

# Routine Laboratory Blood Tests May Diagnose Significant Fibrosis in Liver Transplant Recipients with Chronic Hepatitis C: A 10 Year Experience

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## Abstract

**Background and Aims:** The aims of our study were to determine whether routine blood tests, the aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) and Fibrosis 4 (Fib-4) scores, were associated with advanced fibrosis and to create a novel model in liver transplant recipients with chronic hepatitis C virus (HCV). **Methods:** We performed a cross sectional study of patients at The University of California at Los Angeles (UCLA) Medical Center who underwent liver transplantation for HCV. We used linear mixed effects models to analyze association between fibrosis severity and individual biochemical markers and mixed effects logistic regression to construct diagnostic models for advanced fibrosis (METAVIR F3-4). Cross-validation was used to estimate a receiving operator characteristic (ROC) curve for the prediction models and to estimate the area under the curve (AUC). **Results:** The mean ( $\pm$  standard deviation [SD]) age of our cohort was 55 ( $\pm$ 7.7) years, and almost three quarter were male. The mean ( $\pm$ SD) time from transplant to liver biopsy was 19.9 ( $\pm$ 17.1) months. The mean ( $\pm$ SD) APRI and Fib-4 scores were 3 ( $\pm$ 12) and 7 ( $\pm$ 14), respectively. Increased fibrosis was associated with lower platelet count and alanine aminotransferase (ALT) values and higher total bilirubin and Fib-4 scores. We developed a model that takes into account age, gender, platelet count, ALT, and total bilirubin, and this model outperformed APRI and Fib-4 with an AUC of 0.68 ( $p < 0.001$ ). **Conclusions:** Our novel prediction model diagnosed the presence of advanced fibrosis more reliably than APRI and Fib-4 scores. This noninvasive calculation may be used clinically to identify liver transplant recipients with HCV with significant liver damage.

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**Keywords:** Hepatitis C; Liver transplant; Hepatic fibrosis.

**Abbreviations:** ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; AUC, area under the curve; EHR, electronic health record; Fib-4, fibrosis 4; HCV, hepatitis C virus; OLT, orthotopic liver transplantation; REDCap, Research Electronic Data Capture; ROC, receiving operator characteristic; SD, standard deviation; UCLA, University of California at Los Angeles.

Received: 8 October 2015; Revised: 30 November 2015; Accepted: 1 December 2015

\*DOI: 10.14218/JCTH.2015.00034.

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## Introduction

Although chronic infection with hepatitis C virus (HCV) is the most common indication for orthotopic liver transplantation (OLT) in the United States, the diagnosis of HCV is associated with one of the worst 5 year patient survival rates.<sup>1,2</sup> Within 5 years of transplant, 20% of liver transplant recipients develop allograft cirrhosis.<sup>3,4</sup> The use of antiviral therapy has been reported to improve long term survival in liver transplant recipients.<sup>5,6</sup> However, widespread use of interferon-based therapy is associated historically with adverse effects, such as hemolytic anemia and graft dysfunction.<sup>7-9</sup> Although liver biopsies are invasive, associated with sample error, and subject to inter-observer variability, they are performed to investigate the cause of liver enzyme elevation on a protocol basis after transplantation.<sup>10,11</sup>

The advent of all oral direct-acting antivirals (DAAs) has transformed the treatment of HCV in liver transplant recipients.<sup>12</sup> Given the tolerability and safety of all oral therapies, the threshold for treating HCV in liver transplant recipients has decreased. In fact, liver transplant recipients are currently considered at highest priority for direct acting agents regardless of fibrosis severity.<sup>13</sup> An expected consequence of the use of DAAs is the avoidance of routine liver biopsies to assess liver disease fibrosis. Liver transplant recipients with cirrhosis are at risk of hepatic decompensation and hepatocellular carcinoma and require close follow-up and surveillance.<sup>3,14</sup>

In the general population, noninvasive tests have replaced liver biopsy as the preferred method to assess for the presence of advanced fibrosis. Noninvasive assessments of advanced fibrosis are usually based on laboratory tests or measuring elastography. Laboratory tests are further stratified according to whether they are proprietary or can be calculated with lab tests checked on a more routine basis (complete blood count [CBC], chemistry panel, hepatic panel). Commonly used proprietary tests include Fibrotest, Fibrospect, and Fibrosure.<sup>15</sup> However, a few studies with small cohorts have examined the role of these laboratory tests in the diagnosis of liver damage in liver transplant recipients.<sup>16-19</sup>

The objective of our study was to determine whether routine blood tests and fibrosis models were correlated with fibrosis in liver transplant patients, and if so, to create a novel predictive model for advanced fibrosis. We hypothesized that fibrosis in the post-transplant setting can be reliably predicted using laboratory fibrosis models.

## Methods

### Study design

We performed a retrospective review of patients who underwent OLT for chronic HCV at University of California at Los Angeles (UCLA) Medical Center between 2002 and 2012. In this cross sectional study, we retrieved data from the UCLA electronic health record (EHR), Care Connect (Epic). We collected data on patient demographics, liver biopsies performed for any indication, and pertinent labs. We recorded the data using Research Electronic Data Capture (REDCap), which is a secure, web-based application used to build and manage large databases. The study protocol was approved by the UCLA Institutional Review Board.

### Data elements

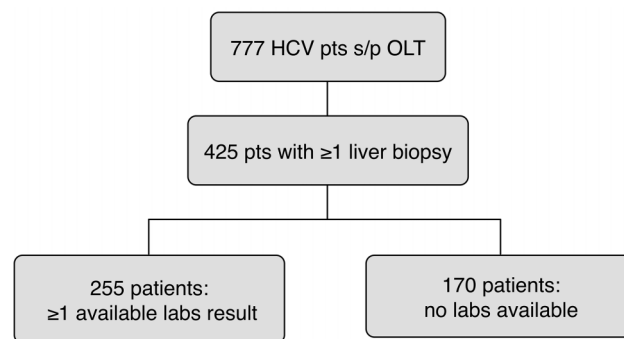
The data elements we collected included patient age and gender, histologic stage of fibrosis by METAVIR classification (FO-F4) on liver biopsies, and routine lab tests, including platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase. We excluded liver biopsy results within 3 months of transplant to minimize confounds in the perioperative setting. Each biopsy finding was associated with the most recent set of lab tests for that subject. Labs were only included if they were obtained within a 1 month time window around the date of biopsy. We also calculated the AST to platelet ratio index (APRI) and fibrosis 4 (Fib-4) scores, which had previously been validated for diagnosing fibrosis in patients with chronic hepatitis C.<sup>20,21</sup> APRI was calculated as  $\text{AST}/\text{upper limit of normal} \times 100/\text{platelet count}$ ; Fib-4 was calculated as  $\text{age} \times \text{AST}/\text{platelet} \times (\text{ALT})^{1/2}$ .

### Statistical analysis

Distributions of markers across biopsies were summarized in terms of means, standard deviations, medians, and quartiles. Due to skewed distributions for the lab values, we transformed them using a natural log transformation. We used linear mixed effects models to analyze associations between degree of fibrosis and individual biochemical markers. For these models, the log transformed lab value was the dependent variable, and the categorical degree of fibrosis was the independent variable. Random subject effects accounted for repeated observations, since most patients had more than one pair of liver biopsy/lab test results. Dot plots were used to visualize patterns of association for individual markers. We used mixed effects logistic regression models to construct predictive models for advanced fibrosis (METAVIR F3-4). To reduce the effect of variable selection and coefficient estimation bias, we performed 10-fold cross-validation to estimate the performance characteristics of the prediction model. Cross validation estimated a receiver operating characteristic (ROC) curve for the prediction models and estimated the area under the curve (AUC).  $p$  values  $<0.05$  were considered statistically significant. All analyses were performed using SAS version 9.3 (SAS Institute Inc., USA).

## Results

There were 777 patients who underwent OLT for chronic hepatitis C at UCLA between 2002 and 2012 (Fig. 1). Four



**Fig. 1. Flow diagram of patients included in study.** There were 777 patients who underwent orthotopic liver transplantation for chronic hepatitis C between 2002 and 2012 at UCLA Medical Center. We identified 425 patients who had at least one liver biopsy, including 255 patients who had at least one retrievable lab result. Only patients with both reported biopsy and laboratory results were included in the study. Due to limitations in electronic medical record reporting, data were not available for all transplant patients.

hundred twenty-five patients had histologic data for at least one liver biopsy, and 255 patients had at least one lab result that could be retrieved. There were no available biopsy results or laboratory data for the other patients due to limitations in electronic medical record reporting. The subject characteristics are presented in Table 1. The mean age at transplant was 55 years. Seventy-four percent of the patients were male. Eighty-nine percent of patients had one liver transplant, and 11% had two or more. The mean number of biopsies per patient was 3.2, with a mean time to biopsy of 19.9 months. Mean laboratory values are shown in Table 2.

As shown in Fig. 2, platelet counts significantly differed across the range of fibrosis severity ( $p < 0.001$ , linear mixed effects model), where higher fibrosis severity was associated with decreased platelet counts. Similarly, ALT decreased with increasing severity of fibrosis ( $p = 0.001$ ), whereas bilirubin increased with increasing severity of fibrosis ( $p < 0.001$ ). Fib-4 score increased with increasing severity of fibrosis. There was no significant difference in AST level, alkaline phosphatase level, or APRI score across the levels of fibrosis severity.

**Table 1. Baseline characteristics (n = 425)**

Variable	Values
Age at transplant, mean (SD)	55 (7.7)
Gender (male)	74%
Number of OLTs	
1	378 (89%)
2	41 (10%)
3	6 (1%)
Number of biopsies per patient, mean (SD)	3.23 (2.41)
Time from OLT to biopsy, mean (SD)	19.9 (17.1) months
Stage of fibrosis, mean (SD)	1.29 (1.03)

Abbreviations: SD, standard deviation; OLT, orthotopic liver transplantation.

**Table 2. Laboratory values (N = 425)**

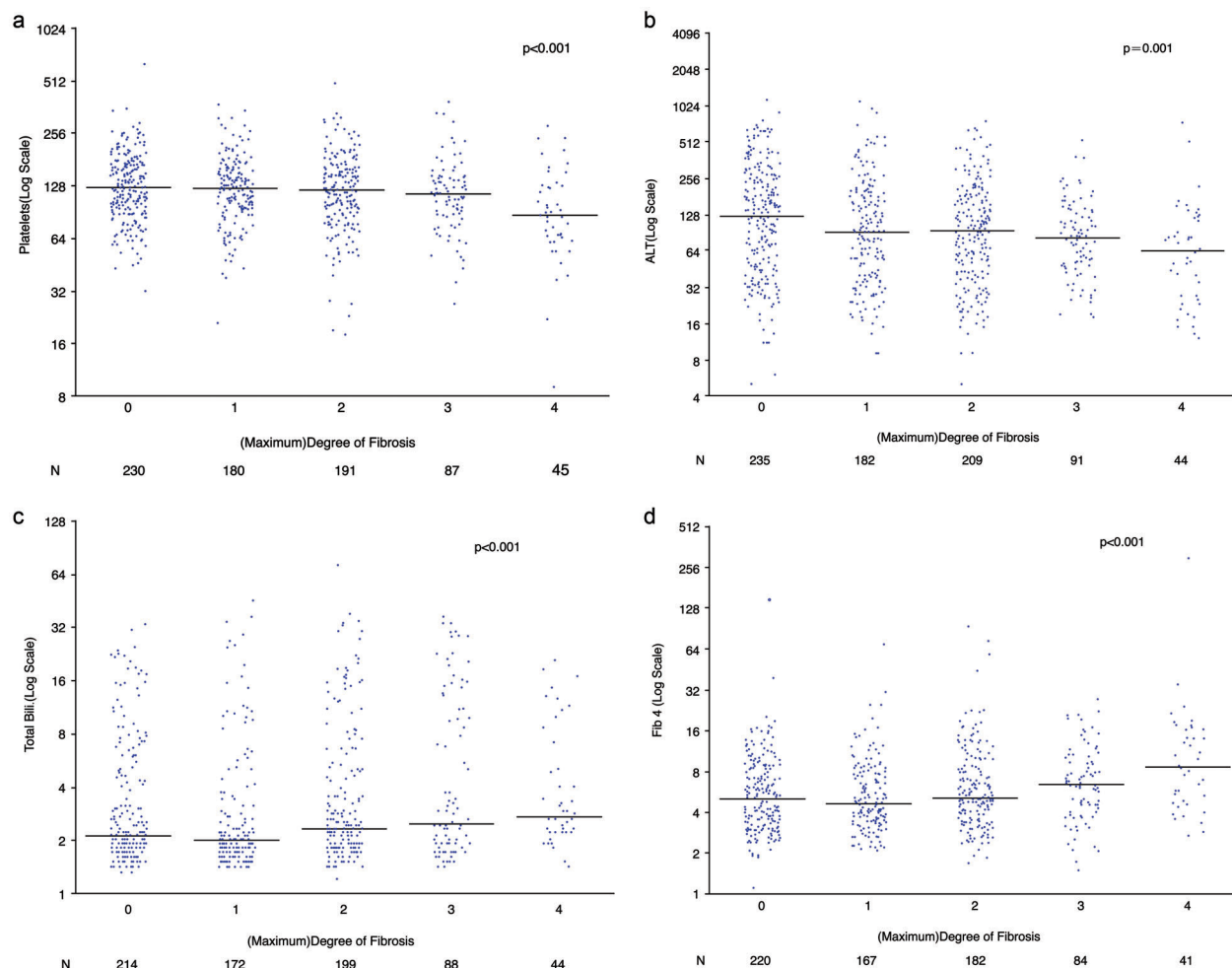
Laboratory test	Mean (standard deviation)
Aspartate aminotransferase (IU/L)	147 (274)
Alanine aminotransferase (IU/L)	152 (194)
Alkaline phosphatase (IU/L)	215 (203)
Total bilirubin (mg/dL)	4 (7)
Platelet (10 <sup>9</sup> /L)	130 (64)
Viral load (millions)	10 (19)
Aspartate aminotransferase to platelet ratio index	3 (12)
Fibrosis-4	7 (14)

After controlling for age and gender and identifying three variables (platelets, ALT, and total bilirubin) as independent predictors of fibrosis, we developed a novel logistic regression prediction model for advanced fibrosis (F3-F4):

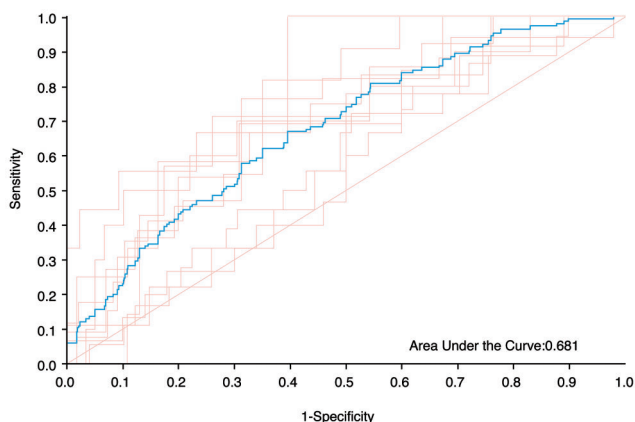
*Male:*  
 $2.73 + 0.02 * \text{Age} - 1.02 * \ln(1 + \text{PLT}) - 0.74 * \ln(1 + \text{ALT}) + 1.01 * \ln(1 + \text{T Bili})$

*Female:*  
 $3.46 + 0.02 * \text{Age} - 1.02 * \ln(1 + \text{PLT}) - 0.74 * \ln(1 + \text{ALT}) + 1.01 * \ln(1 + \text{T Bili})$

The 10-fold cross-validated ROC curve is displayed in Fig. 3. The AUC was 0.68 ( $p < 0.001$ ), which was greater than those for APRI and Fib-4 scores (0.55 and 0.63, respectively, Table 3). While simply adding total bilirubin to the existing models improved their AUCs, our full model was still more diagnostic of advanced fibrosis.



**Fig. 2. We used linear mixed effects models and dot plots to visualize patterns of association between the log transformed lab value or composite score and degree of fibrosis (METAVIR classification). Each blue dot represents an individual liver biopsy, and the total number of biopsies in each categorical degree of fibrosis is listed as N. The horizontal lines represent the median values across each degree of fibrosis. A, Platelet counts decreased with increasing severity of fibrosis ( $p < 0.001$ ); B, Alanine aminotransferase (ALT) levels decreased with increasing severity of fibrosis ( $p = 0.001$ ); C, Total bilirubin levels increased with increasing severity of fibrosis ( $p < 0.001$ ); D, Fibrosis 4 (Fib-4) scores increased with increasing severity of fibrosis ( $p < 0.001$ ). Since the dependent variables are on a log scale, incremental changes were not insignificant. No significant differences in AST, alkaline phosphatase, or AST to Platelet Ratio Index (APRI) across levels of fibrosis severity were identified.**



**Fig. 3. Receiver operating characteristic (ROC) curve using 10-fold cross validation, showing an AUC of 0.681.  $p < 0.001$ .**

**Discussion**

Using a large well-described cohort of liver transplant recipients, we developed a model that could predict the presence of advanced fibrosis in patients with chronic hepatitis C. Moreover, our model was more accurate than the commonly used laboratory models of APRI and Fib-4. Even with the addition of serum bilirubin, our model was still more accurate than APRI and Fib-4 scores.

Noninvasive assessments of fibrosis in patients with HCV are becoming increasingly utilized in clinical practice. Historically, liver biopsies have held an important role in the management of patients with HCV. Liver biopsies are important to determine not only the severity of fibrosis but also to assess for concomitant liver conditions and to estimate prognosis.<sup>22</sup> In addition, liver biopsies were believed to be an important tool to identify candidates for interferon-based therapies. Patients with mild liver damage were often recommended not to initiate noninterferon based therapy, whereas the benefits were believed to outweigh the risks in patients with more advanced liver disease. Given the substantially improved efficacy, tolerability, and safety of all oral DAAs against HCV, there is increasing enthusiasm regarding avoidance of the potential complications of a percutaneous liver biopsy altogether. It is important to continue to assess the degree of fibrosis even with DAAs because patients with cirrhosis who are cured remained at risk for developing hepatocellular carcinoma and, thus, require continual screening.<sup>23</sup> Furthermore, prioritization for antiviral therapy depends on fibrosis staging.<sup>13</sup>

The results of our study demonstrate that noninvasive lab tests are promising and can be useful tools for the detection of advanced fibrosis in liver transplant recipients with HCV. Lower platelet count and ALT values and higher total bilirubin and Fib-4 scores were associated with advanced fibrosis. Platelet count and total bilirubin have been well correlated with severity of liver fibrosis. Thrombocytopenia can predict the presence of portal hypertension, and increasing bilirubin is associated with liver-related mortality.<sup>24,25</sup> Of the two commonly used laboratory models of advanced fibrosis, the Fib-4 performed better than the APRI. A potential explanation for the decreased accuracy of the APRI is its reliance on AST. Indeed, AST was not significantly associated with advanced fibrosis in our analysis.

Of all the laboratory models used to predict fibrosis and advanced liver disease, APRI has been shown to be among the most accurate.<sup>15</sup> In liver transplant recipients, the APRI has also been found to predict the presence of advanced fibrosis. In fact, its performance was comparable to transient elastography.<sup>17</sup> However, the AUC for APRI in predicting advanced fibrosis was 0.55, lower than that reported in a recent systematic review.<sup>17</sup> Reasons for this discrepancy could be the use of a small cohort and inclusion of heterogeneous causes of liver disease.<sup>17,18</sup> Our study cohort consisted of over 400 transplant recipients. Moreover, we focused exclusively on the presence of advanced fibrosis (F3-F4). Our model appears to be more predictive of advanced fibrosis than APRI and Fib-4 and even enhanced APRI/Fib 4 with bilirubin.

Our novel predictive model differed slightly between males and females. This is consistent with prior predictive models of fibrosis.<sup>19</sup> This potential difference between genders has been highlighted in multiple studies.<sup>26-28</sup> Differences in fibrosis rates were also noted in a recent systematic review by Thein *et al*.<sup>29</sup> A number of theories have been developed to explain gender discrepancy in fibrosis progression, including protective influence of female hormones.<sup>30,31</sup>

We decided in this model to focus on patients transplanted for HCV. Indeed, HCV is the most common indication for liver transplantation.<sup>32</sup> Another hepatotropic virus that is an important indication for liver transplantation is hepatitis B. However, unlike HCV, survival for patients transplanted for HBV is among the highest of all indications for liver transplantation.<sup>32</sup> The post-transplant management differs between these two viral infections. Whereas the goal of HCV is to treat recurrent infection or disease, the goal of HBV is to prevent reinfection.<sup>33-35</sup>

Our study has a number of important limitations. First, it was a single center retrospective analysis. We were not able to

**Table 3. Comparison of prediction models for advanced liver disease due to hepatitis C (F3-F4)<sup>1</sup>**

	Optimal threshold	Sensitivity	Specificity	AUC
APRI	0.61	0.92	0.21	0.55
Fib 4	4.63	0.63	0.59	0.63
TB + APRI <sup>2</sup>	-2.51	0.66	0.53	0.60
TB + Fib 4 <sup>3</sup>	-2.52	0.73	0.52	0.64
Our New Formula	-3.04	0.68	0.57	0.68

<sup>1</sup> Thresholds were selected to optimize Youden's J (= sensitivity + specificity - 1)

<sup>2</sup> TB + APRI formula:  $-3.03 + 0.70 * \ln(1+TB) - 0.02 * \ln(1+APRI)$

<sup>3</sup> TB + Fib 4 formula:  $-4.00 + 0.49 * \ln(1+TB) + 0.64 * \ln(1+Fib\ 4)$

Abbreviations: APRI, AST to Platelet Ratio Index; Fib-4, fibrosis 4; TB, total bilirubin.



consider other comorbidities such as fatty liver or medications that could affect the lab parameters. Second, we did not rely on protocol biopsies at our institution, so most of the liver biopsies were performed to evaluate elevated liver enzymes. A third limitation is that laboratory values were missing in almost half of all the patients who had a liver biopsy. This was a result of the evolution of the electronic medical record, where a substantial amount of data has been lost, particularly among patients not followed on a regular basis. Nevertheless, it is the largest cohort for whom the accuracy of noninvasive assessments of advanced fibrosis has been performed. Furthermore, we did not assess for dynamic changes in liver fibrosis by evaluating serial liver biopsies. Incremental changes in fibrosis may identify recipients requiring close follow-up and urgent need for antiviral therapy.

## Conclusions

These findings deepen our understanding of the potential for noninvasive blood tests to help diagnose significant fibrosis and may help discriminate patients who can avoid unnecessary liver biopsies. Further studies are needed to validate these results using our proposed model and to optimize a useful scoring system after liver transplantation for HCV and other etiologies of liver failure.

## Acknowledgments

The authors thank Elena G Saab for manuscript assistance.

## Conflict of interest

None

## Author contributions

Study concept and design (VS, SS), acquisition of data (VS, HN, MJ, VA), analysis and interpretation of data (VS, SV, DE, RWB, SS), drafting of the manuscript (VS, HN, SS), critical revision of the manuscript for important intellectual content (VS, HN, SV, DE, SS), statistical analysis (VS, HN, SS, SV, DE), obtained funding (not applicable), administrative, technical, or material support, study supervision (DE, RWB, SS).

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Sheen V. *et al*: Blood tests predict significant fibrosis

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