Research Article

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Viral Hepatitis

Disparities in hepatitis C testing in U.S. veterans born 1945–1965

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Background & Aims: Universal one-time antibody testing for hepatitis C virus (HCV) infection has been recommended by the centers for disease control (CDC) and the United States preventative services task force (USPSTF) for Americans born 1945–1965 (birth cohort). Limited data exists addressing national HCV testing practices. We studied patterns and predictors of HCV testing across the U.S. within the birth cohort utilizing data from the national corporate data warehouse of the U.S. Veterans Administration (VA) health system.

Methods: Testing was defined as any HCV test including antibody, RNA or genotype performed during 2000–2013.

Results: Of 6,669,388 birth cohort veterans, 4,221,135 (63%) received care within the VA from 2000–2013 with two or more visits. Of this group, 2,139,935 (51%) had HCV testing with 8.1% HCV antibody and 5.4% RNA positive. Significant variation in testing was observed across centers (range: 7–83%). Older, male, African-Americans, with established risk factors and receiving care from urban centers of excellence were more likely to be tested. Among veterans free of other established risk factors (HIV negative, HBV negative, ALT $\leqslant$40 U/L, FIB-4 $\leqslant$1.45, or APRI <0.5), HCV antibody and RNA were positive in 2.8% and 0.9%, respectively, comparable to established national average. At least 2.4–4.4% of veterans had scores suggesting advanced fibrosis (APRI $\geqslant$1.5 or FIB-4 >3.25) with >30–43% having positive HCV RNA but >16–20% yet to undergo testing for HCV.

Conclusions: Significant disparities are observed in HCV testing within the United States VA health system. Examination of the predictors of testing and HCV positivity may help inform national screening policies.

Lay summary: Analysis of United States Veterans Administration data show significant disparities in hepatitis C virus testing of veterans born 1945–1965 (birth cohort). A fifth of those not tested had evidence of advanced liver fibrosis. Our data suggests some predictors for this disparity and will potentially help inform future policy measures in the era of universal birth cohort testing for HCV.

Introduction

Modern treatment of patients with chronic hepatitis C virus (HCV) infection has been transformed by the advent of highly effective, all-oral, interferon-free treatment regimens [1–6]. Chronic HCV infection is associated with substantial morbidity and mortality [7,8] and since 2007 has surpassed HIV as a cause of death in the United States (U.S.) per The National Center for Health Statistics [9]. Viral eradication, defined as a sustained virologic response (SVR) 12 weeks following completion of treatment, is attainable in over 90% of patients of nearly all sub-populations of patients with HCV infection, and associated with improved quality of life [10,11], stabilization of liver disease [12], and decreased mortality [7]. However, approximately half of all infected individuals remain undiagnosed, and available data suggest that significant deficits exist in HCV testing [13–15]. Based on epidemiologic survey data confirming that greater than 75% of chronically infected individuals were born within the 1945–1965 birth cohort [16–19], one-time universal HCV antibody screening of all adults born 1945–1965 is recommended by the centers for disease control and prevention (CDC) and the U.S. preventative services task force (USPSTF) [13,16,20].

The U.S. Veterans Administration (VA) is the largest integrated health network in the U.S. The projected U.S. veterans' population is 21.7 million (9% females) with a total of 8.97 million enrollees in the VA system. Among U.S. veterans, HCV prevalence is presumed to be three-fold that of the general population based on cross-sectional analysis of enrolled veterans [18,21]. Since 1998 [22,23], the VA health system has employed national directives, education programs, practice guidelines, electronic medical record screening reminders, among other programmatic interventions, to promote HCV testing in veterans. High rates of HCV screening within national VA has been described within a one-year population sample [18], although data addressing broader

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Research Article

trends and variation in HCV testing are limited. Examination of predictors of HCV testing and positive antibody and RNA may identify targets for intervention and refinement of testing strategy. In this study we use data from the national VA Corporate Data Warehouse (CDW) to study national, regional and local HCV testing in the VA Birth Cohort from 2000–2013.

Materials and methods

The VA CDW is a data repository of over 8 million veterans in care and includes VA laboratory test results starting on October 1, 1999, from veterans with at least one VA outpatient visit [18]. Institutional review board approval was obtained both from the West Haven VA and Yale University. VINCI (VA informatics and computing infrastructure) approval using data access request tracker was obtained for access and use of CDW/VA electronic data. The CDW data was queried with MS SQL Server 2012R2/2014 and data was imported using SQL Import/Export tool utilizing well-established algorithms [24,25].

Data on all veterans born 1945–1965 and accessing care at a VA facility from January 1st, 2000 to December 31st, 2013 were initially extracted. Veterans who had at least two VA center visits in that time period were included in the study cohort. Veterans born outside 1945–1965, or with fewer than two visits from 2000–2013 were excluded. Baseline was established as a veteran's first VA encounter after January 1, 2000. Demographic data such as race, sex and year of birth were extracted. Baseline alanine transaminase (ALT) value was set as the ALT measurement closest to baseline visit. The first HCV test in the study time period (2000–2013) performed after the first VA encounter was queried to determine HCV testing or screening status. Individuals tested prior to the year 2000 were excluded (n = 45,333). HCV testing was defined as completion of any HCV laboratory assay including HCV antibody, genotype or RNA (to include individuals referred from outside providers for treatment). A positive HCV test was defined as any positive anti-HCV antibody, HCV RNA or HCV genotype, based on all HCV testing codes employed by the VA from 2000–2013. All anti-HCV testing codes employed by the VA from 2000–2013 were utilized for coding. We reasoned that patients with positive HIV and hepatitis B virus (HBV) and high scores for markers of chronic liver disease such as elevated ALT and fibrosis-4 score (FIB-4)/aspartate transaminase (AST) to platelet ratio Index (APRI) would have a higher likelihood of being tested for HCV. Thus we also determined HCV testing in the cohort of individuals without established risk factors (ALT <40 or missing, FIB-4 <1.45 or missing, APRI $\leqslant$0.5 or missing and not infected or negative for HIV or HBV). HBV positive was defined as any positive test for hepatitis B surface antigen (HBsAg), hepatitis Be antigen (HBeAg) and/or hepatitis B DNA (HBV DNA). HBV uninfected or negative were defined as those without these positive tests. HIV positive was defined by positive HIV positive antibody or RNA or by one inpatient ICD9 or two or more outpatient ICD9 codes. Number of visits per veteran from 2000–2013 was included in the final adjusted model. FIB-4 calculations were done as previously described [26,27] utilizing the formula FIB-4 = (Age $\times$ AST)/(platelets $\times$ (sqr (ALT); (APRI = [(AST/ULN AST) $\times$ 100]/platelets (109/L)).

Statistical analysis

Descriptive statistics (frequencies and percentages) were used to describe the patient, center and veterans integrated service network (VISN) level characteristics (VISN and VA administrative regions defined in detail in the results section). Generalized linear mixed models with a logistic link function were used to model the association between individual's screening status (screened at all during the cohort period) and the following *a priori* individual-level (race, gender, year of birth, ALT, FIB-4, APRI, number of visits, HIV status, HBV status), center level (rural/urban status, complexity level) and VISN level (Hepatitis C Resource Centers (HCRC) status, primary care of excellence status) covariates. We took into account that individuals are nested within centers and centers are nested within VISN. Shared frailty models were used to determine the association between time to screening (individuals not screened by December 31, 2013 were censored) and the same *a priori* covariates. We present odds ratios (OR) and 95% confidence intervals (CI). Multiple imputation (number of imputations = 10) was used to impute the missing data for ALT, FIB-4, and APRI using the SAS (version 9.4, Cary NC) PROC MI procedure; the MIANALZE procedure was used to combine estimates across imputations. Variables included in the imputation were: testing, HCV RNA (positive or negative), HCV AB (positive or negative), time to testing, year of birth, encounter year, race, gender, center, HCV status (positive or negative), HIV status (positive or negative), HBV status (positive or negative) number of visits, number of rural and urban centers, number of low, medium and high complexity centers, VISN HCRC status, VISN primary care of excellence status, ALT, platelets, AST and age. All results presented utilize the imputed data.

Results

There were a total of 6,669,388 veterans born between 1945 and 1965 who presented at the VA from 2000 to 2013 across the United States and its territories; among them 4,221,135 veterans had two or more visits, creating the study cohort (VA Birth Cohort). Overall 2,139,935 (51%) were tested for HCV as of December 31, 2013.

The VA Birth Cohort was predominantly male (84.7%) and white (54.7%), and born between 1945 and 1949 (39.9%) (Table 1). ALT $\leqslant$40 U/L was noted in 56.1% while 16.8% had ALT tests missing or not done. Surrogate liver fibrosis scores based on FIB-4 and APRI [26,27] showed that a majority of veterans (56.1% and 69.5%) had scores suggestive of minimal or no fibrosis. The majority of birth cohort veterans were HIV (99.4%) and HBV (90.9%) negative. Analysis of corresponding HCV antibody (Ab) and RNA testing show an overall rate of 8.1% HCV Ab and 5.4% HCV RNA positivity. Those born between 1950–1954 and 1955–1959 had the highest rate of HCV Ab and RNA positivity of 11.9%/8.5% and 10.8%/7.7%, respectively. Black patients had a 14.7%/10.5% HCV Ab/RNA positive rate; Caucasian patients had a 7.6%/5% positive HCV Ab/RNA, and Asian patients had a HCV Ab/RNA rate of 2.6%/1.6%. A higher number of clinic visits was associated with increased testing rates along with higher HCV Ab and RNA positivity rates, likely representing patients who were sicker and had more medical visits. Patients with ALT >40 U/L, was HIV or HBV positive, or had FIB-4 >3.25/APRI $\geqslant$1.5 (suggesting advanced fibrosis), demonstrated the highest rates of HCV antibody and RNA positivity. We also considered veterans who did not have established risk factors (ALT $\leqslant$40/missing, FIB-4 <1.45/missing, APRI $\leqslant$0.5/missing, HIV negative and HBV negative) in Supplementary Table 1. Thirty nine percent of the 2,401,686 veterans were tested for HCV and had an HCV antibody positive rate of 2.8% and RNA of 0.9%.

Analysis of predictors of being tested for HCV and for testing positive for HCV RNA is presented in Table 2. A multivariate generalized linear mixed model was created for determining the association between the probability of being tested and the *a priori* covariates. Younger veterans (born 1960–1965) had lower odds (OR: 0.81 CI: 0.81, 0.82) of being tested and for being HCV RNA positive (OR: 0.76 CI: 0.74, 0.77).

Female veterans had lower odds of being tested (OR: 0.53 CI: 0.53, 0.53). Black veterans had the highest odds of being tested (OR: 1.10 CI: 1.09, 1.11) and being HCV RNA positive (OR: 1.70 CI: 1.68, 1.72). Asian veterans had lower odds (OR: 0.85 CI: 0.83, 0.88) of being tested and being HCV RNA positive (OR: 0.22 CI: 0.20, 0.25). Veterans with ALT >40 (Testing: OR: 1.22 CI:1.21, 1.22; RNA: OR 3.53 CI:3.49, 3.58), FIB-4 >3.25 (Testing: OR:1.22 CI:1.21, 1.22; RNA: OR: 1.70 CI: 1.66, 1.75), APRI $\geqslant$1.5 (Testing: OR: 2.32 CI: 2.26, 2.38; RNA: OR: 6.99 CI: 6.78, 7.20), HIV positive (Testing: OR: 1.54 CI: 1.48,1.60; RNA: 1.07 CI: 1.03, 1.11) or HBV positive (Testing: OR: 7.48, CI: 7.41, 7.56); RNA: OR: 7.96 CI: 7.87, 8.06) had high odds of being tested and being positive for HCV RNA.

The overall testing for HCV varied from 7% to 83% across VA centers (Fig. 1). The VA is divided into multiple geographically