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Noninvasive Marker, Fibrospect II, Overestimates Fibrosis in Hepatitis C-Infected Patients with Chronic Renal Insufficiency

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ABSTRACT

Aim: Liver biopsy is the gold standard for determining liver fibrosis stage, but it is an invasive test with fallibility including sampling error and observer variability. Many non-invasive markers including Fibrospect II, a proprietary formula, have been developed to replace liver biopsy, but their accuracy in patients with chronic renal insufficiency (CRI) is unclear. We aimed to investigate the accuracy of Fibrospect II in chronic hepatitis C (HCV) infected patients with CRI.

Methods: Liver biopsies and serum Fibrospect II scores of 20 patients with HCV and CRI (HCV+CRI) defined as glomerular filtration rate (GFR) <55 ml/min were compared to 18 patients with HCV infection and normal renal function (GFR ≥55 ml/min (HCV). Ten non-HCV infected hemodialysis (HD) patients also had Fibrospect II scores drawn before and after a HD session.

Results: The HCV+CRI cohort had a higher mean Fibrospect II score of 92.5±10.2 than the HCV (58.5±27.7) and hemodialysis (68.7±28.0) groups ($p = 0.0001$). Fibrospect II scores correlated poorly with the histologic fibrosis stage in the HCV+CRI cohort, with an area under the receiver operator curve (AUROC) of 0.48, while the HCV group had a good AUROC of 0.89. In the HD patients, Fibrospect II scores decreased following a hemodialysis session 68.7 to 58.4, but this was not statistically significant ($p = 0.3$).

Conclusion: While Fibrospect II is a useful noninvasive tool to stage fibrosis in HCV infection, it overestimates the amount of liver fibrosis in patients with CRI, thereby limiting its utility in this population.

ABBREVIATIONS:

A2M: Alpha-2 macroglobulin

ALT: Alanine aminotransferase

APRI: Aspartate aminotransferase to platelet ratio

AST: Aspartate aminotransferase

AUROC: Area under receiver operating characteristic

CI: Confidence Interval

COMP: Cartilage oligomeric matrix protein

CRI: Chronic renal insufficiency

GFR: Glomerular Filtration Rate

GGT: Gamma-glutamyl-transpeptidase

HA: Hyaluronic acid

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HIV: Human immunodeficiency virus

HD: Hemodialysis

NAFLD: Non-alcoholic fatty liver disease

NPV: Negative Predictive Value

PPV: Positive Predictive Value

TE: Transient Elastography

TIMP-1: Tissue inhibitor of metalloproteinase-1

INTRODUCTION

The World Health Organization estimates over 185 million people are infected with hepatitis C virus (HCV) worldwide, and up to 4.7 million people have active infection within the United States [1, 2]. Liver fibrosis is an important predictor of disease progression and mortality in HCV infection [3, 4]. While liver biopsy remains the gold standard in determining liver fibrosis stage, it is limited by its invasive nature, sampling error and observer variability [5, 6]. To replace liver biopsy in fibrosis detection, many non-invasive serum markers such as serum Fibrospect II, hyaluronic acid (HA), aspartate aminotransferase (AST) to platelet ratio (APRI), Fibrotest, Hepascore, and cartilage oligomeric matrix protein (COMP), and radiologic methods such as transient elastography acoustic radiation force impulse imaging and magnetic resonance elastography have been developed [7-15]. Adoption of these non-invasive markers of fibrosis has been gaining momentum [16]. The most recent joint HCV recommendations from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America, and from the European Association for the Study of the Liver advocate for non-invasive markers and transient elastography as first line tests for liver fibrosis, and to proceed to a liver biopsy only in patients with inconclusive results or when more information is necessary [17, 18].

Fibrospect II score, a proprietary matrix of serum tissue inhibitor of metalloproteinase-1 (TIMP-1) measured by ELISA, alpha-2 macroglobulin (A2M) measured by nephelometry, and HA measured by ELISA, was initially studied in 294 patients with chronic HCV and validated in an external cohort of 402 patients. A Fibrospect II score > 0.36 was associated with significant fibrosis (F2-F4), with 75% accuracy [7]. A more recent study showed the Fibrospect II score to have a sensitivity of 72%, specificity of 74%, positive predictive value (PPV) of 61% and negative predictive value (NPV) of 82% in the detection of significant fibrosis in chronic HCV patients [19].

At our institution, we have noted that the Fibrospect II may have a lower accuracy in predicting the degree of fibrosis in HCV patients with renal insufficiency or renal failure. To investigate this anecdotal observation further, we compared the accuracy of Fibrospect II in estimating hepatic fibrosis in HCV patients with significant renal insufficiency to a control group of HCV patients with normal renal function. Secondly, we also sought to identify the component of the Fibrospect II score that may affect its accuracy in patients with renal dysfunction. Lastly, the study aimed to determine if a hemodialysis (HD) session has any impact on the Fibrospect II scores in non-HCV infected patients who were dialysis-dependent.

METHODS

This was a combined retrospective and prospective study. Twenty consecutive patients with HCV infection, confirmed by a positive serum HCV RNA, and chronic renal insufficiency (CRI) [defined as glomerular filtration rate (GFR) <55 ml/min], who had a Fibrospect II score drawn and a liver biopsy within twelve months of the Fibrospect II score, were identified from the Liver and Pathology databases of the University of Chicago Medicine. Eighteen additional patients with HCV infection and normal renal function were identified as a control group. Liver biopsy was obtained as indicated by their medical management. Another 10 patients who were on dialysis at an outpatient HD center and had a negative serum HCV antibody or HCV RNA and no known liver disease were prospectively enrolled into the study. In this population, Fibrospect II scores were drawn before and after a HD session. Patients were excluded if they had a liver transplant, hepatocellular carcinoma, clinical history of significant alcohol use, non-alcoholic fatty liver disease (NAFLD) diagnosed either by liver biopsy or on imaging studies, or co-infection with either human immunodeficiency virus (HIV) or hepatitis B virus (HBV).

For all patients, demographic data and laboratory tests including serum creatinine, calculated GFR per Modification of Diet in Renal Disease (MDRD) method, serum alanine aminotransferase (ALT) and Fibrospect II scores were obtained. MDRD is the methodology utilized to calculate GFR in the electronic medical record at our institution. Histologic data was obtained from the Liver and Pathology databases of the University of Chicago Medicine. Liver biopsies were graded and scored according to the Batts and Ludwig criteria with significant fibrosis defined as F2 – F4 staging [20].

Continuous variables were expressed as means and medians and categorical variables were expressed as percentages. Data was subjected to ANOVA, t-test, chi^2 test, area under receiver operating characteristic (AUROC) and regression analysis using Stata 10 software (StataCorp, LP, Texas). A p - value of < 0.05 was deemed significant.

The University of Chicago Medicine Institutional Review Board approved this study. All authors had unlimited access to the study data and approved the final manuscript prior to publication.

RESULTS

Demographics

A total of 48 patients were included in this study. The study group included 20 patients with chronic HCV and CRI (HCV+CRI group), and the control group included 18 HCV-infected patients with normal renal function (HCV group). Ten non-HCV infected patients on HD (HD group) were also studied. There was no significant difference in age or gender distribution amongst the study groups, but the HCV+CRI and the HD groups had significantly lower mean GFR's at 16.7±13.4 ml/min and 11.7±6.8 ml/min, respectively, than the HCV group, (p < 0.001). Notably, the mean serum ALT was lower in the HCV+CRI group at 39±24 IU/L than the HCV group at 75±38 IU/L (p < 0.001). Both the HCV+CRI and HCV groups had a similar distribution of significant fibrosis (Table 1). Causes of renal disease in the HCV+CRI group included hypertensive nephropathy in 50%, diabetic nephropathy in 22% and other causes (focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous glomerulonephritis, post-streptococcus glomerulonephritis, and calcineurin-inhibitor toxicity) in the rest. The HD group, on the other hand, had hypertensive nephropathy in 20%, diabetic nephropathy in 50%, and other causes (polycystic kidney disease, primary glomerulonephritis, and membranous glomerulonephritis) in the rest.

Table 1: Demographic, histologic and Fibrospect II data.

	HCV+CRI	HCV	HD	p-value
Age (years)	55.2	52	59	0.23
Gender (% Male)	67	45	30	0.17
Mean serum ALT (IU/ml)	39±24	75±38	18±10	<0.0001
Mean GFR (mL/min)	16.7±13.4	84.0±12.5	11.7±6.8	<0.0001
Significant fibrosis on histology (%)	30	22	NA	0.43
Mean serum Fibrospect II Score	92.5±10.2	58.5±27.7	68.7±28.0	0.0001
Mean serum TIMP-1 (ng/ml)	3120±997	1610 ±645	2140±743	<0.00001
Mean serum A2M (mg/ml)	328±83.4	317±88.2	146±54.6	<0.00001
Mean serum HA (ng/ml)	259±449	79.3±80.9	240±283	0.17

ALT – alanine aminotransferase, GFR – glomerular filtration rate, TIMP-1 – tissue inhibitor of metalloproteinase-1, HA - hyaluronic acid, A2M - alpha-2-macroglobin.

Fibrospect II Score and Components

The HCV+CRI group had a mean Fibrospect II score of 92.5 ± 10.2 which was significantly higher compared to that in the HCV and HD groups (p = 0.0001) (Table 1). When evaluating the components of the Fibrospect II score individually, the mean TIMP-1 and A2M were each significantly higher in the HCV + CRI group (p < 0.0001). The HA levels trended higher but did not reach statistical significance (p < 0.17). Fibrospect II score decreased from 68.7 to 58.4 following an HD session, but this change was not significant (p = 0.3). The individual values of the Fibrospect II components also remained un-

changed. There were no liver biopsies performed in this patient population given the absence of a clinical indication.

Correlation Between Fibrospect II Score and Histologic Stage

Significant fibrosis was present in only 22% of the HCV+CRI group, but 83% of these patients had a Fibrospect II score >90 (Figure 1). Serum TIMP-1 was significantly higher in the HCV+CRI group than in the HCV group ($p < 0.0001$), while serum HA and A2M levels were similar between the two groups. Only the serum TIMP-1 correlated with the overall Fibrospect II score in the HCV+CRI cohort ($p = 0.024$), while all three components correlated with the Fibrospect II score in the HCV cohort.

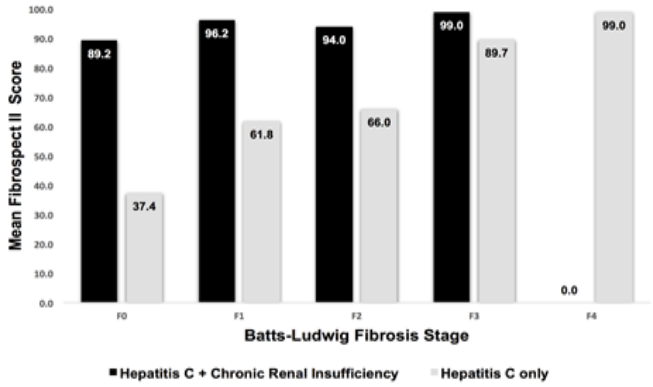
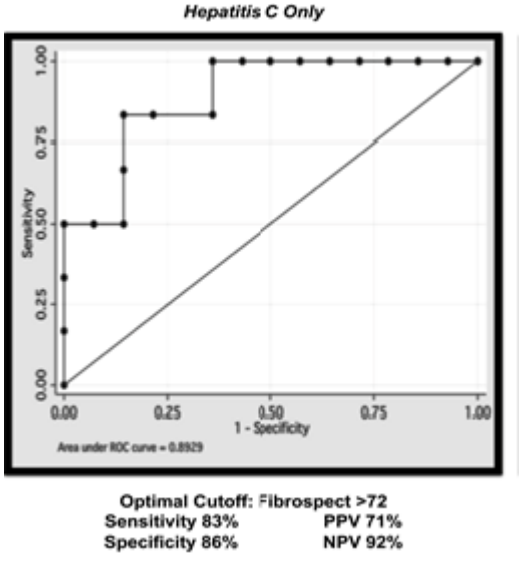


Figure 1: Fibrospect II scores (y axis) and liver biopsy stages (x axis) in hepatitis C cohort and hepatitis C and renal insufficiency cohort.

There was poor correlation of the Fibrospect II scores with the histologic stages in the HCV+CRI cohort, with an AUROC of 0.48 and a poor optimal cut-off of 97 to detect significant fibrosis. Conversely, the HCV group had an AUROC of 0.89 with an optimal cut-off value for significant fibrosis detection > 72. The sensitivity was 83% and specificity was 86% with a PPV 71% and NPV 92%. The AUROCs were significantly different between the two groups ($p = 0.02$) (Figure 2).



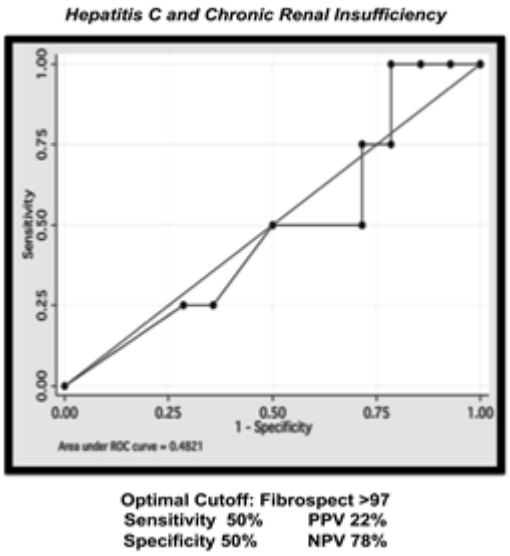


Figure 2: Area under the receiver operator curve (AUROC) of the Fibrospect II scores in hepatitis C cohort and hepatitis C and chronic renal insufficiency cohort ($p = 0.02$).

DISCUSSION

Fibrospect II score was confirmed to be useful in estimating liver fibrosis from hepatitis C in patients with normal renal function in this study, but it was seen to overestimate the degree of liver fibrosis in patients with hepatitis C who had renal insufficiency. Patients who maybe at risk for advanced fibrosis need to have determination of the fibrosis stage to predict their risk for the development of hepatocellular carcinoma and other complications of cirrhosis. In addition, lack of access to the costly anti-HCV medications forces deferral of therapy in many patients, despite the intent for universal treatment of all HCV-infected patients who have reasonable life expectancies. These patients need to be monitored for progression of fibrosis while they remain untreated. Although liver biopsy is the diagnostic gold standard, its risks for complications, sampling error, and observer variability have prompted the increasing adoption of non-invasive measurements of fibrosis into clinical care. Such non-invasive tests are in the form of models incorporating indirect serum biomarkers included in routine tests, direct serum biomarkers that represent components of the extracellular matrix produced by activated hepatic stellate cells, and measurements of liver stiffness. The recommended approach to measure fibrosis non-invasively at the present time is a combination of direct serum biomarkers with transient elastography [17, 18]. Accuracy of fibrosis measurement is greater when two testing modalities are used, but discordant results may occur and should lead to consideration of a liver biopsy [21].

Fibrospect II is a single blood test that is readily obtained in clinical practice; despite the components that need to be measured for the analysis, the result is expressed as a single

score that correlates to the fibrosis stage of the liver. Multiple studies have depicted Fibrospect II scores to have good correlation with fibrosis stage. One study of 136 treatment-naïve chronic HCV patients showed a strong correlation of Fibrospect II scores to the Ishak and Knodell fibrosis stages with an AUROC of 0.86 and 0.87 respectively, ($p < 0.0001$) [22]. Furthermore, a study in a heterogenous population of HCV, HCV and HIV co-infected, and post-transplant patients showed Fibrospect II scores to correlate fibrosis stages with an AUROC of 0.823 (95% CI 0.720 – 0.927) [23]. In patients who received interferon-based therapy for HCV, the AUROC was 0.90 for Fibrospect II scores, with sensitivity and specificity for detection of F2-F4 fibrosis of 95% and 66% respectively [24]. A cohort of HCV patients, some of whom were receiving therapy, and HBV patients, the AUROC for Fibrospect II scores was 0.77 (95% CI 0.672-0.867) in the comparing significant fibrosis versus non-significant fibrosis [25]. Combining Fibrospect II with APRI to measure fibrosis in HCV infection led to an excellent AUROC of 0.931 (95% CI 0.859 – 0.973) [26]. Fibrospect II has demonstrated its utility in other liver diseases as well, such as NAFLD where both linear and multi-regression analyses showed significant correlation between the score and fibrosis stage [27].

Similar to previously published data, our study showed that Fibrospect II had a good AUROC of 0.89 in the HCV group without renal insufficiency; however, the HCV+CRI group had a low AUROC of 0.48, ($p = 0.02$), suggesting that Fibrospect II scores are inaccurate in patients with renal dysfunction. Amongst the components of Fibrospect II score, TIMP-1 appears to be the marker most affected by renal function in our study. This marker has been reported to change with the type of dialysis membrane used during HD, with lower post-HD TIMP-1 levels in patients where a methyl methacrylate membrane had been used, in contrast to higher post-HD levels in those where polysulfone membrane was used [28-30]. The duration of an HD session also affects TIMP-1 levels [31]. The effect of HD on A2M levels is less clear with conflicting data showing an increase in A2M levels over the course of an HD session in some studies, and unchanged in another [32-35]. HA levels have also been shown to increase with the duration of HD in patients with HCV and in those without the infection [36-40]. Interestingly, in our study, HD did not significantly affect the Fibrospect II score or its individual components. Nevertheless, the mean Fibrospect II score was higher in the HCV+CRI group when compared to the HCV group despite a similar proportion of significant fibrosis in both groups, suggesting that renal dysfunction artificially increases the Fibrospect II scores in the HCV-infected population.

Other non-invasive measures of fibrosis such as HA, Fibrotest, and APRI (AST to Platelet Ratio Index) have also been studied in patients with renal insufficiency. Plasma HA levels required a higher cutoff to discriminate significant fibrosis in patients with HCV who were on HD when compared to those who were not on HD (984.8 ng/ml vs. 222.3 ng/ml) [41]. Fibrotest had an unacceptably low AUROC of 0.47 for significant fibrosis in HD patients [42]. The APRI, on the other hand, had an AUROC of 0.801±0.038 in patients with HCV who were on HD [43]. These findings suggest that renal dysfunction may affect the accuracy of direct noninvasive markers of liver fibrosis that measures components of extracellular matrix production.

Our study is limited mainly by the small sample size and the retrospective nature of the data collection in two (HCV and HCV+CRI) groups. Nevertheless, its results clearly demonstrate the significant increase in the Fibrospect II scores in HCV-infected patients with renal insufficiency, and its poor ability to predict the histologic stage in this patient population.

In conclusion, while Fibrospect II has been shown to be a useful direct serum biomarker to measure fibrosis in patients with HCV infection, its utility is greatly limited in HCV patients who have renal insufficiency. The reliability of other non-invasive fibrosis markers that measure extracellular matrix components in patients with chronic renal insufficiency also come into question.

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