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Association of Hepatitis C Virus Infection With Prevalence and Development of Kidney Disease

Sharon M. Moe, MD[1,2], **AJ Pampalone, MD**[1], **Susan Ofner, MS**[1], **Marc Rosenman, MD**[1,3], **Evgenia Teal, MS**[3], and **Siu L. Hui, PhD**[1,3]

1*Indiana University School of Medicine, Indianapolis, IN*

2*Roudebush VAMC, Indianapolis, IN*

3*Regenstrief Institute, Indianapolis, IN*

Abstract

Background—Hepatitis C and CKD are both highly prevalent diseases in the United States. Data has demonstrated that hepatitis C may be causally linked to some glomerular diseases, and that patients who are positive for hepatitis C have increased risk for albuminuria.

Study Design—To determine if hepatitis C infection is associated with increased likelihood of CKD, we performed retrospective cross-sectional and longitudinal analyses of a large clinical database.

Setting and Participants—Data on a study population of 13,139 African American and white patients tested for hepatitis C between 1994 and 2004 was extracted from a computerized database from a clinical population of an urban hospital and affiliated clinics.

Predictor—Hepatitis C by ELISA.

Outcome—In cross-sectional analysis, CKD was defined as a minimum estimated GFR (eGFR) value < 60 ml/min/1.73 m2, using the 4 variable MDRD Study equation, or proteinuria. In longitudinal analysis, CKD was defined as eGFR < 60 ml/min/1.73 m2.

Measurements—Potential confounders investigated included sex, age, race, HIV status, chronic hypertension, diabetes, and other laboratory abnormalities.

Results—A total of 3938 patients (30.0 %) were positive for hepatitis C, and 2549 (19.4%) had CKD. Of those with CKD, 1999 (78.4%) had eGFR < 60 ml/min/1.73 m2, 186 (7.3%) had proteinuria, and 364(14.3%) had both. In cross-sectional analysis, after controlling for diabetes, hypertension, age, alanine serotransferase (AST), and HIV status, patients who tested positive for hepatitis C had a decreased risk of CKD (OR=0.69, 95% CI 0.62–0.77). A total of 7,038 subjects without CKD were followed for a median of 3.5 years. Of these, 2243 (31.8%) were hepatitis C positive at onset of follow-up. In longitudinal analysis, after adjustment for age, baseline eGFR, diabetes, hypertension, AST and HIV, the HR (95% CI) for development of CKD compared to those who were hepatitis C negative was 1.024 (0.908 1.156).

Address correspondence to: Sharon M. Moe, MD, Professor of Medicine, Vice-Chair for Research, Department of Medicine, Indiana University School of Medicine, 1001 W. 10th Street; OPW 526, Indianapolis, IN 46202, smoe@iupui.edu, (317) 278-2868, FAX: (317) 278-2860.

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Limitations—Retrospective design, clinical database with missing values, different hepatitis C assays used over the study time period, limited data on proteinuria.

Conclusions—Our results do not support the hypothesis that infection with the hepatitis C virus per se is associated with an increased risk of having or developing CKD.

Keywords

CKD; hepatitis C; proteinuria; GFR

In the United States 4 million people, 1.4%–2.2% of the population, are serum positive for antibody to hepatitis C virus (HCV) [1, 2]. Chronic infection is most common in African American males with a prevalence of 9.8% in men ages 40–49[1, 2]. The estimated cost of hepatitis C infection in the US is over 5 billion dollars[3] due in part to the many extra-hepatic manifestations [4]. More recently, hepatitis C has been implicated as a possible cause of chronic kidney disease (CKD), a common disease in the United States, affecting nearly 11% of the adult population [5]. While the greatest prevalence of CKD can be found among diabetic and hypertensive individuals, other risk factors for CKD have been proposed, including hepatitis C[6].

Hepatitis C has been associated with several glomerulopathies, most notably cryoglobulin-associated membranoproliferative glomerulonephritis (MPGN) [7]. However, other glomerular diseases have also been found in hepatitis C populations [8–11]. More recently, two studies using data from the Third National Health and Nutrition Examination Survey (NHANES III) have found an increased risk of albuminuria in patients with hepatitis C[2, 12], and another study found an increased risk of developing ESRD[13]. In addition, two studies have demonstrated that the progression of diabetic nephropathy is more rapid when patients are infected with hepatitis C[14, 15], and other studies have found the presence of hepatitis C viral particles or antigens in glomeruli or tubules of kidney biopsies[16, 17]. These data support that hepatitis C may also cause CKD, but this has not been clearly demonstrated.

We hypothesized that infection with hepatitis C increased the risk of CKD and accelerated progression to CKD. To test our hypotheses we compared a cross-section of hepatitis C positive patients to hepatitis C negative patients in their likelihood of having CKD, and we followed forward over time a retrospective cohort of hepatitis C positive patients without CKD to assess the risk of developing CKD. The data demonstrated, both in cross-sectional and longitudinal analyses, no increased risk of having or developing CKD in patients with hepatitis C.

METHODS

Patients and Definitions

We utilized the Regenstrief Medical Record System (RMRS), a state-of-the-art electronic information system that includes diagnoses, laboratory results, progress notes, discharge summaries, vital signs, and a computerized physician order entry system [18,19]. The system is used for Wishard Health Services, which serves primarily an inner-city indigent population. Although this is a clinical database, the data has been used extensively for research purposes with well defined queries and extensive validation procedures. Only African American and white subjects were included in this study, as less than 6% of the population was of other race/ethnicity. Patients in the system who were tested for hepatitis C from 1994–2004 in the RMRS were identified. Excluded from all analyses were subjects who underwent any dialysis treatment (n = 468) and subjects with AST or ALT > 200 U/L due to the possibility of acute hepatic failure leading to acute kidney injury rather than CKD.

A positive hepatitis C test was defined as a positive antibody result by first, second or third generation ELISA with or without RIBA confirmation. For all study subjects, the index date was defined as the date of the first positive result or as the date of the first test if all tests in the period were negative. For the cross-sectional study, all other variables were measured in time windows relative to the index date. In the cross-sectional study, CKD and other chronic conditions (e.g. hypertension) were defined (as described below) by data from the 5 years before or one year after the index date of hepatitis C testing. Other laboratory values were retrieved from one year before or after the index date. For the longitudinal study, all covariates were measured during comparable pre-index date time windows and time to CKD was measured from the index date forward.

The primary outcome of CKD was defined as a minimum eGFR value < 60 ml/min/1.73m^2 (to convert to milliliters per second per 1.73 m^2, multiply by 0.01667) using the 4 variable MDRD Study equation[5, 20] and/or the presence of proteinuria defined by a random protein/Cr ratio > 200 mg/g, a random albumin/Cr ratio > 250 mg/g in males or > 355 mg/g in females, a 24 hour urine protein collection > 300 mg/24hrs, or microalbuminuria > 30 mg/dl. For a sensitivity analysis, a more stringent secondary outcome of CKD was defined as at least two eGFR values < 60 ml/min/1.73m^2 measured at least 90 days apart within the chronic disease window (up to 5 years before or 1 year after the index date), with at least one of the measurements within one year of the index date.

We investigated potential confounders of the relationship between hepatitis C status and CKD, including sex, age, race, HIV status, chronic hypertension, diabetes, and other laboratory abnormalities. Hypertension was defined as any of the following: diagnosis in problem list or discharge summary, prescriptions for any blood pressure medicines, average systolic blood pressure > 140, or average diastolic blood pressure > 90[19, 21]. Of note, a single value above 140/90 without other evidence was not considered hypertension. Diabetes was defined as any diagnosis in problem list or discharge summary, any complication of diabetes (i.e. diabetic retinopathy) in problem list or discharge summary, prescriptions for any diabetic medications, a fasting glucose > 140 mg/dl (to convert to micromoles per liter, multiply by 0.05551), any glucose > 200 mg/dl, or any glycated hemoglobin tests > 10[19]. Laboratory values examined included cryoglobulin, rheumatoid factor, and AST. The liver enzyme tests were used as a surrogate marker, albeit imperfect, for liver disease. Both AST and ALT were evaluated, and there was less missing data for AST and thus this laboratory value was included as a covariate. Visual inspection of the relationship between AST and CKD showed a near constant risk of CKD at AST values below 50 U/L, and linearly increasing log odds of CKD with AST > 50 U/L. Thus, AST values lower than 50 were set to 50 in subsequent analyses.

Missing data were common for rarely ordered tests: 98.3% for cryoglobulin and 94.4% for rheumatoid factor. The non-missing data were screened univariately and removed from further modeling procedures if uncorrelated with CKD. For more commonly ordered tests, when the test has never been ordered for a patient, it is reasonable to assume that the result would likely be negative; thus, negative results were imputed. For example, 10.9% of subjects with missing AST in the cross sectional analysis had an imputed value of 50 while 89% of subjects with missing HIV tests were assumed to be negative. The exception was missing creatinine, which was not imputed because it was used to define the primary outcome of CKD, even though eGFR was more likely to be missing for younger subjects most of whom were negative for hepatitis C, hypertension, HIV and diabetes. We did, however, use negative CKD status imputed from missing creatinine, in sensitivity analyses.

Cross-sectional study

The association of hepatitis C positivity and CKD in our urban population was examined in a series of logistic regression models. The unadjusted association was estimated from a

univariate logistic regression model with the primary outcome CKD as a binary variable, and hepatitis C positivity as the predictor. To identify potential confounders, we screened each covariate by adding its main effect with hepatitis C to the unadjusted model. Variables significant at the 0.3 level were then allowed into an overall multiple logistic model; if they were no longer significant at the 0.1 level, they were removed from the model.

In order to determine if our results may be biased due to clinician selection of patients to test for hepatitis C, we re-ran our cross sectional analysis using sampling weights inversely proportional to the probability of being tested. The probability was derived from a logistic model for being tested for hepatitis C among all patients who had been tested for either hepatitis C or creatinine in the database during the study period (n = 134,480). For subjects not tested for hepatitis C, a randomly chosen date of one of their creatinine tests was used as an index date. Similar to the hepatitis C tested cohort, subjects with AST or ALT > 200 U/L or who had no creatinine tests were excluded, and only white and African American subjects were included. Potential predictors of being tested for hepatitis C included the same covariates as predicting a positive hepatitis test, together with additional covariates of the number of years a subject had been in the RMRS system, having CKD prior to the time of the hepatitis C test and having elevated liver function (AST > 40 U/L or ALT > 45 U/L), as well as two-way interactions among the covariates. The fitted model was used to calculate the probability of being tested for each individual who was actually tested. The inverses of these estimated probabilities were used as weights in the logistic model predicting outcomes among those tested for hepatitis C. Thus subjects who were less likely to be tested for hepatitis C were given more weight because they represented more untested patients who were similar to them. Other sensitivity analyses included rerunning the final model based on imputing missing eGFR as normal and thus CKD as negative, and using the stringent definition of CKD as the outcome.

Longitudinal study

To investigate whether hepatitis C infection leads to the development of CKD, we followed forward in the RMRS a smaller cohort of patients without CKD to determine if hepatitis C accelerated the onset of CKD. The cohort consisted of subjects who were tested for hepatitis C and did not have CKD as of the index date in the cross-sectional study, and who had at least one subsequent visit recorded. We compared the incidence of CKD after the index date between subjects who ever tested positive for hepatitis C with those who always tested negative. Time to CKD was defined as time to first eGFR < 60 ml/min/1.73m^2. If all eGFR post index visit were > 60 ml/min/1.73m^2, then the follow up time was censored at the last recorded visit. If there was no creatinine data, CKD was treated as missing. Covariates examined included age, sex, race, diabetes, hypertension, AST, and HIV status at the time of the index date, as well as baseline eGFR, which was defined the closest measurement in time preceding or on the index date. A Cox proportional hazard model was used to model the time to CKD with baseline hepatitis C positivity as the predictor of primary interest. To screen for confounders, covariates were first tested individually in separate models that always included hepatitis C. If they were significant at the 0.25 level they were eligible for inclusion into a multivariable Cox model. Stepwise variable selection was used to select variables which were then allowed to remain if significant at the 0.15 level. The proportional hazard assumption was verified by examination of plots of log (−log) survival functions. Again, a sensitivity analysis was performed with negative CKD incidence imputed from missing eGFR.

RESULTS

Cross-sectional study

Between 1994–2004, 19,303 patients (of known race and sex) were tested for hepatitis C. After excluding the 6% of subjects who were not white or African American, and the approximately

2000 subjects who had an AST or ALT > 200 U/L and 434 subjects on dialysis, there were 15,918 subjects, 16.0% with CKD. Of those with CKD, 1999 (78.4%) had eGFR < 60 ml/min/1.73 m2, 186 (7.3%) had proteinuria, and 364(14.3%) had both. with all but 550 of these subjects fulfilling a definition of CKD by eGFR alone. Of the 550 subjects with proteinuria, 186 had normal eGFRs. Both creatinine and proteinuria were missing in 2779 (17.5%) subjects. Among the remaining 13,139 subjects, the median difference in days between hepatitis C testing and assessment of eGFR was 0 (25^{th} to 75^{th} percentiles, 0 to 0) for those with CKD and 0 (25^{th} to 75^{th} percentiles, −25 to 0) for those without CKD.

Table 1 reports the study subjects' demographic and clinical characteristics. CKD was significantly more prevalent in the hepatitis C negative than in the hepatitis C positive subjects, although all other covariates but diabetes also differed significantly by hepatitis C status, indicating that they could potentially confound the relationship between hepatitis C and CKD. When each covariate was added to hepatitis C in models to predict CKD, hepatitis C was still significantly associated with decreased risk of CKD. The magnitude of the association increased when each of the other variables was included, with the greatest change being in models which included AST and hypertension. In the multivariable model, CKD was strongly associated with the presence of hypertension and diabetes, and weakly with age and HIV positivity. However, hepatitis C remained negatively associated with CKD, even after adjusting for other factors associated with CKD.

Sensitivity analyses were performed to rule out potential biases that might yield this unexpected result. First, we accounted for the non-random selection of patients for hepatitis C testing by repeating the logistic regression with weights inverse to the selection probability of being tested for hepatitis C, based on a fitted model with area under the ROC curve = 0.71. The weighted analysis yielded no changes in the direction or strength of association between hepatitis C and CKD. In another sensitivity analysis, inclusion of subjects with imputed CKD in multivariable analyses did not change the results. Finally, using the more stringent definition of CKD, the prevalence of CKD in the total sample decreased from 19.4% to 7.6% (Table 1), but the estimated odds ratio between hepatitis C and CKD remained significant at 0.76 univariately and 0.78 (95% CI 0.66–0.92) after controlling for covariates.

Longitudinal study

The cohort of patients who did not have CKD (n = 9137) at the time of testing for hepatitis C and who had at least one visit post the date of hepatitis C testing was examined longitudinally to determine if hepatitis C increased the risk of developing CKD. Of these subjects, 7,038 (77.0%) had at least one creatinine measured post the index date. Median length of follow-up time was 1266 days (interquartile range 684 to 2040) and median number of creatinines measured per subject was 4 (interquartile range 2 to 11). The baseline characteristics of this cohort, summarized by hepatitis C status, are shown in Table 3. Univariately, positive hepatitis C predicted a non-significant increased risk of developing CKD. When covariates were added individually to the model, hypertension, diabetes, AST value, age and baseline eGFR were statistically significant. The estimated hazard ratio of hepatitis C always remained non-significant, but was slightly attenuated by the addition of sex, diabetes, and hypertension, and even reversed with the addition of age and AST, the strongest confounders (as also found in the cross-sectional analyses). The multivariable Cox model in Table 5 showed that, once adjusted for all other significant factors, being hepatitis C positive predicted a non significant decreased risk of developing CKD. Subjects in the longitudinal cohort with missing CKD data had characteristics similar to those of subjects with missing CKD data in the cross sectional analysis. In a sensitivity analysis, including these subjects with imputed negative incident CKD did not change any of the findings.

DISCUSSION

In this study we tested the hypothesis that hepatitis C was associated with CKD. This hypothesis was generated based on observations that hepatitis C is associated with some forms of glomerular disease [7–11], that the co-existence of hepatitis C appears to increase the progression of CKD [14], that viral particles or antigenicity is found in glomeruli and tubules of kidney biopsies[16, 17], and that CKD is very prevalent in areas with particularly high rates of hepatitis C infection [22]. Our results demonstrated no increased risk of having or developing CKD in patients who are hepatitis C positive in cross-sectional and longitudinal analyses after controlling for multiple other known risk factors for CKD.

Surprisingly, our cross-sectional study demonstrated a reduced likelihood for the presence of CKD in patients with hepatitis C. These results confirm cross-sectional results from a study utilizing the NHANES database, in which 366 subjects with hepatitis C seropositivity, compared to subjects without seropositivity, were found to have a reduced odds ratio of CKD defined as an eGFR < 60 ml/min/1.73 m^2 (0.45, CI 0.24 to 0.85; p = 0.02), although after adjustment it was no longer significant (0.89; 0.49–1.62). [2]. Our results also corroborate a study using the Veterans Administration Medical Record system where the adjusted odds ratio for having CKD in hepatitis C positive patients was 0.91 (95% CI, 0.88–0.95). To try to explain our findings and that of the above studies, we performed a weighted analysis to adjust for possible bias resulting from the selection of patients tested for hepatitis C, and found no difference in the results. The reasons for these findings in both research and clinical databases are unclear but may include decreased creatinine production from muscle wasting or altered creatinine metabolism due to liver disease such that the eGFR is artificially low in patients with hepatitis C.

To further understand how hepatitis C relates to CKD, we also performed a longitudinal analysis to determine if patients who were hepatitis C positive, but without CKD, had an increased risk of developing CKD when compared with those who were hepatitis C negative. By univariate analysis, patients with hepatitis C seropositivity were more likely to develop CKD, but this was not significant and after adjustment for known risk factors for CKD, there was a non-significant decreased risk of development of CKD. In a study of patients in the Veterans Administration (VA) database, Tsui et al also found that HCV-seropositive patients were slightly less likely to experience a decline in eGFR compared with seronegative patients (56% vs 57%, *P*<.01). However, the decline in GFR was more rapid when they did progress, and the risk of developing ESRD was greater in the hepatitis C seropositive subjects[13]. Our study involved a very different cohort, selected from the population served by a large urban hospital and its clinics. Our population has a much higher prevalence of hepatitis C (30% of the population tested versus 11% in the VA cohort). This high positivity in our cohort is similar to that of tested patients who abused intravenous drugs[23], which supports the notion that our study population is generally at high risk for the disease. In addition, our cohort compared to the VA cohort had more African Americans (48% versus 16%), more women (51% versus 5%), younger patients (on average 15 years younger), and were more likely to have HIV disease (11% versus 2%). The VA Cohort also had more patients with diabetes and hypertension. The latter may explain why progression of CKD was rapid when there was progression, as others have found that hepatitis C worsens the progression of diabetic nephropathy [14, 15]. This study suggests that hepatitis C may not cause CKD, as corroborated by our study, but rather accelerate the decline of GFR when CKD is present.

There are several limitations to this study. First, we had 17 % and 23 % missing data for CKD (creatinine or proteinuria) in the cross-sectional and longitudinal data, respectively, with limited data on proteinuria because our hospital system relies predominately on dipstick testing for screening yet we felt these would be unreliable as diagnostic tests. This magnitude of

missing data is inherent to clinical databases as opposed to research databases. Specifically, this may lead to under diagnosis of CKD as proteinuria generally precedes the development of abnormal eGFR. Second, the diagnosis of hepatitis C positivity was based on different assays due to the 10-year span in which this data were collected. Third, it is possible that we included cases of acute kidney injury rather than CKD, which may have led to underestimating the risk of hepatitis C on CKD. Fourth, the eGFR formula may not be an accurate measure of a true GFR at levels close to and above 60. Lastly, this study evaluated only white and African American patients in the Midwest of the United States, and a cohort with a high prevalence of HIV, suggesting intravenous drug use or multiple sexual partners as the major etiology for the high prevalence of hepatitis C. Thus the results may not be generalizable to other races and geographic areas.

In summary, our results indicate there is no increased risk of developing CKD in patients who are hepatitis C positive, when controlled for other risk factors known to lead to CKD. These data do not support widespread testing for hepatitis C as a means to identify patients at risk for CKD. However, our data do not preclude testing patients with known CKD for hepatitis C as there is some data that hepatitis C may worsen the rate of progression of CKD, especially in patients with diabetic nephropathy[13–15]. In addition, seropositivity is high in dialysis units and may lead to more problems with transplantation[24].

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Table 1

Demographics and Associations for the Cross-Sectional Analysis

	Hep C −	Hep C +	Total	p-value*
Sample N (%)	9201 (70.0%)	3938 (30.0%)	13139	
African American	4276 (46.5%)	2005 (50.9%)	6281 (47.8%)	<0.001
Female	5145 (55.9%)	1560 (39.6%)	6705 (51.0%)	<0.001
Age in years (mean ± sd)	41.2 ± 13.8	43.6 ± 9.4	41.9 ± 12.7	<0.001
AST value U/L (mean ± sd)	60.2 ± 25.7	72.3 ± 33.8	63.8 ± 28.9	<0.001
Cryoglobulin positive	13 (0.1%)	46 (1.2%)	59 (0.5%)	<0.001
Diabetes	2075 (22.6%)	921 (23.4%)	2996 (22.8%)	0.3
eGFR closest to index date	97.1 ± 32.0	99.3 ± 29.2	97.7 ± 31.2	<0.001
CKD (min eGFR<60 or proteinuria)**	1872 (20.4%)	677 (17.2%)	2549 (19.4%)	<0.001
CKD***	745 (8.1%)	248 (6.3%)	993 (7.6%)	<0.001
HIV	1181 (12.8%)	312 (7.9%)	1493 (11.4%)	<0.001
Hypertension	4274 (46.5%)	1999 (50.8%)	6273 (47.7%)	<0.001
rheumatoid factor +	54 (0.6%)	57 (1.5%)	111(0.8%)	<0.001

* comparisons between hep C− and hep C+ groups.

** Of those with CKD, 1999 (78.4%) had eGFR < 60 ml/min/1.73 m2, 186 (7.3%) had proteinuria, and 364(14.3%) had both.

*** stringent definition of CKD: 2 eGFRs<60 more than 90 days apart

To convert eGFR in ml/min/1.73 m2 to ml/s/1.73 m2, multiply by 0.01667.

Table 2

Cross-Sectional Univariate and Multiple Regression Models

	Estimate	(SE)	Odds Ratio	95% CI		p-value
Univariate Models						
Hep C+	−0.207	(0.050)	0.813	0.738	0.896	<.0001
Hep C+	−0.211	(0.050)	0.810	0.735	0.892	<.0001
African American (reference is white)	0.087	(0.044)	1.091	1.000	1.189	0.0499
Hep C+	−0.203	(0.050)	0.816	0.740	0.900	<0.001
Female	0.026	(0.045)	1.026	0.940	1.120	0.6
Hep C+	−0.256	(0.052)	0.774	0.699	0.857	<0.001
Age (years)	0.068	(0.002)	1.070	1.066	1.075	<0.001
Hep C+	−0.327	(0.051)	0.721	0.652	0.797	<0.001
AST (U/L)	0.009	(0.0007)	1.009	1.007	1.010	<0.001
Hep C +	−0.476	(0.285)	0.621	0.356	1.086	0.1
Cryoglobulin +	0.320	(0.320)	1.377	0.736	2.580	0.3
Hep C+	−0.244	(0.052)	0.784	0.708	0.868	<0.001
Diabetes	1.540	(0.048)	4.665	4.250	5.121	<0.001
Hep C+	−0.214	(0.050)	0.807	0.732	0.890	<0.001
HIV +	−0.149	(0.072)	0.861	0.748	0.992	0.04
Hep C+	−0.303	(0.052)	0.739	0.667	0.818	<0.001
HTN	1.756	(0.053)	5.791	5.221	6.424	<0.001
Hep C +	−0.004	(0.195)	0.996	0.680	1.461	1.0
rheumatoid factor +	0.040	(0.234)	1.041	0.658	1.646	0.9
Multiple Regression Model						
Age (years)	0.046	0.002	1.047	1.043	1.052	<0.001
AST (U/L)	0.006	0.0008	1.006	1.005	1.008	<0.001
Diabetes	0.963	0.052	2.620	2.365	2.903	<0.001
Hep C +	−0.365	0.056	0.694	0.622	0.774	<0.001
HIV +	0.379	0.081	1.461	1.248	1.711	<0.001
HTN	1.066	0.058	2.903	2.589	3.255	<0.001

Table 3

Characteristics of longitudinal cohort

	Hep C −	Hep C +	Total	p-value*
Sample N (%)	4795 (68.1%)	2243 (31.8%)	7038	
African American	2315 (48.3%)	1167 (52.0%)	3482 (49.5%)	0.003
Female	2620 (54.6%)	937 (41.8%)	3557 (50.5%)	<0.001
Age (mean ± SD, yrs)	41.3 ± 12.4	44.1 ± 8.5	42.2 ± 11.4	<0.001
Diabetes	872 (18.2%)	447 (19.9%)	1319 (18.7%)	0.09
Baseline eGFR	104.5 ± 28.0	105.7 ± 25.6	104.9 ± 27.3	0.06
Hypertension	1997 (41.7%)	1002 (44.7%)	2999 (42.6%)	0.02
HIV +	644 (13.4%)	182 (8.1%)	826 (11.7%)	<0.001
AST (U/L)	60.1 ± 25.1	71.9 ± 33.2	63.8 ± 28.5	<0.001

* comparison between hep C− and hep C+ groups

Table 4

Univariate Cox Models for Time to CKD

	Estimate	(SE)	Hazard Ratio	95% CI		p-value
Hep C+	0.024	0.062	1.024	0.908	1.156	0.7
Hep C+	0.025	0.062	1.025	0.909	1.157	0.7
African American (reference is white)	−0.042	0.059	0.959	0.855	1.076	0.5
Hep C+	0.008	0.062	1.008	0.893	1.139	0.9
Female	−0.109	0.059	0.896	0.798	1.007	0.06
Hep C+	−0.067	0.062	0.936	0.828	1.057	0.3
Age (years)	0.126	0.016	1.134	1.098	1.172	<0.001
Age ^{2}	−0.0007	0.0002	0.999	0.999	1.000	<0.001
Hep C+	−0.061	0.063	0.941	0.832	1.064	0.3
AST (U/L)	0.007	0.0008	1.007	1.005	1.008	<0.001
Hep C+	0.005	0.062	1.005	0.891	1.134	0.9
Diabetes	0.655	0.065	1.925	1.696	2.185	<0.001
Hep C+	0.032	0.062	1.032	0.915	1.165	0.6
Baseline eGFR	−0.008	0.001	0.992	0.989	0.994	<0.001
Hep C+	0.030	0.062	1.031	0.913	1.164	0.6
HIV +	0.104	0.090	1.110	0.931	1.324	0.2
Hep C+	0.009	0.062	1.009	0.894	1.138	0. 9
HTN	0.920	0.061	2.510	2.229	2.826	<0.001

Table 5

Multiple Regression Cox Model for Time to CKD

Variable	Estimate	(SE)	Hazard Ratio	95% CI		p-value
Age (year)	0.104	0.017	1.109	1.073	1.147	<0.001
Age^2	−0.0006	0.0002	0.999	0.999	1.000	<0.001
Baseline eGFR	−0.005	0.001	0.995	0.993	0.997	<0.001
Diabetes	0.365	0.067	1.440	1.264	1.642	<0.001
Hep C +	−0.110	0.064	0.896	0.790	1.015	0.09
HTN	0.460	0.066	1.584	1.392	1.802	<0.001
AST (U/L)	0.006	0.0009	1.006	1.004	1.008	<0.001
HIV +	0.449	0.091	1.567	1.311	1.872	<0.001