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Use of Transient Elastography in Patients with HIV-HCV Co-infection: A Systematic Review and Meta-analysis

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Abstract

Background—Patients with HIV-HCV co-infection progress towards liver fibrosis and cirrhosis more rapidly compared to HCV mono-infected individuals. This necessitates an accurate assessment of liver stiffness with transient elastography to guide treatment.

Methods—Searches of PubMed, EMBASE, Web of Science, and the Cochrane Library databases were performed through January 2016 to assess the diagnostic accuracy of transient elastography for liver stiffness in the HIV-HCV population. Included studies were analyzed according to the Cochrane DTA Working Group methodology. Bivariate and hierarchical models were used to compute pooled sensitivity and specificity. Positive and negative likelihood ratios (LRs) were also determined. A Fagan nomogram was constructed. Meta-regression analysis was performed with assessment of publication bias using Deeks' funnel plot asymmetry testing.

Results—A total of 6 studies (n=756) met inclusion criteria. The diagnostic accuracy of elastography for the diagnosis of moderate (F2) fibrosis was 88% (95% CI, 0.85–0.90). The pooled sensitivity and specificity of moderate fibrosis was 97% (95% CI, 0.82–0.91) and 64% (95% CI, 0.45–0.79), respectively. The diagnostic accuracy of elastography for the assessment of cirrhosis was 94% (95% CI, 0.91–0.95). The pooled sensitivity and specificity for cirrhosis was 90% (95% CI, 0.74–0.97) and 87% (95% CI, 0.80–0.92), respectively. Meta-regression analysis demonstrated that CD4 cell count did not impact diagnostic accuracy of elastography.

Conclusion—Transient elastography is a non-invasive imaging modality with excellent ability to assess for cirrhosis in patients with HIV-HCV co-infection.

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Keywords

Hepatitis; HCV; HIV; Elastography; Fibrosis

Introduction

Chronic liver disease as a result of the hepatic C virus (HCV) remains a significant cause of morbidity and mortality afflicting millions of individuals in both the United States and worldwide. While the burden of HCV in the United States is expected to decline with the expanded use of direct acting antivirals (DAA), the past several decades have demonstrated that the ability to assess disease progression and fibrosis is paramount to determine prognosis and appropriate medical therapy.^{1,2} In the new era of approved DAA combination therapy, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDSA) treatment guidelines have identified specific populations that require special consideration for HCV management.³ One of these special subgroup populations involves HCV patients with human immunodeficiency virus (HIV) co-infection.

Of the approximately 3 million people in the United States who have been diagnosed with HCV, up to 25% are estimated to be co-infected with HIV.⁴ Amongst the patient population with HIV, an estimated 10% of those individuals will have co-existing HCV.⁵ While 20% of untreated HCV mono-infected patients will have natural progression of fibrosis to cirrhosis over an estimated 20 to 30 years, studies have shown that HIV co-infected patients have a faster rate of liver fibrosis progression.⁶ Additionally, HIV patients have a high rate co-existing non-alcoholic fatty liver disease and non-alcoholic steatohepatitis further accelerating progression to cirrhosis.⁷ The survival rate of this patient population is considerably reduced as a result of complications of cirrhosis, including gastrointestinal bleeding, ascites, hepatic encephalopathy, and hepatocellular carcinoma.⁸

Given the more rapid progression to fibrosis and sequelae of liver disease, an accurate assessment of liver fibrosis is essential for establishing the prognosis and guiding the treatment of HCV in both mono- and HIV co-infected patients. While liver biopsy is the current gold standard for staging liver fibrosis in individuals with HCV, it is an expensive and invasive procedure that is limited by adverse events that include bleeding, pain, hemobilia, low patient acceptance, sampling error, inter-observer variability, and low accessibility.^{9,10} As a result, multiple indirect, non-invasive measures for assessing liver fibrosis have been developed which include both serologic and radiographic tests.^{11,12}

One such imaging modality for the assessment of liver fibrosis is ultrasound-based elastography. Studies have shown that transient elastography can reliably detect advanced fibrosis (F3 or F4 disease) in patients with HCV.^{13,14} Recent studies assessing the diagnostic value of transient elastography in HIV-HCV co-infected patients suggest similar findings.¹⁵ However, results of these studies are difficult to apply as they offer varying transient elastography score cutoffs for distinguishing moderate and advanced fibrosis. Given these recent study results, the primary aim of this study was to evaluate the diagnostic accuracy of

transient elastography in the staging of moderate (F2) and advanced (F4) liver fibrosis as compared to liver biopsy in patients who are co-infected with HIV and HCV.

Methods

Literature Search and Data Extraction

A comprehensive search of the literature was performed to identify articles that examined the diagnostic accuracy of ultrasound-based elastography for staging of liver fibrosis. A systematic search of PubMed, EMBASE, Web of Science, and the Cochrane Library database was performed through January 2016. The following search terms were used: “human immunodeficiency virus”, “HIV”, hepatitis C virus”, “HCV”, “co-infection”, “ultrasound”, “Fibroscan”, and “elastography”. All relevant articles irrespective of language, year of publication, type of publication, or publication status were included. The titles and abstracts of all potentially relevant studies were screened for eligibility with the reference lists from studies of interest manually reviewed for additional articles by cross checking bibliographies. Two reviewers (JL and BN) independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. Any differences were resolved by mutual agreement and in consultation with the third reviewer (TRM).

Study Selection Criteria

Only studies including patients with HIV-HCV co-infection were included. If a study included both HCV mono-infected and HIV-HCV co-infected individuals, authors were contacted for further stratification of data. Studies involving alternative imaging or radiologic modalities as well as serum biomarkers were not included. Liver biopsy as a standard reference was not a requirement of all patients in the included studies. Review articles, editorials, and correspondence letters that did not report the author's original research were excluded. Other studies were excluded if determined to have insufficient data. Additionally, case series and reported studies with fewer than 5 patients were excluded.

Outcome Measures

The primary outcome measures in this study were the diagnostic accuracy, sensitivity, and specificity of transient elastography for liver stiffness measurement.

Assessment of methodological quality—Quality assessment of diagnostic accuracy studies (QUADAS-2), an evidence-based tool for assessment of quality in systematic reviews of diagnostic accuracy studies, was used to evaluate the studies. Each key domain has a set of signaling questions to assess bias and applicability.^{16,17} Disagreement among raters was resolved by consensus with the other authors. We used tabular and graphical displays in Review Manager 5 (RevMan 5.3) to summarize the QUADAS-2 assessments.

Statistical Analysis

Included studies were analyzed according to the Cochrane DTA Working Group methodology. Measured outcomes included sensitivity and specificity of ultrasound-based elastography. Data were analyzed using the Stata 13.0 software package (Stata Corp LP, College Station, TX). Bivariate and hierarchical models were used to compute the pooled

sensitivity and specificity and to plot the summary receiver operating characteristics (ROC) curve with summary point and corresponding 95 % confidence region. The area under the ROC curve was used to define accuracy. This method fits a two-level model, with binomial distributions for the combined TP and the TN conditional on study-specific sensitivity and specificity, and a bivariate normal model for the logit transformations for sensitivity and specificity between studies. This was performed separately for both moderate (F2) liver fibrosis and cirrhosis (F4). Positive likelihood ratio (LR) and negative LR were also determined. A Fagan plot, a graphical tool for estimating how much the result on a diagnostic test changes the probability that a patient has a disease, was also employed to determine the meaningfulness or clinical utility.^{18,19}

Assessment of Publication Bias

The assessment of publication bias was performed using Deeks' funnel plot asymmetry testing as proposed by The Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.²⁰ Briefly, the test was developed especially for test accuracy reviews and plots the diagnostic odds ratio against the inverse of the square root of the effective sample size. Funnel plots were constructed using Stata 13.0 software package (Stata Corp LP, College Station, TX).

Results

Characteristics of Included Studies

The literature search yielded 6 studies from 2006 to 2014 that met inclusion criteria for this meta-analysis.²¹⁻²⁶ A PRISMA flow chart of search results is shown in Figure 1. Data on a total of 756 patients was assessed. All included studies based degree of fibrosis upon the validated METAVIR fibrosis scoring system: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with few septa; F3 = portal fibrosis with numerous septa without cirrhosis; and F4 = cirrhosis.^{27,28} Baseline characteristics of included studies including percentage of moderate liver fibrosis and cirrhosis are demonstrated in Table 1. As shown in the table, heterogeneity existed between cut-offs applied to F2 and F4 disease. de Ledinghen and colleagues utilized a cut-off of 4.5 kPa to define F2 disease while Vergara et al derived this degree of fibrosis from a cut-off of 7.2 kPa.^{22,23} There was a similar disparity between the cut-offs chosen for advanced fibrosis as well.

Quality Assessment of Included Studies

The quality of the eligible studies assessed by QUADAS- 2 criteria is reported Figure 2. Overall, the vast majority of studies possessed a low risk of bias with low acceptability concerns. In all but one study, there was a low risk of bias for patient selection, index test, and reference standard. Sanchez-Conde et al demonstrated an unclear risk of bias and acceptability concern due to the vague description of liver biopsy use and number of patients in which this procedure was performed.²⁵

Transient Elastography for Moderate Fibrosis

A total of 6 studies evaluated stage F2 liver fibrosis amongst patients co-infected with HIV-HCV. A forest plot of all included studies is demonstrated in Figure 3 with pooled

sensitivities and specificities of each study. The diagnostic accuracy was determined to be 88% (95% CI, 0.85 – 0.90), Figure 4. The pooled sensitivity and specificity of ultrasound-based elastography for the assessment of moderate fibrosis was 97% (95% CI, .82 – 0.91) and 64% (95% CI, 0.45 – 0.79), respectively. The pooled positive LR and negative LR were 2.4 (95% CI, 1.5 – 3.8) and 0.20 (95% CI, 0.15 – 0.26), respectively. The diagnostic odds ratio was 12 (95% CI, 7 – 22). A Deeks' funnel plot was used to demonstrate no evidence of publication bias ($p=0.32$), Supplemental Figure 1.

A Fagan plot with regard to liver stiffness in HIV-HCV co-infected patients demonstrated that with a low pre-test probability (20%) of moderate fibrosis, if elastography demonstrated F2 fibrosis, then the post-test probability that the patient truly has moderate fibrosis would be approximately 38%. In the face of a negative test, the post-test probability that the patient actually has moderate fibrosis would be less than 2%, Figure 5.

Transient Elastography for Advanced Fibrosis

These 6 studies also evaluated cirrhosis in HIV-HCV patients. The diagnostic accuracy of elastometry for the assessment of advanced liver disease was 94% (95% CI, 0.91 – 0.95), Figure 6. The pooled sensitivity was lower when compared to the assessment of moderate fibrosis at 90% (95% CI, 0.74 – 0.97). Despite this lower sensitivity, ultrasound-based elastography demonstrated a higher pooled specificity for cirrhosis at 87% (95% CI, 0.80 – 0.92). The pooled positive LR and negative LR were 7.0 (95% CI, 4.1 – 11.9) and 0.11 (95% CI, 0.04 – 0.34), respectively with a diagnostic odds ratio of 62 (95% CI, 12 – 261). There was no evidence of publication bias ($p=0.25$), Supplemental Figure 2.

The Fagan nomogram regarding cirrhosis demonstrated that even with a low pre-test probability (20%), the post-test probability of true disease in the face of a positive test was 64%, Figure 7.

Meta-regression and Subgroup Analyses

In an attempt to identify the potential individual factors on diagnostic accuracy, a meta-regression was performed, Figure 8. Based upon available study data, age, sex, and CD4 cell count did not influence the diagnostic accuracy of transient elastography for the diagnosis of moderate fibrosis.

Discussion

This study demonstrates that ultrasound-based elastography is an accurate modality to measure liver stiffness in patients with HIV-HCV co-infection. While liver biopsy remains the most accurate modality, there has been a paradigm shift in clinical practice within the United States and worldwide with the expanded use of non-invasive tests. As this select HIV-HCV co-infected patient population progresses towards liver fibrosis at a more rapid rate as compared to mono-infected individuals, the utilization of transient elastography is pivotal to determine prognosis and appropriate medical therapy.

An accurate assessment of fibrosis at a moderate or early stage is critical in order to halt progression and even potentially reverse the effects of liver damage. With the increasing

reliance upon non-invasive testing to assess presence or degree of fibrosis in patients with liver disease, a review of available testing is paramount to understanding the impact of transient elastography on the HIV-HCV population. Non-invasive biomarkers, including FIB-4 score, SHASTA index, and Fibrometer HICV, have been designed and validated in patients with HIV-HCV co-infection; however, these markers may be imprecise due to the confounding effects of CD4 cell count, viral replication, and combination anti-retroviral therapy (cART) on component lab parameters.^{11,15,29-32} Ultrasound-based elastography is one imaging modality that rapidly and indirectly measures liver stiffness (i.e. degree of fibrosis) and offers an advantage to serum biomarkers in that results are typically not affected by the natural history of HIV nor HIV-directed treatment.³³ Additionally, as shown in this study through meta-regression analysis, CD4 cell count did not impact the diagnostic accuracy of elastography. Therefore, this non-invasive radiographic modality may be preferred in this subgroup population.

Amongst this HIV-HCV population, a variety of studies have assessed DAA combination therapy and found impressive results of sustained viral response (SVR) rates.³⁴⁻³⁷ Specifically, the C-EDGE study sought to evaluate additional drug combinations including the use of grazoprevir plus elbasivir for treatment naïve patients with co-infection and attained an SVR rate of 95%.³⁷ With the impressive results shown in this select patient population, the AASLD-IDSa treatment guidelines recommend similar treatment algorithms for mono-infected patients.³ The ability to achieve excellent SVR rates that are comparable to HCV mono-infected individuals again highlights the pivotal role of transient elastography. This non-invasive modality may not only provide a threshold for DAA initiation, but should also be key to assess for fibrosis regression after treatment in HIV-HCV patients given the comparable SVR to HCV mono-infected individuals.

Previous studies have demonstrated that transient elastography does not distinguish between mild versus moderate fibrosis in patients with HCV alone. In our study, the pooled accuracy for detection of F2 disease was 88% (95% CI, 0.85 – 0.90). Similar to studies in HCV mono-infected patients, our results show that ultrasound-based elastography performed better in the diagnosis of advanced fibrosis (F4) compared to moderate fibrosis in HIV-HCV co-infected patients (94% versus 88% accuracy, respectively). Notably, specificity of transient elastography for detection of moderate (F2) disease was low at 64%. This lower specificity leaves the potential for patients with mild fibrosis (F1) to be falsely diagnosed with higher fibrosis stage.

Despite this, from a clinical perspective, the benefits of diagnosing more moderate (F2) disease likely outweigh the risk of false positives. Moderate fibrosis is often the threshold at which DAA therapy is covered by some insurers and initiated by some providers. Additionally, therapy at the moderate (F2) stage does not require modification of treatment regimen or duration. Perhaps more importantly, patients with F2 disease are also not exposed to radiation for HCC screening and the risks of endoscopy for variceal screening. Therefore, in spite of a lower specificity that may lead to more falsely positive diagnoses of moderate fibrosis, the perceived risks of ultrasound-based elastography to the patient are minimal, with little to no impact on treatment, cost, or rate adverse events.

While the specificity of this modality remains less than ideal, other limitations of transient elastography include high inter-operator variation of results, particularly when performed by inexperienced operators. This inter-operator variability may result from even slight repositioning of the transducer and may affect patients with lower grades of liver fibrosis.³⁸ Accurate interpretation of transient elastography results is also challenging in patients who are obese or who have acute hepatitis, alcohol abuse, congestive heart failure, or recent oral intake.¹ Despite these limitations, a recent study by Fraquelli et al in non-HIV patients with chronic liver disease found transient elastography to be a highly reproducible and user-friendly technique.³⁸ However, even these authors acknowledge excess body weight and steatosis may affect the signal-to-noise ratio, a fundamental parameter to assess liver stiffness. At this time, liver stiffness measurement may fail or be unreliable in this subset of patients. Given this, further studies are warranted to specifically examine these subgroups.

Aside from the inherent heterogeneity limitations of meta-analyses that exist between studies, the lack of a homogenous or standard cut-off (kPa) for staging of fibrosis limits further extrapolation to real world clinical care. As demonstrated in Table 1, de Ledinghen et al utilized a cut-off of 4.5 kPa for the definition of moderate disease while Vergara and colleagues determined a much higher threshold of 7.2 kPa (almost double).^{22,23} A similar disparity was shown for the criteria used to define advanced disease which may predispose to spectrum bias.³⁹ This heterogeneity and lack of a standardized definition of moderate and advanced disease, coupled with intrinsic inter-operator variability, limits the ability to generalize these results. However, this heterogeneity was addressed by the Baveno VI consensus recently that proposed the cutoffs of 10 kPa and 15 kPa for excluding and diagnosing severe fibrosis/cirrhosis respectively.⁴⁰ Ultimately, the impressive accuracy as demonstrated in this meta-analysis warrants further studies aimed at validating this standardized cut-off for F2 and F4 fibrotic disease.

Despite these limitations, this meta-analysis possesses several strengths. This study summarized all methodologically rigorous data on transient elastography with regard to HIV-HCV co-infected patients. This allowed for determination of a pooled sensitivity, specificity, and accuracy to further support the use of this non-invasive imaging modality in this specialized subgroup population. To these authors' knowledge, this is the first ever pooled analysis of transient elastography for the assessment of fibrosis in patients with HIV-HCV co-infection. By combining data from all available studies, we were able to report the best evidence on the effectiveness of ultrasound-based elastography for liver stiffness. This pooled data may provide a pivotal tool to guide primary care physicians, practicing gastroenterologists, and hepatologists caring for patients with HIV-HCV co-infection.

In conclusion, non-invasive testing to evaluate the degree of liver fibrosis has supplanted traditional liver biopsy in current clinical practice. With the expanded use of a variety of modalities (serum biomarkers and radiographic), the assessment of chronic liver disease within a specialized HIV population is paramount to management and treatment. As this HIV-HCV population has been identified as a distinctive subgroup and traditionally viewed as more difficult to treat or cure, the requirement for non-invasive testing and subsequent assessment of its accuracy to stage liver fibrosis is essential. Given this high priority for DAA treatment in HIV-HCV co-infected patients, the assessment of advanced fibrosis and

cirrhosis is important to initiate appropriate liver cancer surveillance. Transient elastography is a unique, non-invasive imaging modality demonstrated in this study to have a high accuracy for detecting moderate fibrosis and excellent ability to assess cirrhosis in patients with HIV-HCV co-infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. PRISMA Flow Chart of Search Results for Transient Elastography

Figure 2. QUADAS-2 Quality Assessment of Included Studies

Figure 3. A Forest Plot of All Included Studies for Transient Elastography

Figure 4. Diagnostic Accuracy of Transient Elastography for Moderate Fibrosis

Figure 5. Fagan nomogram for Transient Elastography for Moderate Fibrosis

Figure 6. Diagnostic Accuracy of Transient Elastography for Cirrhosis

Figure 7. Fagan nomogram for Transient Elastography for Cirrhosis

Figure 8. Meta-regression Analysis for Transient Elastography

Table 1
Diagnostic Characteristics of Transient Elastography in HIV-HCV co-infection

Author	Year	No of Patients	Degree of Fibrosis	Cut-off in kPA	Sensitivity	Specificity	Accuracy
Castera et al	2014	116	F2	7.1	85%	76%	87%
			F4	12.5	77%	86%	92%
Kirk et al	2009	192	F2	9.3	86%	75%	81%
			F4	12.3	75%	86%	81%
Sanchez-Conde et al	2009	100	F2	7	77%	75%	80%
			F4	14	100%	93%	90%
Macias et al	2008	97	F2	9	87%	67%	86%
			F2	7.2	88%	66%	83%
Vergara et al	2007	169	F4	14.6	93%	88%	95%
			F2	4.5	94%	33%	74%
de Ledinghen et al	2006	72	F4	11.8	100%	93%	97%