysis concluded that the primary utility of APRI is in excluding significant fibrosis [20]. Two studies evaluated performance of APRI in subgroups defined by CD4 and ALT. Most previous studies have included persons with high CD4 and elevated ALT. The first study by Singal et al compared the performance of APRI among 106 co-infected patients to 105 HCV mono-infected patients [11]. The median CD4 cell count among HIV/HCV coinfected patients was 430 cells/μl. Overall, the AUROC for predicting significant fibrosis was slightly lower in co-infected compared to monoinfected patients (0.77 vs. 0.86, p=0.18) Notably, performance was substantially lower in those with CD4 cell counts <250 cells/ul. (0.64 vs. 0.86, p=0.05). Given this poor performance in the low CD4 strata, the authors compared the results with that of FIB-4, which did not have differential performance by CD4 strata. The conclusions of the prior meta-analysis that APRI has utility for excluding significant fibrosis were not supported by this study for patients with low CD4 cell counts [20].

The second study by Shah et al compared APRI and FIB-4 among 295 biopsies from 237 HIV/HCV coinfected patients [12]. The median CD4 among these patients was 525 cells/μl. Results were stratified by ALT (elevated vs. normal). Among those with elevated ALT, the AUROC for APRI was 0.76 for FIB-4 was 0.80. For those with normal ALT, performance was better (0.90 for FIB-4 and 0.85-0.95 for APRI). While negative predictive value (for excluding fibrosis among those with a negative result) for both was high, positive predictive value (identifying significant fibrosis in those with a positive result) was low (0.50 for FIB-4 and 0.67 for APRI) even in those with normal ALT. Both appear to be able to accurately rule out fibrosis in patients with normal ALT; however, these findings support others in that positive predictive value is suboptimal [20].

Macias et al compared APRI and Forns among 519 HIV/HCV co-infected patients from a multicenter study in Spain. The AUROC for detection of significant fibrosis for both was 0.67. Overall positive predictive value at established cutoffs was higher for APRI than Forns. Each panel on its own would have resulted in 22% of biopsies being avoided but a sequential application of APRI and then Forms could have avoided 30% of biopsies [16]. Diagnostic yield improved slightly with biopsies >15 mm in length, but overall the percentage of correctly classified was 10% lower than what has been previously observed [21-27].

New serum marker panels

Others sought to develop new marker panels using existing candidates to optimize performance in co-infected patients. For example, Cales et al used components of the five marker panels that had previously been applied to HIV/HCV co-infected patients (e.g., APRI, FIB-4, Fibrotest, Fibrometer and Hepascore) to determine whether a new marker panel developed from these components would have superior performance in co-infected patients [17]. The study included 467 patients (183 derivation, 284 validation) from four centers in France. Two strategies were used: 1) the components of Fibrometer, the highest performing panel, were considered and 2) the components of all five marker panels were considered. The new Fibrometer panel determined from the components of Fibrometer to be specific to HIV/HCV co-infection was called Fibrometer HICV and the new panel developed from the five tests was called HICV and included variables (AST, α-2-macroglobulin and prothrombin index). Overall, for diagnosis of significant fibrosis, Fibrometer HICV and the HICV had the best performance in the derivation set (AUROC 0.83 and 0.82, respectively). Among existing panels, Fibrometer had the best performance (0.78) and APRI the worst (0.72). Performance in the validation sample diminished (0.74 and 0.74, respectively) but after the AUROC was weighted as a function of fibrosis stage and the reference population (Obuchowski index), performance improved. The authors also

assessed other performance characteristics that account for biases related to disease prevalence (e.g., test performance profile, reliable diagnosis and diagnostic reproducibility). All three criteria supported HICV, FIbrometer HICV and Fibrometer as having highest performance.

Another new marker panel was developed by Resino et al among 195 HIV/HCV co-infected patients (127 in derivation group and 68 in validation group) [15]. Using 14 candidate direct and indirect markers, they identified a panel of five markers [HGM-3] which included platelet count, alkaline phosphatase (ALP), hepatocyte growth factor (HGF), tissue inhibitor of metalloproteinase-1 (TIMP-1). The formula is: $x = -5.0596 – (1.210 \times 10^{-2} \times \text{Platelet}) + (1.203 \times 10^{-2} \times \text{ALP}) + (1.220 \times 10^{-3} \times \text{HA}) + (4.526 \times 10^{-4} \times \text{HGF}) + (6.312 \times 10^{-3} \times \text{TIMP} – 1)$. Compared to HGM-2, FIB-4, APRI and Forns, the performance of HGM-3 was superior in terms of detecting advanced fibrosis (≥F3) and cirrhosis (≥F4) but comparable for significant fibrosis (≥F2). Two cutoffs were established; using the low cutoff in the validation set, only 1 false negative was detected and with the high cutoff only 3 false positives were detected.

Macias et al examined direct markers MMP-2 and TIMP-1 in combination with routinely available data (including APRI, ALT, AST, GGT, bilirubin, cholesterol levels and platelet counts) among 90 co-infected patients [10]. AST, platelet count and MMP-2 were predictors of significant fibrosis (≥F2) and cirrhosis (≥F4). A score that included these variables had an AUROC of 0.76 for significant fibrosis and 0.88 for cirrhosis. Two cutoffs were identified for both significant fibrosis and cirrhosis; applying these cutoffs for significant fibrosis reduced the proportion of biopsies needed by 34%. The authors also explored using a sequential approach of APRI and MMP-2. Using this approach, all those with APRI<1.5 would be tested with MMP-2 resulting in a reduction of 46% of biopsies.

Serum marker panels developed using novel methodology

The standard approach to development of serum fibrosis marker panels has been to identify a series of candidate markers, dichotomize individuals into two groups (e.g., fibrosis vs. no fibrosis) and use logistic regression and AUROC to assess performance of different combinations of markers. While this approach has yielded a number of panels, there are inherent limitations. Two reports in the past year used novel approaches to overcome some of these limitations.

Resino et al considered a artificial neural network approach (ANN) among 362 HIV/HCV co-infected patients [14]. Compared to a simple regression model approach, these are computational models that incorporate a set of artificial neurons linked together through weighted connections. The weights for each connection can be established through examples and then the neural network can assign outputs (e.g., different outcomes) to new data that was not used in the learning process. In this analysis, they considered 10 markers (fibrinogen, glucose, AST, ALT, GGT, ALP, cholesterol, platelet, INR and age) that make up four validated marker panels (HGM-1, FIB-4, APRI and Forns) and compared predictive accuracy of the ANN to each panels alone. The ANN for significant fibrosis had an AUROC of 0.87 in the estimation set and 0.85 in the validation set; this was significantly higher than in the established panels. In general, predictive accuracy was higher for predicting presence of significant fibrosis (93% certainty) vs. absence (85% certainty).

A second study by Cales et al [18] focused on ‘optimizing’ serum marker panels through: 1) classification into multiple fibrosis stages vs. a dichotomous classification; 2) an adapted vs. fixed diagnostic target and 3) developing a HA-free blood test (given expense and availability) with comparable accuracy and reliability to Fibrometer. The derivation population included 1056 patients from five centers in Europe and there were 6 validation

subsets. Through bootstrap resampling, the robustness of each variable in the FibroMeter was assesed; HA appeared the least robust. Using stepwise logistic regression, a score that replaced HA with GGT was developed with no significant change in test performance (FibroMeter^{3G}). Robustness was confirmed through bootstrap resampling where each variable was selected in 63% of samples. Fibrometer^{2G}and Fibrometer^{3G} demonstrated no significant differences in terms of diagnostic performance or ability to distinguish between fibrosis stages. The reduction in cost was 26 Euros. One of the validation populations included HIV/HCV co-infected patients and in this population of 176 individuals, the agreement between the FibroMeters was excellent with AUCs of 0.82 for Fibrometer^{2G} and 0.83 for Fibrometer^{3G}.

Transient Elastography (Te, Fibroscan®)

Imaging studies in 2010-11 focused on TE. Two studies focused on performance of TE vs. the biopsy drawing comparisons with other non-invasive strategies (Table 2).

The first study by Sanchez-Conde et al [13] focused exclusively on HIV/HCV co-infected patients and compared TE to APRI, Forns, FIB-4 and HGM-2. The AUROC for TE for ruling out any fibrosis, identifying advanced fibrosis and cirrhosis were 0.80, 0.93 and 0.99 respectively. The following cutoffs were identified as most suitable to the data (≤F1: <7kPa; ≥F3: ≥11 kPa; and F4: ≥14 kPa). The AUROCs for TE were significantly higher than Forns, APRI, FIB-4 and HGM-2.

A second study by Degos et al [28] focused on predictive accuracy of TE vs. biopsy among HIV/hepatitis coinfected patients (n=110) and compared to mono-infected patients (n=913). Among HIV/HCV coinfected patients, the AUROC for cirrhosis and significant fibrosis was 0.95 and 0.84, respectively. Interestingly predictive accuracy was greater in co-infected vs. mono-infected patients. Compared to previously validated marker panels (e.g., Fibrotest, Fibrometer, APRI, Heapscore), predictive accuracy was higher for TE. Of note, data from the serum markers was not presented separately for co-infected vs mono-infected patients. Cutoffs for TE used in this study were 12.9 kPA for cirrhosis and 5.2 for fibrosis [29].

Other studies examined factors that might impact accurate classification of fibrosis/cirrhosis by TE among HIV/HCV co-infected patients. A study by Neukam et al [30] assessed interoberver concordance of TE among 188 patients and found that values of two independent observers were highly correlated (intraclass correlation index = 0.98) and yielded high kappa statistics for identification of cirrhosis (kappa = 0.89) [30]. The kappa statistic was lower for significant fibrosis (0.60) but increased with use of two cutoffs (<6kPa and ≥9kPA); however, with the two cutoffs, 46% in the middle range remained unclassified. Factors associated with lower agreement were high interquartile ranges and elevated triglycerides.

A second study by Sanchez-Conde et al focused on factors associated with misclassification by TE compared to biopsy in 110 patients [31]. Based on a cutoff of 9.5 kPa to distinguish patients with advanced fibrosis (≥F3) from those without advanced fibrosis, misclassification rates were higher among patients with steatosis compared to those without (25% vs. 5%, p=0.01). The majority of misclassifications in the steatosis group were false positive for ≥F3. A limitation of this study was that there was no information on body mass index which is known to impact TE results.

Summary and Conclusions

Overall, performance of TE for the detection of fibrosis and cirrhosis among HIV/HCV co-infected patients appears superior to other previously validated and newly developed serum

marker panels. However, there still some concerns related to the accuracy, performance and widespread applicability of TE. First, as has been previously demonstrated, steatosis appears to be associated with a high rate of misclassification. Second, studies continue to observe different optimal cutoffs for the designation of significant fibrosis and cirrhosis; the lack of standardized cutpoints limits widespread applicability. Third, to date there is limited longitudinal data in either untreated or treated patients. Finally, TE is still not widely available in many countries because of high cost and regulatory issues.

In terms of serum marker panels, when panels are developed specifically for use in HIV/HCV co-infection they appear to have superior performance compared to those developed for mono-infected patients. The recent studies confirm the limitations of APRI and support that its use should be primarily in excluding significant fibrosis; this appears to apply to all subgroups except those with low CD4 cell count. Panels like APRI, FIB-4 and Forns remain attractive because they are cheap and include widely available markers. While performance of panels like HGM-3 and Fibrometer were superior, these panels include some nonroutine tests that may be expensive and not widely available. The panels that were newly developed (e.g., HGM-3, Fibrometer HICV) will require additional external validation before conclusions about their predictive accuracy can be made.

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Summary

- A number of efforts continue to examine the performance of previously validated surrogates for liver fibrosis and cirrhosis among HIV/HCV co-infected patients. New surrogates, in particular serum marker panels, continue to be developed.
- In head to head comparisons, performance of transient elastography (TE) appeared superior to the majority of serum marker panels for the detection of significant fibrosis and cirrhosis in HIV/HCV co-infected patients; however challenges to widespread application of TE remain including lack of widespread availability, lack of standardized cutpoints and lack of longitudinal data in treated and untreated patients.
- Panels that were newly developed in 2010-11 specifically for HIV/HCV appeared to perform better than existing panels such as APRI and FIB-4; however additional external validation will be needed to confirm their accuracy.

Table 1

Performance of serum marker panels to assess liver fibrosis/cirrhosis in HIV/HCV co-infected patients, 2010-2011

				≥F2 (significant fibrosis)		≥F3 (advanced fibrosis)		≥F4 (cirrhosis) AUROC	
				≥F2 (significant fibrosis)		≥F3 (advanced fibrosis)		≥F4 (cirrhosis) AUROC	
Score	**Serum Markers**	**Reference**	**N**	**%**	**AUROC**	**%**	**AUROC**	**%**	**AUROC**
Direct									
	Hyaluronic acid (HA)	[9]	201	58	0.67	32	0.77	11	0.86
	Matrix metalloproteinase 2 (MMP-2)	[10]	90	66	0.64	37	---	18	0.79
	Tissue inhibitor of metalloproteinase-1 (TIMP-2)	[10]	90	66	0.57	37	---	18	0.64
Indirect									
APRI	Platelets, AST	[9,11-17][A]	2025[B,C]	43-81	0.67-0.79	15-34	0.76-0.82	8-20	0.80
FIB-4	Age, Platelets, AST, ALT	[9,11-15,17][A]	1506[B,C]	43-81	0.67-0.76	15-34	0.69-0.85	8-20	0.82
Forns Index	Age, Platelets, GGT, Cholesterol	[9,13-16]	1178	43-58	0.67-0.74	15-32	0.75-0.78	8-12	0.82
HGM-1	Platelets, AST, Glucose	[9,14,15]	563	57-58	0.78-0.80	27-32	---	11	---
HGM-2	Platelets, AST, Alkaline Phosphatase, INR,	[9,13-15]	659	43-58	---	15-32	0.80-0.85	8-11	0.92
HICV	Alpha-2-macroglobulin, AST, Prothrombin Index	[17][A]	444	66-72	0.73-0.82	33-34	---	10-20	---
Artificial Neuronal Network (ANN)	Fibrinogen, glucose, AST, ALT, GGT, ALP, cholesterol, platelet count, INR, age	[14]	362	56	0.85	27	0.87	11	---
Direct & Indirect									
HGM-3	Platelets, Alkaline Phosphatase, HA, TIMP-1, Hepatocyte growth factor (HGF)	[15]	195	58	0.78	31	0.93	12	0.93
Fibrometer	Age, Sex, Alpha-2-macroglobulin Platelets, AST, HA, Prothrombin Index, Urea	[17][A]	444	66-72	0.74-0.78	33-34	---	10-20	---
Fibrometer HICV	Age, Sex, Alpha-2-macroglobulin Platelets, AST, HA, Prothrombin Index, Urea	[17][A]	275	66-72	0.74-0.83	33-34	---	10-20	---
Fibrometer 2G	Age, Sex, Alpha-2-macroglobulin Platelets, AST, HA, Prothrombin Index, Urea	[18]	176	67	0.82	33	---	20	----
Fibrometer 3G	Age, Sex, Alpha-2-macroglobulin Platelets, AST, Prothrombin Index, Urea	[18]	176	67	0.83	33	---	20	----
Hepascore	Age, Sex, Alpha-2-macroglobulin, GGT, Bilirubin, Hyaluronic acid (HA)	[17][A]	444	66-72	0.69-0.78	33-34	---	10-20	---

[A] Includes data from derivation and validation populations.

[B] Liver fibrosis stage was assessed using the Batts-Ludwig system for 105 samples

[C] Data included from 295 biopsies sampled from 237 patients. Liver fibrosis stage was assessed using the Ishak Histologic Activity Index (HAI) and Ishak 4–6 fibrosis represented advanced fibrosis corresponding to Metavir >F3.

Table 2

Performance of Transient Elastography (TE) in Patients with Viral Chronic Hepatitis C and HIV Co-infection, 2010-2011

Reference	Test	N	% > F2	AUC > F2	% > F3	AUC > F3	% F4	AUC F4
Sanchez-Conde [13]	TE	100		0.80		0.93		0.99
	APRI	100	43	---	15	0.77	8	---
	FIB-4	99		---		0.69		---
	Forns	97		---		0.75		---
	HGM-2	96		---		0.80		---
Degos [28]	TE	110	60	0.84	---	---	24	0.95

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