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The Association of Abnormal Liver Tests with Hepatitis C Testing in Primary Care

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Abstract

Background: As hepatitis C virus birth cohort (1945–1965) screening in primary care improves, testing patterns in response to persistently abnormal liver tests are less well known.

Methods: This retrospective cohort study of a patient-centered medical home between 2007 and 2016 evaluates the association of abnormal liver chemistries and other clinical and demographic factors with Hepatitis C antibody (HCV Ab) testing in patients with persistently abnormal liver tests. Patients with at least 2 consecutive abnormal liver tests were categorized by the clinical pattern of liver chemistry abnormality, including cholestatic, hepatocellular, and mixed patterns. The primary outcomes were: (1) completed HCV Ab tests; and (2) positive HCV Ab results for those patients tested.

Results: Of 4,512 patients with consecutive abnormal liver tests, only 730 (16%) underwent HCV Ab testing within 1 year of the second abnormality; 81/730 (11%) had HCV Ab detected. A logistic regression model revealed that mixed (OR, 2.20; 95% CI, 1.72–2.82) and hepatocellular (OR, 1.43; 95% CI, 1.15–1.79) patterns of liver test abnormality, female gender, alcohol and tobacco abuse were associated with higher odds of HCV Ab testing. Hepatocellular (OR, 7.51; 95% CI 2.18, 25.94) and mixed patterns (OR, 5.88; 95% CI, 1.64–21.15) of liver test abnormalities, male gender, Medicaid enrollment, and drug and tobacco abuse had higher odds of positive HCV Ab results.

Conclusions: There is opportunity to improve Hepatitis C diagnostic testing in patients with consecutively elevated liver tests, and hepatocellular and mixed patterns of abnormality should prompt primary care providers to action.

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Presentations

This data was presented by Andrew Schreiner as an oral presentation titled “The Association of Abnormal Liver Tests with Hepatitis C Testing in Primary Care” at the Southern Society of Clinical Investigation – Southern Regional Meeting in New Orleans, LA on February 23, 2019.

Keywords

diagnosis; HCV; PCMH; aspartate aminotransferase; alanine aminotransferase

Introduction

Hepatitis C virus infection is associated with significant burdens of morbidity and mortality, with 2.4–3.5 million Americans chronically infected and approximately 19,000 HCV-related deaths per year.^{1–4} Chronic Hepatitis C is a leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation with total costs possibly exceeding \$10 billion in the U.S.^{5–7} With the advent and dissemination of new oral, direct-acting antiviral therapy, clinicians can effectively treat the infection, reducing morbidity and mortality in patients with and without advanced liver disease.^{8,9} The complications of long-standing, untreated infection coupled with the availability and efficacy of new anti-viral agents make the study and improvement of Hepatitis C diagnosis a healthcare imperative.

Since more than half of the patients living with Hepatitis C in the U.S. are unaware of their HCV-positive status, accurate HCV diagnosis presents an enormous opportunity to improve the care of chronically infected patients.¹⁰ In 2012, the Centers for Disease Control (CDC) recommended a 1-time Hepatitis C antibody (HCV Ab) test for all patients born between 1945 and 1965.^{11,12} This resulted in measurable increases in birth cohort Hepatitis C virus screening, but opportunities for continued improvement are vast.^{13–16} Prior to 2012, Hepatitis C testing was recommended in patients with signs of late stage liver disease, or with known risk factors for infection, including injection drug use, high risk sexual practices, and a history of blood transfusion. These testing strategies relied upon late-stage presentations and patient histories, resulting in delayed and missed diagnoses.^{10,11,17}

Abnormal liver tests, including serum bilirubin, aminotransferases, and alkaline phosphatase, affect up to 30% of primary care patients.^{18–21} These abnormalities can serve as early signals of liver disease, and past CDC guidelines (1998), identified a positive association between elevations in alanine aminotransferase (ALT) and HCV infection.^{1,22–28} Despite this association, Hepatitis C testing in response to liver test abnormalities has been suboptimal.^{26,27}

We hypothesized that demographic and clinical factors, with emphasis on clinical patterns of liver test abnormality, are associated with HCV Ab testing in primary care patients with consecutively abnormal liver tests. Further, we aimed to identify variables associated with positive Ab results in those patients with Hepatitis C testing.

Methods

We conducted a retrospective cohort study of electronic health record data from a patient-centered medical home. Patients with abnormal liver tests on two consecutive occasions were evaluated for the outcomes of completing an HCV Ab test, and possessing a positive result. We chose two consecutive abnormal tests to reflect a persistent abnormality identified on repeat testing as suggested by multiple abnormal liver test practice guidelines.^{20,29}

Patterns of liver test abnormality and different demographic and clinical variables were evaluated for their association with the outcomes using multivariable logistic regression models. This study was approved by the Institutional Review Board at the Medical University of South Carolina (MUSC).

Study Population

All patients seen in the Internal Medicine patient-centered medical home at MUSC between January 1, 2007 and September 30, 2015 were evaluated. The practice delivers care to a diverse (49.1% non-white) adult (mean age 58.6 years) population with chronic and complex medical problems. The clinicians providing care included more than 25 faculty physicians, more than 200 resident physicians in training, and 6 advanced practice providers. These care providers conduct approximately 38,000 patient visits yearly. Key patient-level information relevant to this study included demographics, lab tests, International Classification of Diseases (ICD)-9 or -10 codes, vital signs, and Medicaid enrollment status. Patient variables incorporate data from January 1, 2007 to September 30, 2016, allowing one year following cohort inclusion.

We constructed a sample of patients with two consecutive abnormal liver tests recorded within 3 years from each other. Due to small numbers within groups, the only racial categories included in this sample were Black and White. Each patient only contributed once to the sample, and the first 2 consecutive abnormal liver tests were analyzed. Abnormal liver tests included any one (or more) of the following: total bilirubin (Bili) > 1.2 mg/dL, aspartate aminotransferase (AST) > 34 U/L, alanine aminotransferase (ALT) > 45 U/L, or alkaline phosphatase (ALP) > 150 IU/L. Using the second of the 2 consecutive abnormal results, patients were categorized into three clinical patterns of liver test abnormality: cholestatic, hepatocellular, and mixed. The cholestatic category included patients with isolated abnormalities in Bili, ALP, or both.²² The hepatocellular pattern was defined as having isolated abnormalities in AST, ALT, or both.²² Mixed patterns were defined as those panels of abnormal liver tests with all other combinations of abnormality, including elevations in all 4 tests.

Patients with diagnoses of Hepatitis C or liver cancer, identified by a positive HCV Ab assessment, positive HCV RNA, or ICD 9/10 codes, prior to the second abnormal liver test were excluded. Patients with HCV RNA testing prior to the second abnormal liver test or HCV Ab assessment were also excluded, given that such direct assessment may indicate previously known HCV infection, an evaluation of response to therapy, or suspicion of acute hepatitis.

Outcome

The primary binary outcomes of interest were: (1) the status of obtaining an HCV Ab test within 365 days of the second abnormal liver test; (2) a positive HCV Ab result for those patients with HCV Ab testing. HCV Ab test results came from all ambulatory settings, including specialty care.

Primary Independent Variable

The clinical pattern of liver test abnormality (cholestatic, hepatocellular, or mixed) was the primary independent variable to analyze the relationship between HCV Ab testing and persistently abnormal liver tests.

Other Independent Variables

Gender and race were coded dichotomously as Male / Female and Black / White, respectively. Age was coded by birth cohort, given the CDC recommendations, and patients belonged to one of three cohorts: born before 1945 (DOB < 1945), born from 1945–1965, or born after 1965. Medicaid enrollment was a proxy for socioeconomic status, and distance from the patient's residence to clinic (in miles) incorporated potential transportation barriers into our models. The distance, calculated by determining the distance in miles between the center of the patient's zip code and the medical campus, was a categorical variable coded as: distance less than 5 miles (<5), 5 distance < 10 miles, 10 distance 30 miles, or distance 30 miles.

Clinical variables of interest included indicators of metabolic syndrome (body mass index [BMI] and hemoglobin A1c) and other viral infections (HIV). BMI was obtained from the electronic dataset and calculated using the height and weight (kg / cm^2) measured just prior to the second abnormal liver test. Patients were categorized as either having a BMI > 30 kg/cm^2 or BMI $\leq 30 \text{ kg}/\text{cm}^2$. Hemoglobin A1c values just prior to the second abnormality were used for categorization: either A1c < 7% or A1c $\geq 7\%$. HIV infection was determined by either evidence of a positive HIV Ab (1 or 2) or HIV viral load during the study period, and coded dichotomously.

Comorbidity and exposure variables included alcohol and drug abuse as identified by ICD-9/10 codes, given their relationships with abnormal liver tests and HCV.^{24,30} Tobacco use was coded dichotomously as those ever reporting tobacco use, and those who never did. This data came from a structured historical field in the Electronic record. Hypertension and hyperlipidemia were chosen given their relationship to metabolic syndrome and non-alcoholic fatty liver disease, potential causes of abnormal liver tests whose presence may relate to the pursuit of diagnostic testing with HCV Abs. Comorbidities were identified by ICD-9/10 codes using an Elixhauser comorbidity coding algorithm, and were dichotomous variables.³¹ The ICD-9/10 codes used for drug and alcohol abuse are available in the Supplement.

To evaluate the potential association between the CDC's birth cohort recommendation and HCV testing in patients with abnormal liver tests, we created a variable Year = 2014 (allowing a 1+ year clinical practice translation after issue in 2012). This variable is dichotomous for the result of the second of 2 consecutive abnormal liver tests occurring before or after January 1, 2014.

Data Sources

All data come from Medical University Hospital Authority Enterprise and EPIC© (EPIC Systems Corporation, WI) Clarity databases. Clinical, laboratory, and demographic data

obtained in the ambulatory, emergency room, and inpatient settings at MUSC during the study period. Laboratory testing ICD-9/10 coding reside within the electronic record in a consistently structured format.

Analysis

All patients were characterized by the clinical pattern of their second of 2 consecutive abnormal liver tests: cholestatic, hepatocellular, or mixed. Follow-up in the analysis extended from the time of cohort inclusion to either the outcome of interest (HCV testing), 365 days following the second abnormal liver test, or the end of the study period (September 30, 2016). This conclusion of the study period allowed for at least 1 year for HCV Ab testing in patients with a second abnormal liver test by September 30, 2015.

Univariate analysis of independent, categorical variables was performed using Fisher's exact test. A multivariable logistic regression model for the dependent variable of an HCV Ab result was developed. A subsequent analysis was performed using a multivariable logistic regression model for the outcome of a positive HCV Ab test, conditional to the patient having had been tested. Variables in the models were tested for multicollinearity.

To understand the association between the CDC guidelines and HCV testing in patients with abnormal liver tests, proportions of patients receiving HCV testing were compared by birth cohort, and by relationship to the recommendation's issue.

SAS version 9.3 (Cary, NC) was used for the statistical analysis.

Results

Overall, 4,512 unique patients met inclusion criteria (Figure 1). Of these, 1,046 (23%) possessed a cholestatic pattern, 2,549 (57%) a hepatocellular pattern, and 917 (20%) had mixed liver test abnormalities (Table 1). Only 730 (16%) patients had an HCV Ab test result within one year of the second abnormality. The median time to HCV Ab testing was 24 days following the second liver test (Inter-quartile range: 0–140 days). In patients with cholestatic patterns, 122 (12%) obtained HCV Ab testing, compared to 399 (16%) patients with hepatocellular patterns, and 209 (23%) patients with mixed liver test abnormalities (Table 1, $p < 0.01$). Liver test patterns for each birth cohort are available in the Supplement.

Of those patients tested, 81 (11%) had positive HCV Ab results. Patients with hepatocellular and mixed liver test abnormalities had higher proportions of positive tests (14% and 12%, respectively), compared to patients with cholestatic patterns (3%) (Table 1, $p < 0.01$).

The multivariable logistic regression model for the outcome of HCV Ab testing demonstrated mixed (OR, 2.20 [CI, 1.72–2.82]) and hepatocellular patterns (OR, 1.43 [CI, 1.15–1.79]) were associated with higher odds of HCV Ab testing than cholestatic abnormalities (Table 2). Patients with comorbidities of alcohol abuse (OR, 1.51 [CI, 1.09–2.08]) and tobacco use (OR, 1.39 [CI, 1.04–1.86]) were associated with higher odds of HCV Ab testing, while male gender was associated with lower odds (OR, 0.79 [CI, 0.67–0.93]).

Patients born before 1945 had lower odds of HCV Ab testing (OR 0.42 [CI, 0.33–0.53]) compared to the 1945–1965 birth cohort. Figure 2 shows the proportion of patients with HCV testing by birth cohort during 2-year time periods both before (2011–2012) and after (2014–2015) the CDC screening guideline. The proportion of patients obtaining HCV Ab testing increased in all three birth cohorts. The similarity of this trend across groups suggests no association of the 2012 CDC recommendation with HCV screening rates among the birth cohort population with abnormal liver tests.

In the multivariable logistic regression analysis of patients with HCV Ab testing, both hepatocellular (OR, 7.51 [CI, 2.18–25.94]) and mixed patterns (OR, 5.88, [CI, 1.64–21.15]) of liver test abnormalities were associated with significantly higher odds of positive HCV Ab test results (Table 2). Male gender, Medicaid enrollment, and drug abuse were all associated with higher odds of HCV Ab positivity. Patients born after 1965 (OR, 0.15 [CI, 0.07–0.32]) had lower odds of positive tests than the CDC's target cohort (1945–1965).

Patients with positive HCV Ab tests obtained confirmatory HCV RNA testing in 57 of 81 cases during the study period (Table 3). In those with RNA testing, 79% (45/57) had confirmed HCV infection. In the 24 patients with HCV RNA testing and negative HCV Ab results, none had RNA detected.

Discussion

In this study, few patients (16%) with persistently abnormal liver tests underwent HCV antibody testing and only 57 of 81 (70.4%) HCV Ab positive patients obtained confirmatory RNA testing. Of those patients with HCV Ab tests, 11% received positive results, surpassing the 3.25% prevalence threshold for cost-effective HCV Ab testing established by the CDC.^{11,32} Future quality improvement efforts will need to address testing in birth cohort patients, testing in those with consecutive liver test abnormalities, and HCV RNA testing in patients who are HCV Ab positive.

Since 2012, primary care efforts have focused on HCV Ab testing for patients in the high risk birth cohort (1945–1965). Previous work demonstrates improvement in this screening, but recent studies also indicate that a large proportion of the cohort remains untested.^{11,13–16} In our study, patients born after the screening cohort were less likely to have positive HCV tests, and those patients older than the birth cohort had lower odds of getting HCV testing (Table 2). The regression models were also run with age as a continuous variable, and there was no change in significance with the other predictor variables, and no appreciable change occurred in the OR point estimates for the significant predictors. As shown in Figure 2, the proportion of patients receiving HCV testing increased across all 3 studied birth cohorts following the recommendation. The parallel increase across the three age groups suggests no association between the recommendation and targeted birth cohort testing among patients with abnormal liver tests. More importantly, this figure highlights a need to increase birth cohort screening.

In addition to birth cohort, abnormal liver tests serve as another signal of possible HCV infection. Previous work and CDC recommendations) identified a positive association of

hepatocellular patterns of injury, and particularly elevations in ALT, with chronic HCV infection.^{1,25,33–35} In this study, hepatocellular and mixed patterns of liver test abnormality were associated with higher odds of HCV testing, and significantly higher odds of positive HCV Ab results. Though these odds ratios are significant, they have moderately wide confidence intervals likely related to the few positive HCV results in the reference group. These findings coincide with recent work in the U.K. where investigators considered elevated ALT (at least twice the upper limit of normal) as an indication for general practitioners to consider HCV testing.^{34,35} As the incidence of Hepatitis C climbs among young people (born after 1965), clinicians need guidance on effective testing strategies beyond birth cohort inclusion.³⁶ Hepatocellular liver test abnormalities provide a meaningful clinical cue to pursue testing and warrant emphasis in future primary care practice guidelines.

We recognize limitations of this study. Providers may directly pursue HCV RNA rather than Ab testing in patients with symptoms and an elevated liver test. We attempted to control for this by excluding those patients with HCV RNA results prior to the outcome of interest, but situations exist where Ab serology is not the preferred strategy for testing (i.e. severe immuno-compromise or end stage renal disease). Additionally, this work limits an appreciation for patients undergoing HCV Ab assessment after 1 liver test abnormality, or those patients ultimately getting HCV testing, but unable to do so within 1 year of the second liver chemistry abnormality. In fact, nearly 25% of the HCV testing included in the study came from tests conducted on the same day as the second abnormal liver test. We wanted to understand the association between consecutive liver test abnormalities and HCV testing as a response, and felt the inclusion criteria allowed for greater focus on the potential role of consecutive liver test abnormalities in HCV testing. In those tests done the same day as the second abnormality, it is difficult to discern if these tests were added upon knowing the second result or in response to the initial liver test abnormality. Also, the outcome of interest in this study is the result of HCV Ab testing, which reflects not only a provider's order, but patient and health system factors that may play a role in a patient's ability to complete the test. Further, comorbidity data relies on accurate coding of sensitive patient historical information, which may be incomplete, limiting observed relationships between these predictors and outcomes. Further, as this is a study of administrative data within a single center, results from any testing outside of the health system and electronic health record are largely unavailable. Knowledge of such studies may certainly influence future testing patterns. However, because our cohort is a primary care based population, there is a higher likelihood that the included patients obtain the majority of their care within this system than might occur in a specialty care setting.

Conclusion

Opportunities exist to improve HCV diagnosis in patients with abnormal liver tests. More of these patients merit HCV testing, and persistently abnormal liver tests, particularly with hepatocellular patterns of abnormality and in conjunction with other demographic and clinical variables, may serve as clinically meaningful signals prompting primary care providers to test for HCV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical significance:

1. Of 4,512 patients with consecutively abnormal liver tests, only 16% had follow-up Hepatitis C antibody testing within 1 year of the second liver test abnormality.
2. Hepatocellular and mixed liver tests, Medicaid enrollment, male gender, and drug abuse were associated with higher odds of a positive Hepatitis C antibody test result.
3. More patients with persistent hepatocellular and mixed liver test abnormalities should receive Hepatitis C testing.

Figure 1:

Consort diagram of patients included in the analysis. Pts=patients; HCV Ab = Hepatitis C virus antibody; yr=year.

Figure 2:
Proportions of patients undergoing HCV antibody testing by birth cohort, before (2011–12) and after (2014–15) the CDC screening recommendation.

Table 1.

Mean Statistics (Proportion) of Patients

<i>Sample</i>	Patients with two consecutive abnormal liver tests (n=4,512)				Patients undergoing HCV antibody testing (n=730)			
Pattern of abnormal tests	Cholestatic	HC	Mixed	P-value	Cholestatic	HC	Mixed	P-value
Sample size	1,046	2,549	917		122	399	209	
<i>(Outcomes)</i>								
Undergoing HCV antibody testing ¹	11.7%	15.7%	22.8%	<0.01				
Tested positive ²					2.5%	13.5%	11.5%	<0.01
<i>(Other Covariates)</i>								
Male	48.0%	47.4%	48.2%	0.89	47.5%	40.9%	46.9%	0.23
Black	54.8%	46.8%	59.2%	<0.01	69.7%	50.1%	56.0%	<0.01
Birth cohort				<0.01				0.19
DOB < 1945	29.5%	27.1%	26.1%		9.0%	16.0%	13.9%	
1945 DOB 1965	44.1%	51.0%	42.6%		54.1%	54.9%	51.2%	
DOB >1965	26.5%	21.9%	31.3%		36.9%	29.1%	34.9%	
Hypertension	31.2%	29.9%	31.8%	0.47	40.2%	30.8%	34.5%	0.15
Hyperlipidemia	18.2%	19.1%	18.7%	0.78	23.0%	17.8%	19.6%	0.44
BMI>30	34.5%	42.0%	34.7%	<0.01	36.9%	42.1%	27.8%	<0.01
A1C>=7	16.0%	13.1%	13.6%	0.07	18.9%	14.0%	13.4%	0.35
Alcohol abuse	4.1%	5.9%	7.6%	<0.01	7.4%	8.3%	12.9%	0.12
Drug abuse	3.5%	5.2%	3.4%	0.02	8.2%	7.3%	5.7%	0.66
Tobacco use ever	8.4%	9.7%	8.6%	0.39	13.9%	13.0%	12.9%	0.96
HIV positive	2.1%	1.7%	2.0%	0.73	3.3%	3.5%	1.9%	0.54
Medicaid enrollment Status	12.3%	10.3%	15.3%	<0.01	19.7%	13.5%	15.8%	0.25
Distance (miles) from clinic				<0.01				0.20
Distance < 5	29.0%	30.6%	26.6%		27.9%	26.6%	25.4%	
5 Distance < 10	29.1%	23.9%	24.3%		27.9%	25.1%	23.9%	
10 Distance < 30	28.2%	32.9%	30.0%		26.2%	34.3%	28.7%	
Distance 30	13.8%	12.6%	19.1%		18.0%	14.0%	22.0%	
Year>=2014	16.9%	15.0%	14.0%	0.17	25.4%	18.8%	16.8%	0.15

¹Status of follow-up HCV Ab tests within 365 days²Status of follow-up positive tests

Table 2.

Estimated Odds Ratios (OR) from Multivariable Logistic Regression

Sample		Patients with two consecutive abnormal liver tests (n=4,512)				Patients undergoing HCV antibody testing (n=730)			
Dependent variables		Undergoing HCV antibody testing ¹				Tested positive ²			
Outcomes		730				81			
		OR	95% CI	P-value		OR	95% CI	P-value	
Pattern									
Cholestatic (reference)									
	Hepatocellular	1.43	1.15	1.79	<0.01	7.51	2.18	25.94	<0.01
	Mixed	2.20	1.72	2.82	<.001	5.88	1.64	21.15	<0.01
Black		1.07	0.90	1.27	0.42	1.22	0.72	2.07	0.46
Male		0.79	0.67	0.93	<0.01	1.89	1.12	3.18	0.02
Birth cohort									
	DOB < 1945	0.42	0.33	0.53	<.001	0.43	0.18	1.02	0.05
	1945 DOB 1965 (reference)								
	DOB >1965	1.14	0.94	1.38	0.19	0.15	0.07	0.32	<.0001
Hypertension		1.10	0.88	1.37	0.39	0.82	0.40	1.66	0.58
Hyperlipidemia		0.96	0.75	1.24	0.76	0.28	0.11	0.71	<0.01
BMI>30		0.85	0.72	1.01	0.07	0.74	0.42	1.32	0.31
A1C>=7		1.18	0.93	1.50	0.17	1.47	0.68	3.17	0.33
Alcohol abuse		1.51	1.09	2.08	0.01	1.10	0.46	2.59	0.83
Drug abuse		1.22	0.85	1.75	0.29	2.61	1.08	6.30	0.03
Tobacco use ever		1.39	1.04	1.86	0.03	1.89	0.81	4.39	0.14
HIV positive		1.59	0.96	2.64	0.07	0.37	0.04	3.06	0.35
Medicaid enrollment Status		0.97	0.76	1.24	0.79	2.96	1.52	5.77	<0.01
Distance (miles) from clinic									
Distance < 5 (reference)									
	5 Distance < 10	1.06	0.84	1.32	0.63	0.80	0.40	1.62	0.54
	10 Distance < 30	1.03	0.83	1.28	0.78	0.82	0.42	1.60	0.56
	Distance 30	1.21	0.93	1.56	0.16	1.31	0.60	2.85	0.50
Year>=2014		1.16	0.92	1.47	0.21	0.84	0.38	1.89	0.68

¹Status of follow-up HCV Ab tests within 365 days²Status of follow-up positive tests

Table 3:

HCV RNA Test Results for the 730 Patients with HCV Ab Testing

		HCV RNA Test Result			Total
		+	–	NA	
HCV Ab Test Result	+	45	12	24	81
	–	0	24	625	649
Total		45	36	649	730