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Hepatitis C Testing and Liver Fibrosis Predictors in the Birth Cohort of a Primary Care Practice

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Abstract

Objective: To determine the prevalence of and risk factors for advanced fibrosis in patients born from 1945 through 1965 (birth cohort) who underwent testing for hepatitis C virus (HCV).

Patients and Methods: Data were extracted from the electronic health record of all patients receiving primary care at a single academic institution who underwent HCV testing between September 8, 2010, and March 5, 2018. The birth cohort patients were the primary focus of the study. Fibrosis 4 (FIB-4) and aspartate aminotransferase to platelet ratio index (APRI) scores were calculated to screen for fibrosis.

Results: During the study period, 7097 birth cohort patients had HCV antibody testing, 3462 (48.8%) of whom were men, 6435 (91.0%) were white, 1028 (14.5%) had diabetes mellitus, 2,034 (36.5%) had an alanine aminotransferase (ALT) level greater than 30 U/L, and 2,396 (34.2%) had body mass index of 30 kg/m^2 or greater. Hepatitis C virus antibody was present in 124 (1.7%), 33 (26.6%) of whom had HCV viremia. Estimated prevalence of METAVIR [Meta-analysis of Histological Data in Viral Hepatitis] stage 4 fibrosis was 4.1% (180 of 4433) by a FIB-4 score of 3.25 or greater and 4.3% (204 of 4763) by an APRI score greater than 1.0. The odds ratio (OR) for fibrosis, determined by APRI, was significant for HCV RNA positivity (OR, 15.98; 95% CI, 7.23-35.32; $P<.001$), diabetes mellitus (OR, 1.98; 95% CI, 1.40-2.79; $P<.001$), and ALT value greater than 30 U/L (OR, 15.07 U/L; 95% CI, 9.27-24.52 U/L; $P<.001$) but not for body mass index of 30 kg/m^2 or greater (OR, 0.77; 95% CI, 0.56-1.06; $P=.11$).

Conclusion: Hepatitis C virus viremia, diabetes mellitus, and elevated ALT levels were associated with increased odds for development of fibrosis. In addition to HCV testing, diabetes mellitus and elevated ALT level are potential parameters to use for recommending noninvasive testing for fibrosis.

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Hepatitis C virus (HCV) infection has been a major public health burden in the United States.[1] The National Health and Nutrition Examination Survey, using data from 2003 through 2010, estimated that at least 4.6 million persons had been infected with HCV and at least 3.5 million persons were actively infected.[2] Patients in the birth cohort, born between 1945 and 1965, have been a major subgroup of this population. They have had a proportionately high prevalence of HCV infections, the majority of which were undiagnosed, and a high risk for development of cirrhosis and complications from end-stage liver disease because of the duration of disease.[3] In August 2012, the Centers for Disease Control and Prevention (CDC) recommended universal one-time HCV testing for persons in the 1945 through 1965 birth cohort.[4] The United States Preventive Services Task Force (USPSTF) adopted the guideline in June 2013.[5] The availability of well-tolerated, highly effective antiviral medications has made identification of HCV in a population at risk even more important.[6] However, little data are available regarding the overall risk for advanced fibrosis in this cohort and available parameters that could guide more targeted screening for both HCV and advanced fibrosis. The USPSTF has recently expanded recommendations for one-time testing to all adults aged 18 to 79 years without liver disease.[6]

We used our electronic health record (EHR) system to identify all patients who

underwent HCV testing before and after the CDC/USPSTF recommendations. Our aim was to determine the prevalence of advanced fibrosis in birth cohort patients tested for HCV and to identify risk factors for fibrosis that could potentially allow for more directed screening in this patient population. Our population was from an academic primary care practice with a low percentage of government-insured or uninsured patients, which is unique from most previously reported data.

PATIENTS AND METHODS

This retrospective study was approved as a minimal risk protocol by the Mayo Clinic Institutional Review Board, and patient informed consent was waived. Data were extracted from the EHR for all patients receiving primary care at a single academic institution who underwent HCV testing between September 8, 2010, and March 5, 2018. This academic institution is a multispecialty urban practice. The primary care practice comprises a group of family practice, women's health, and general internal medicine health care professionals and includes advanced practice professionals and internal medicine residents. At the time of the study, we had 99 primary care practitioners caring for 47,336 patients. Patients assigned to a primary care practitioner were either self-referred or referred by specialists from the institution.

The EHRs were created from patient real-time data reports. Demographic data extracted were birth date, sex, race/ethnicity, and insurance status. Clinical data retrieved included body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), presence of diabetes mellitus, hypertension, date/age at HCV testing, antibody testing result for HCV, HCV RNA detection by quantitative polymerase chain reaction, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count. Laboratory test results were obtained within 6 months of HCV testing. If more than one HCV laboratory test was performed, only data from the initial test were collected.

In the birth cohort, fibrosis 4 (FIB-4)[7] and AST to platelet ratio index (APRI)[8] scores were calculated to assess for the presence of fibrosis. FIB-4 and APRI scores were first used as

surrogate markers of liver fibrosis in patients with chronic hepatitis C or HIV infections, or both.[9,10] For FIB-4, we used cutoffs of 1.45 and 3.25 to assess for cirrhosis, as defined by an Ishak fibrosis score of 4 to 6 vs 0 to 3. As described by Sterling et al,[9] a cutoff of less than 1.45 has a negative predictive value for cirrhosis of 90% (sensitivity, 70%), and a cutoff of greater than 3.25 has a positive predictive value for cirrhosis of 65% (specificity, 97%). For APRI, we used cutoffs of 1.0 for Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) stage 4 (cirrhosis) (77% sensitivity, 75% specificity; area under the receiver operating characteristic curve, 0.84).[10] The APRI and FIB-4 were correlated to ALT, BMI, presence of diabetes mellitus, and positive HCV RNA testing results.

On October 30, 2017, a reminder message to screen for HCV was incorporated into the EHR. To determine whether the reminder made a difference in testing behavior, we also reviewed data for all hepatitis C tests performed in the birth and non—birth cohorts for 2018.

Demographic and clinical characteristics were summarized as number and percentage. The associations between HCV RNA positivity and ALT level (>30 U/L, 30-60 U/L, and >60 U/L [to convert values to μkat/L, multiply by 0.0167]) were tested using the Fisher exact test. The χ^2 test was used to explore the association between fibrosis and diabetes mellitus. The odds ratio (OR) of METAVIR stage 4 fibrosis, defined by an APRI of greater than 1.0, was determined by using multivariable logistic regression with HCV RNA positivity, ALT greater than 30 U/L, age at HCV test, presence of diabetes mellitus, BMI of 30 kg/m^2 or greater, sex, and race as independent variables. Data were analyzed using SAS Studio 3.7 (SAS Institute Inc). All tests were 2-sided, and $P<.05$ was set as the significance level.

RESULTS

During the study period, 7097 birth cohort patients were tested for HCV antibody (Supplemental Figure, available online at http://www.mcpiqojournal.org). Of these patients, 3462 (48.8%) were men, 6435 (90.7%) were white, and 6955 (98.0%) had insurance (commercial, 71%; government,
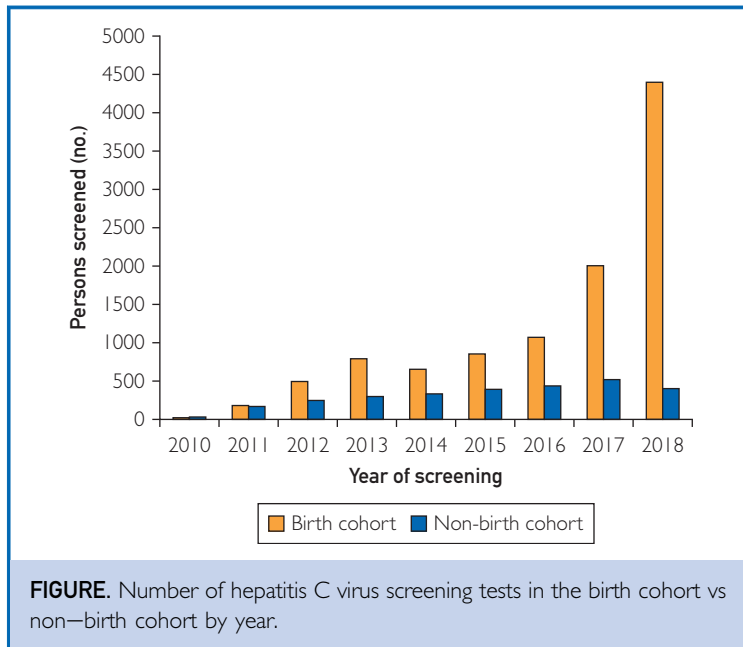
FIGURE. Number of hepatitis C virus screening tests in the birth cohort vs non—birth cohort by year.

27%. There were 1028 patients (14.5%) who had diabetes mellitus, and 2396 of 7005 (34.2%) had a BMI of 30 kg/m^2 or greater. From 2011 (the year before the CDC recommendations) to 2017, there was a marked increase in the number of patients tested (188 vs 2009). There was a more dramatic increase in testing after a reminder was added to the EHR to screen the birth cohort for HCV (Figure); 6876 of the 7097 patients (96.9%) were tested from 2012 to the end of the study. Of the patients tested, 124 (1.7%) had HCV antibody positivity, and of those, 33 (26.6%) had positive test results for HCV RNA.

Test results for ALT were available for 5578 patients: 30 U/L or less in 3544 (63.5%) patients, 31 to 60 U/L in 1499 (26.9%), and greater than 60 U/L in 535 (9.6%). The ALT level correlated with RNA positivity (Table 1). Of the 3544 patients with an ALT level of 30 U/L or less, only 4 (0.1%) had detectable HCV RNA. Three of these patients had risk factors for HCV documented in their EHR: 1 patient had a history of intravenous drug use, another was screened because of previous contact with a partner who used intravenous drugs, and the third was screened because the spouse had died of hepatitis C infection. There was

a strong correlation between AST and ALT (Pearson correlation coefficient, 0.89; $P<.001$).

The estimated prevalence of METAVIR stage 4 fibrosis was 4.1% (180 of 4433) by a FIB-4 score of 3.25 or greater and 4.3% (204 of 4763) by an APRI of greater than 1.0 for the entire birth cohort and 8.0% (58 of 729) (FIB-4) and 9.0% (69 of 765) (APRI) for patients with diabetes mellitus (Table 2).

There were increased odds for METAVIR stage 4 fibrosis based on APRI in patients with HCV viremia (OR, 15.98; 95% CI, 7.23-35.32; $P<.001$), diabetes mellitus (OR, 1.98; 95% CI, 1.40-2.79; $P<.001$), and ALT value greater than 30 U/L (OR, 15.07; 95% CI, 9.27-24.52; $P<.001$) but not for BMI of 30 kg/m^2 or greater (OR, 0.77; 95% CI, 0.56-1.06; $P=.11$) (Table 3). The FIB-4 score correlated with APRI (Pearson correlation coefficient, 0.77; $P<.001$).

Although patients with HCV viremia were predicted to have very high rates of METAVIR stage 4 fibrosis, those with HCV antibody without active HCV viremia had fibrosis rates similar to those of the overall birth cohort (Table 4).

DISCUSSION

This study analyzed a population of patients in a primary care academic center practice who were tested for HCV from 2010 to 2018. The study period was chosen to include time before and after the CDC recommendations for one-time HCV testing of the birth cohort. Over the study period, there was a marked increase in HCV testing performed in the birth cohort, which correlated with the recommendations. There was a further, more dramatic, increase after the addition of a prompt in the EHR to initiate testing. We could not determine the total population from which testing was derived, so the increased testing could have been due to an increase in the size of the practice, but given the magnitude of increase compared with that for patients not in the birth cohort, we hypothesize that most of the increase was due to change in the behavior of the practitioners. We used this cohort to evaluate the prevalence of HCV and advanced fibrosis in the birth cohort population and to determine if there were risk factors that could be used for targeted testing.

TABLE 1. Association Between HCV RNA Positivity and ALT[a,b]

HCV RNA+		ALT, No. (%)				
Status	Missing	≤30 U/L	31-60 U/L	>60 U/L	Total	P Value[c]
HCV RNA+	0	4 (0.1)	13 (0.9)	16 (3.0)	33	<.001
Not HCV RNA+	1519	3540 (99.9)	1486 (99.1)	519 (97.0)	5545	
Total		3544	1499	535	5578	

[a]ALT = alanine aminotransferase; HCV = hepatitis C virus; + = positive.
[b]SI conversion factor: To convert ALT values to μkat/L, multiply by 0.0167.
[c]Fisher exact test.

Hepatitis C virus exposure and HCV viremia in our birth cohort were less than expected: 1.7% had been exposed to HCV compared with 3.2% in the National Health and Nutrition Examination Survey group. In that group, non-Hispanic whites had the lowest prevalence of HCV exposure (2.8%).[4] Most of our patients were white and insured, which may have accounted for the lower exposure rate. In addition, only 26.6% of those with HCV antibody had HCV RNA−positive results compared with 78% of those described in US data,[4] far less than what could be accounted for by false-positive test results or spontaneous viral clearance. A recent community-based study utilizing data from 2015 to 2016 from previously untested persons in the birth cohort found a prevalence of HCV antibody of 3.8% with 59.8% viremia.[11] These results suggest that many patients in our population could have been treated previously for HCV, but the medical records had not been accurately updated. The prevalence of active HCV infection of the birth cohort patients tested was low (46.X%); however, the implications of viremia in this population was high, as 53.1% to 59.4% of patients with viremia were predicted to have METAVIR stage 4 fibrosis. In addition, the prevalence of HCV viremia was still above the threshold of 0.07% proposed by Eckman et al[12] as the prevalence of disease required for one-time screening to be cost effective for adults 18 years or older in the United States. Therefore, we determined it prudent to continue universal screening in our birth cohort population.

Patients tested for hepatitis C in the birth cohort at our center had an estimated prevalence of METAVIR stage 4 fibrosis of 4.1%

TABLE 2. Association Between Advanced Fibrosis and Diabetes Mellitus[a]

	Diabetes mellitus, No. (%)			
Variable	No	Yes	Total	P value[b]
FIB-4 ≥3.25				
Missing	2365	299		<.001
No	3582 (96.7)	671 (92.0)	4253 (95.9)	
Yes	122 (3.3)	58 (8.0)	180 (4.1)	
Total	3704	729	4433	
APRI >1.0				
Missing	2071	263		<.001
No	3863 (96.6)	696 (91.0)	4559 (95.7)	
Yes	135 (3.4)	69 (9.0)	204 (4.3)	
Total	3998	765	4763	

[a]APRI = aspartate aminotransferase to platelet ratio index; FIB-4 = fibrosis 4.
[b]χ^2 test.

TABLE 3. Multivariate Logistic Regression for APRI >1.0[a,b]

| Covariate | APRI >1.0 | | | |
	Level	Event (%)	Odds ratio (95% CI)	P value
Age at HCV screening	NA	NA	0.98 (0.95-1.00)	.08
Sex	Women	90/2297 (3.9)	0.89 (0.65-1.21)	.44
	Men	10/20296 (5.2)		
White	No	9/387 (2.3)	2.46 (1.20-5.05)	.01
	Yes	187/3939 (4.8)		
ALT >30 U/L	No	19/2702 (0.7)	15.07 (9.27-24.52)	<.001
	Yes	177/1624 (10.9)		
HCV RNA status	Negative	1774294 (4.1)	15.98 (7.23-35.32)	<.001
	Positive	19/32 (59.4)		
Diabetes mellitus	No	130/3611 (3.6)	1.98 (1.40-2.79)	<.001
	Yes	66/715 (9.2)		
BMI ≥30 kg/m²	No	1202820 (4.3)	0.77 (0.56-1.06)	.11
	Yes	76/1506 (5.1)		

[a]ALT = alanine aminotransferase; APRI = aspartate aminotransferase to platelet ratio index; BMI = body mass index; HCV = hepatitis C virus.
[b]SI conversion factor: To convert ALT value to μkat/L, multiply by 0.0167.

(by FIB-4 ≥3.25) and 4.3% (by APRI >1.0). Hepatitis C virus RNA viremia, diabetes mellitus, and ALT level were all strongly correlated with METAVIR stage 4 fibrosis. However, given that diabetes mellitus and ALT elevation were much more common, they represented more important risk factors for advanced fibrosis in this population.

Obesity (BMI ≥30 kg/m²) did not correlate as a predictor of fibrosis. Data from the Veterans Health Administration also revealed that steatosis without elevated liver enzyme levels or diabetes mellitus was not associated with worsening liver outcomes. Patients with hepatic steatosis and normal liver enzyme levels had a similar risk for development of cirrhosis and hepatocellular carcinoma as did the general population, whereas those with steatosis and abnormal ALT values had a higher risk.[13] Bertot et al[14] evaluated data from a multicenter

TABLE 4. Association Between Advanced Fibrosis and HCV RNA[a]

| Variable | HCV RNA, No. (%) | | | P value[b] |
	Negative	Positive	Total	
FIB-4 ≥3.25				<.001
Missing	2663	1		
No	4238 (96.3)	15 (46.9)	4253	
Yes	163 (3.7)	17 (53.1)	180	
Total	4401	32	4433	
APRI >1.0				<.001
Missing	2333	1		
No	4546 (96.1)	13 (40.6)	4559	
Yes	185 (3.9)	19 (59.4)	204	
Total	4731	32	4763	

[a]APRI = aspartate aminotransferase to platelet ratio index; FIB-4 = fibrosis 4; HCV = hepatitis C virus.
[b]χ² test.

international cohort of 299 patients with biopsy-proven nonalcoholic fatty liver disease and compensated cirrhosis. Of all the components of metabolic syndrome, only diabetes mellitus was associated with increased risk of death or liver transplant, hepatic decompensation, and worse overall survival.

Hepatitis C virus has been replaced as the most prevalent chronic liver disease in the United States by nonalcoholic fatty liver disease, which affects an estimated 75 to 100 million persons, or 30% to 40% of the adult population.[15] The increasing prevalence of nonalcoholic steatohepatitis (NASH) in the setting of the obesity and metabolic syndrome epidemic is beginning to have a substantial impact on the development of cirrhosis, complications of liver disease, and liver cancer. NASH is expected to continue to increase in prevalence and surpass HCV in all of these categories in the next decade. Without identification and effective treatment, NASH will create a tremendous economic burden[16] and make cirrhosis resulting from NASH the main indication for liver transplant.[17] Successful programs to screen for advanced fibrosis in those at risk are needed so that treatments and interventions can be initiated.

Our study has several limitations. It was retrospective, and evaluation of predictors for advanced liver disease were limited to the tested patients in the birth cohort; therefore, we had no clinical or diagnostic data to compare with the nontested birth cohort, and findings could not be compared between the birth and non—birth cohorts. In addition, we were unable to determine whether HCV testing was done as part of a screening test or as a diagnostic evaluation. The low percentage in our population of HCV RNA viremia in those with HCV antibodies, as compared with national data, suggested that many of the patients in our study had been treated before, but this information was not given to or recorded by the primary care practitioner. We do not believe that this issue affects our conclusion.

CONCLUSION

Hepatitis C virus viremia was a major risk factor for advanced fibrosis in the birth cohort population, and our data support the one-time universal screening in this population. METAVIR stage 4 fibrosis was predicted to be 4.1% to 4.3%; however, most of our cases were not due to HCV infection. On the basis of our data, we conclude that additional screening is needed for advanced fibrosis besides the recommendations for universal HCV screening of the birth cohort. Targeting risk factors for NASH, such as diabetes mellitus or elevated ALT levels, is a potential parameter to consider for utilizing noninvasive testing. Studies from other large primary care clinical practices are needed to confirm these findings.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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