AJKD
Original Investigation

HCV Infection and the Incidence of CKD

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Background: The risk of hepatitis C virus (HCV) infection upon incident chronic kidney disease (CKD) in the presence of traditional risk factors and renal-modifying therapy is not well known.

Study Design: National cohort study.

Setting & Participants: HCV-infected and -uninfected veterans in ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans) in 2001-2006.

Predictor: HCV infection.

Outcomes: Incident CKD stages 3-5.

Results: We identified 18,002 patients with HCV infection and 25,137 controls with estimated glomerular filtration rate >60 mL/min/1.73 m^2 at baseline. HCV-infected patients had a lower prevalence of several CKD risk factors, including diabetes (22.9% vs 26.6%), hypertension (52.4% vs 60.8%), and dyslipidemia (39.3% vs 73.9%; $P < 0.001$). HCV infection was associated with a higher risk of developing CKD stages 3-5 (HR, 1.30; 95% CI, 1.23-1.37). Increasing age, hypertension, and diabetes were associated with significantly higher risks of developing CKD in HCV-infected patients and controls. Decompensated liver disease was a strong predictor of CKD in HCV-infected patients (HR, 3.37; 95% CI, 3.10-3.66) and HCV-uninfected controls (HR, 2.04; 95% CI, 1.84-2.25). In Kaplan-Meier analysis, HCV-infected persons had a shorter time to CKD.

Limitations: Lack of proteinuria data; small number of women.

Conclusions: HCV infection is associated with higher risk and shorter time to CKD despite having a lower prevalence of many CKD risk factors. HCV-infected persons should have targeted monitoring for the development and progression of CKD.

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INDEX WORDS: Hepatitis C virus (HCV); chronic kidney disease (CKD); renal; liver disease; Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES).

Individuals in the United States with end-stage renal disease (ESRD) have a higher prevalence of hepatitis C virus (HCV) antibody positivity compared with the general population.[1] Before testing of blood products for HCV and the availability of erythropoiesis-stimulating agents, dialysis patients commonly acquired HCV through blood transfusions.[2] Transmission still may occur because of contaminated medical equipment or transmission from person to person in hemodialysis units.[1,3] The prevalence of HCV infection in patients on hemodialysis therapy ranges from 6%-23%.[4-7] It is projected that the ESRD population on dialysis therapy will reach 774,386 nationally by 2020.[8] With an estimated HCV prevalence of 7.8% in this group,[9] the estimated number of HCV-infected persons on dialysis therapy by 2020 would reach about 60,402.

Although transmission of HCV in dialysis units has been described, the high prevalence of HCV in patients new to dialysis therapy is less appreciated.[10,11] This suggests that HCV is being acquired not from transmission in the dialysis unit, but before dialysis therapy. It has been proposed that HCV is associated with kidney disease, but studies have been conflicting.[12-14] A recent study reported that HCV-infected persons were at a higher risk of progression to ESRD compared with HCV uninfected persons.[12] However, this study did not control for renal-modifying therapy (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]). Additionally, the definition of chronic kidney disease (CKD) at baseline was based on a single creatinine measurement, and the primary outcome was hemodialysis therapy or kidney transplant. We studied the association of HCV with incident CKD (stages 3-5) in a national cohort of HCV-infected persons and HCV-uninfected controls and whether the relationship was independent of traditional risk factors.

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METHODS

Description of the Cohort

We used the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) to identify HCV-infected patients and HCV-uninfected controls who were free of stages 3-5 CKD (defined next) at baseline. These patients were followed up through their last encounter in the Veterans Affairs (VA) health care system or the development of stage 3 or higher CKD. The creation of ERCHIVES has been described in previous publications.[15-18] Briefly, we retrieved demographic and clinical data from the National Patient Care Database, laboratory data from the Decisions Support System, pharmacy data from the Pharmacy Benefits Management database, and mortality data from the Beneficiary Information Records Locator System and the National Death Index. HCV-infected persons initially were identified based on *International Classification of Diseases, Ninth Revision* codes, and HCV-uninfected controls were chosen matched on age, race, sex, and year of entry into the VA health care system. Data from all these sources were merged to form a composite cohort of HCV-infected persons and HCV-uninfected matched controls.

For the present study, we retained patients with a first HCV diagnosis in 2001-2006 and their corresponding controls because laboratory data were available from 2001 onward. To be included in the study, HCV-infected patients had to have confirmation of HCV by either positive antibody test result or positive result for HCV RNA testing. They also needed to have at least 2 serum creatinine measurements before the baseline visit and at least 2 measurements after baseline, with each measurement at least 3 months apart. Patients (both the HCV-infected group and controls) were retained if they were free of CKD stages 3-5 at baseline and had hemoglobin, alanine or aspartate aminotransferase, and lipid measurements available. Persons with human immunodeficiency virus (HIV) infection were excluded.

CKD was defined by calculating estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) Study equation: $eGFR = 186 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if African American})$, where SCr is serum creatinine.

Consistent with the National Kidney Foundation's definition of kidney disease, CKD was defined as 2 eGFR values <60 mL/min/1.73 m^2, determined at least 90 days apart (stages 3-5 CKD). Patients were considered to be free of CKD at baseline if they had at least 2 values 3 months or longer apart that were ≥ 60 mL/min/1.73 m^2 and no 2 eGFR values were <60 mL/min/1.73 m^2. Patients were followed up through their last encounter in the VA health care system, death, or development of CKD stages 3-5. Again, to be considered to have CKD, at least 2 eGFR values <60 mL/min/1.73 m^2 were required.

Definitions of Comorbid Conditions

Anemia was defined as a hemoglobin value <13 g/dL for men and <12 g/dL for women. The presence of liver injury was defined as an increase in either serum alanine or aspartate aminotransferase level to greater than the upper limit of the reference range on 2 or more occasions. Decompensated liver disease was defined as presence of any 1 of the following criteria twice or any 2 of them once: (1) international normalized ratio >1.5, (2) serum albumin level <2.5 g/dL, (3) total bilirubin level >2.0 mg/dL, and (4) diagnosis of esophageal varices, ascites, or hepatic encephalopathy. Hyperlipidemia was defined as total cholesterol level >200 mg/dL, total cholesterol level >200 mg/dL once plus low-density lipoprotein cholesterol level >130 g/dL once, or use of lipid-lowering agents for more than 30 days. Other comorbid conditions were defined by the presence of at least 1 inpatient or 2 outpatient *International Classification of Diseases, Ninth Revision* codes. All comorbid conditions were determined at baseline, which was defined as the time window 12 months before and up to 6 months after the diagnosis of HCV infection for cases and the corresponding match date for HCV-uninfected controls. Patients with incomplete or missing data that precluded us from defining CKD were dropped.

Renal-Modifying Therapy

We retrieved information about the use of ACE inhibitors and ARBs from the Pharmacy Benefits Management database. This was treated as a categorical (yes/no) variable, and participants were considered to have received this therapy if they were prescribed any agent from either class for more than 30 consecutive days.

Statistical Analyses

Baseline characteristics of HCV-infected and -uninfected participants and those with and without CKD were compared using *t* test for continuous and χ^2 test for categorical variables. Cox regression analysis was used to determine predictors of the development of CKD stages 3-5. Kaplan-Meier survival plots were used to compare time to the development of CKD stages 3-5 between HCV-infected and -uninfected participants. Log-log survival plots and Schoenfeld residuals were used to test for assumptions of proportional hazards. To further understand some of the associations among HCV-infected participants, we also compared characteristics of those with detectable versus undetectable HCV RNA at baseline and those with versus without decompensated liver disease at baseline. We used STATA, version 8.2 (www.stata.com) for statistical analyses.

RESULTS

We retained participants in the ERCHIVES cohort for whom we could reliably determine the presence or absence of CKD stages 3-5 according to the National Kidney Foundation definition. We identified 24,711 HCV-infected and 43,574 HCV-uninfected patients for whom multiple serum creatinine values were available to satisfy our definitions for the presence or absence of CKD stages 3-5. In HCV-infected patients, we excluded 3,666 because they had CKD stages 3-5 at baseline and an additional 3,043 for missing laboratory values. In HCV-uninfected patients, we excluded 8,871 and 9,566, respectively. This yielded a final assessable data set of 18,002 HCV-infected participants and 25,137 HCV-uninfected controls (Fig 1).

HCV-infected participants were younger (mean age, 51.9 $\pm$ 7.2 [SD] vs 52.8 $\pm$ 7.5 years; $P < 0.001$) and more likely to be black (33.9% vs 30.9%; $P < 0.001$). Mean baseline eGFR was 99 $\pm$ 22.6 mL/min/1.73 m^2 in the HCV-infected group and 92 $\pm$ 22.2 mL/min/1.73 m^2 in the HCV-uninfected group, and mean follow-up was 3.15 $\pm$ 1.4 and 3.00 $\pm$ 1.3 years, respectively. The prevalence of other comorbid conditions and risk factors for kidney disease at baseline are listed in Table 1. Overall, 3,140 (17.4%) participants in the HCV-infected group and 3,738 (14.9%) in the HCV-uninfected group developed CKD stages 3-5 ($P < 0.0001$). Comparing participants with and with-

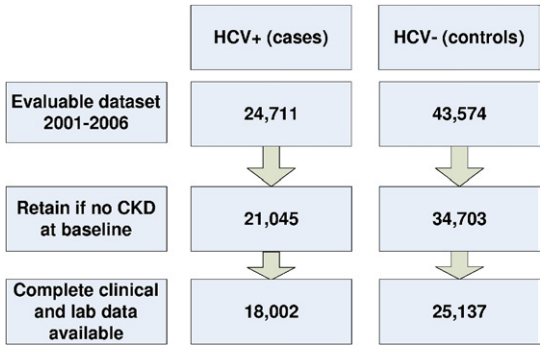

Figure 1. Study flow diagram. Abbreviations: CKD, chronic kidney disease; HCV, hepatitis C virus.

out incident CKD, those with CKD were older and had a higher prevalence of HCV infection at baseline (45.7% vs 41.0%; $P < 0.001$). They also were more likely ($P < 0.001$ for all comparisons) to have a diagnosis of hypertension (72.1% vs 54.5%), diabetes (37.6% vs 22.7%), or chronic obstructive pulmonary disease (19.7% vs 15.6%). Those with CKD were more likely to have evidence of liver injury (45.6% vs 41.6%) and decompensated liver disease (12.8% vs 4.6%) and to have been on ACE-inhibitor/ARB therapy (51.0% vs 33.1%; $P < 0.001$ for all comparisons; data not shown).

In multivariable analysis, HCV infection was associated with a higher risk of developing CKD (hazard ratio [HR], 1.30; 95% confidence interval [CI], 1.23-1.37; Table 2). Black race was associated with a lower risk of developing CKD, whereas increasing age, hypertension, and diabetes were associated with significantly higher risks of developing CKD in HCV-infected patients and controls. Decompensated liver disease was a strong predictor of CKD in HCV-infected patients (HR, 3.37; 95% CI, 3.10-3.66) and HCV-uninfected controls (HR, 2.04; 95% CI, 1.84-2.25). Because there was a significant interaction between the presence of liver injury and decompensated liver disease, we conducted separate analyses with and without liver injury in the model, and the overall associations were not significantly different.

To understand some of the associations, especially with chronicity of HCV infection and decompensated liver disease/liver injury, we compared participants with detectable and undetectable HCV RNA and those with and without decompensated liver disease at baseline within the HCV-infected group (Tables 3 and 4, respectively).

In Kaplan-Meier survival analysis, HCV-infected participants were significantly more likely to develop CKD earlier than HCV-uninfected participants, although the absolute difference between groups was not large (Fig 2). Comparing participants with versus without detectable HCV RNA at baseline, there was no significant difference in time to development of CKD (Fig 3A). However, participants with decompensated liver disease at baseline had a significantly shorter time to the development of CKD compared with those without decompensated liver disease at baseline (Fig 3B).

We conducted multiple sensitivity analyses to validate our study results and understand any potential bias (Tables S1-S3; Fig S1; available as online supplementary material). In HCV-infected and -uninfected participants, those with complete laboratory data were compared with those who were excluded because of incomplete data and found to be similar in terms of demographics and having nearly similar proportions of patients with hypertension, diabetes, dyslipidemia, and ACE-inhibitor/ARB use. We reanalyzed data using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to estimate GFR and found that all baseline variables were similar to analyses using the MDRD Study equation. eGFR was

Table 1. Baseline Characteristics of Participants With and Without HCV Infection

	HCV Infected (n = 18,002)	HCV Uninfected (n = 25,137)	*P*
Age (y)	51.9 ± 7.2	52.8 ± 7.5	<0.001
Race (%)			<0.001
White	55.1	57.4	
Black	33.9	30.9	
Hispanic	1.8	1.9	
Other/unknown	9.2	9.8	
Men (%)	97.3	97.3	0.8
Baseline eGFR (mL/min/1.73 m^2)	99 ± 22.6	92 ± 22.2	<0.001
Cryoglobulinemia (%)	0.11	0.04	0.02
Hypertension (%)	52.4	60.8	<0.001
Smoking (%)	41.6	29.4	<0.001
COPD (%)	17.2	15.6	0.001
Diabetes (%)	22.9	26.6	<0.001
Dyslipidemia (%)	39.3	73.9	<0.001
Anemia (%)	10.3	10.9	0.04
Alcohol abuse or dependence (%)	39.0	16.5	<0.001
Drug abuse or dependence (%)	30.7	9.3	<0.001
Liver injury (%)	70.7	21.9	<0.001
Decompensated liver disease (%)	8.5	4.0	<0.001
ACEi/ARB use (%)	29.7	40.4	<0.001
Follow-up (y)	3.15 ± 1.4	3.0 ± 1.3	<0.001

Note: Values expressed as mean ± standard deviation or percentage.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus.

Table 2. Multivariable Factors Associated With Incident CKD (stages 3-5) in All Participants and by HCV Infection

	Model 1: All Participants	Model 2: HCV Infected	Model 3: HCV Uninfected
Demographics			
Baseline eGFR	0.97 (0.97-0.98)	0.98 (0.98-0.98)	0.97 (0.96-0.97)
Age (/5-y increase)	1.12 (1.10-1.14)	1.12 (1.10-1.15)	1.12 (1.10-1.14)
Race			
White	1.00 (reference)	1.00 (reference)	1.00 (reference)
Black	0.95 (0.90-1.00)	1.02 (0.94-1.10)	0.89 (0.83-0.96)
Hispanic	0.84 (0.70-1.00)	0.65 (0.47-0.90)	0.98 (0.79-1.22)
Other/unknown	0.92 (0.84-1.00)	0.88 (0.76-1.00)	0.96 (0.86-1.08)
Female sex	1.42 (1.24-1.64)	1.25 (1.01-1.56)	1.62 (1.34-1.95)
Risk factors/comorbid conditions			
HCV	1.30 (1.23-1.37)	—	—
Hypertension	1.47 (1.38-1.57)	1.53 (1.40-1.67)	1.41 (1.30-1.54)
Smoking	1.06 (1.01-1.12)	1.06 (0.98-1.14)	1.08 (1.00-1.17)
Chronic obstructive pulmonary disease	1.19 (1.12-1.27)	1.08 (0.98-1.18)	1.31 (1.21-1.42)
Diabetes	1.59 (1.51-1.68)	1.60 (1.48-1.73)	1.57 (1.46-1.69)
Dyslipidemia	1.00 (0.94-1.05)	1.05 (0.98-1.13)	0.95 (0.88-1.03)
Anemia	1.89 (1.77-2.01)	1.77 (1.61-1.95)	2.00 (1.83-2.18)
Alcohol abuse or dependence	1.13 (1.06-1.21)	1.09 (1.00-1.19)	1.17 (1.05-1.30)
Drug abuse or dependence	1.21 (1.12-1.31)	1.26 (1.15-1.38)	1.11 (0.97-1.27)
HCV RNA positivity	—	0.92 (0.85-1.00)	—
Decompensated liver disease	2.70 (2.53-2.87)	3.37 (3.10-3.66)	2.04 (1.84-2.25)
ACEi/ARB use	1.36 (1.28-1.44)	1.44 (1.32-1.57)	1.31 (1.21-1.42)

Note: Analysis was performed using a Cox proportional hazards model. Values expressed as hazard ratio (95% confidence interval).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD chronic kidney disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus.

95.1 ± 15.7 mL/min/1.73 m^2 in the HCV-infected and 90.1 ± 15.6 mL/min/1.73 m^2 in the HCV-uninfected group ($P < 0.001$). Finally, we reanalyzed the risk of CKD in all participants after excluding those with decompensated liver disease at baseline. Results were similar with the exception of HCV infection, which was no longer significantly associated with CKD.

DISCUSSION

There is controversy about the association of HCV infection with the development and progression of CKD.[12,13] We found that HCV infection was associated with the development of kidney disease, although HCV-infected persons had on average a higher baseline eGFR. Our findings contradict the study by Moe et al.[13] They evaluated the association of hepatitis C with CKD in a population of 13,139 individuals in their medical system. HCV infection was not associated with CKD cross-sectionally or longitudinally. In fact, HCV infection was associated cross-sectionally with a lower risk of CKD. It is possible that the lower risk of CKD is an artifact of muscle wasting in liver disease, which decreases creatinine generation. Tsui et al,[14] in an analysis of a National Health and Nutrition Examination Survey (NHANES) population, also found that HCV infection was associated with proteinuria, but not CKD. In contrast to these findings, a prior veterans study found that HCV positivity was associated with the development of ESRD.[12] In that study, the major cause of ESRD was diabetes (43%) or hypertension (26%), not glomerulonephritis.

Risk factors for the development of CKD include diabetes, hypertension, and dyslipidemia.[19] We found that all these factors were less prevalent in HCV-infected persons in our study compared with controls, emphasizing the importance of the HCV itself or other unknown factors on the progression of CKD. Although control of diabetes and hypertension has been well established to slow the progression of kidney disease, aggressive management of dyslipidemia has not been associated with improvement in clinical renal outcomes.[20] In our analysis, dyslipidemia was associated with a higher risk of CKD in the univariable model, but this relationship was not significant in the multivariable model, suggesting that the risk associated with dyslipidemia is mediated through other factors. The finding of a lower prevalence of diabetes is in contrast to conventional wisdom and other studies that have reported a positive association between HCV infection and diabetes. However, this is consistent with our previous finding of a lower prevalence of diabetes in HCV-infected persons on dialysis therapy (28.7% vs 32.2%; $P < 0.001$).[21] The reasons for this are unclear, but because diabetes is associated with alterations in levels of several inflammatory cytokines,[22,23] the relatively immune-suppressed state in

patients with CKD or altered clearance of cytokines may lead to abnormalities in those cytokine levels and consequently a lower risk of diabetes. Further studies are needed to confirm this.

HCV RNA positivity was not associated with CKD. The reasons for this disparity are not clear. HCV-associated glomerulonephritis is associated with HCV RNA positivity, and viral eradication or remission leads to remission of the kidney disease. This suggests that the risk of kidney disease in HCV-infected persons is caused by other mechanisms or is a marker of another unmeasured risk factor. Because ACE-inhibitor/ARB therapy slows the progression of kidney disease in randomized studies, especially in individuals at increased renal risk, the lower use of ACE-inhibitor/ARB therapy in HCV-infected patients and the positive association of ACE-inhibitor/ARB therapy suggest there may be an unmeasured risk. However, we found that risk factors for stages 3-5 CKD were similar for individuals with and without HCV infection. In addition, controlling for these risks did not eliminate the association of HCV infection with CKD.

Table 3. Participant Characteristics by HCV RNA Positivity at Baseline

	HCV RNA+ (n = 11,822)	HCV RNA− (n = 1,793)	*P*
Age (y)	51.9 ± 7.1	52.8 ± 8.4	<0.001
Race (%)			<0.001
White	53.5	67.4	
Black	34.9	20.3	
Hispanic	1.7	2.8	
Other/unknown	9.9	9.5	
Men (%)	97.4	95.8	<0.001
Baseline eGFR (mL/min/1.73 m^2)	98.8 ± 22.3	95.0 ± 21.8	<0.001
Cryoglobulinemia (%)	0.12	0.06	0.5
Hypertension (%)	52.4	54.7	0.08
Smoking (%)	41.6	39.9	0.2
COPD (%)	16.5	20.7	<0.001
Diabetes (%)	23.4	21.6	0.1
Dyslipidemia (%)	36.0	65.7	<0.001
Anemia (%)	10.0	11.4	0.08
Alcohol abuse or dependence (%)	38.2	33.8	<0.001
Drug abuse or dependence (%)	29.8	24.2	<0.001
Liver injury (%)	76.2	32.2	<0.001
Decompensated liver disease (%)	8.4	6.8	0.01
ACEi/ARB use (%)	29.8	31.1	0.3
Follow-up (y)	3.1 ± 1.4	3.1 ± 1.4	0.9

Note: Values expressed as mean ± standard deviation or percentage.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus.

Table 4. Comparison of HCV-Infected Participants With and Without DLD at Baseline

	DLD+ (n = 1,527)	DLD− (n = 16,475)	*P*
Age (y)	52.3 ± 7.2	51.9 ± 7.2	0.04
Race (%)			<0.001
White	67.0	54.0	
Black	23.5	34.8	
Hispanic	2.0	1.8	
Other/unknown	7.5	9.4	
Men (%)	98.1	97.2	0.04
Baseline eGFR (mL/min/1.73 m^2)	107 ± 30.6	97.8 ± 21.6	<0.001
Cryoglobulinemia (%)	0.2	0.1	0.2
Hypertension (%)	52.1	52.4	0.8
Smoking (%)	39.6	41.8	0.1
COPD (%)	18.5	17.1	0.2
Diabetes (%)	34.9	21.8	<0.001
Dyslipidemia (%)	24.4	40.7	<0.001
Anemia (%)	30.6	8.4	<0.001
Alcohol abuse or dependence (%)	52.5	37.8	<0.001
Drug abuse or dependence (%)	29.1	30.8	0.2
ACEi/ARB use (%)	27.8	29.8	0.1
Follow-up (y)	2.43 ± 1.5	3.22 ± 1.4	<0.001
HCV RNA+ at baseline (%)	65.4	65.7	0.01

Note: Values expressed as mean ± standard deviation or percentage.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DLD, decompensated liver disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus.

We found that evidence of liver injury, measured using repeated alanine or aminotransferase level increases, was more common in participants with CKD. Decompensated liver disease was highly predictive of the development of CKD even after adjusting for other risk factors. The magnitude of association was much higher in HCV-infected than HCV-uninfected participants with no overlap in 95% CIs, suggesting a greater role of decompensated liver disease in the risk of CKD in HCV-infected persons. Whether this is a marker of hepatorenal syndrome or another mechanism is unclear at present. The presence of nonalcoholic fatty liver disease has been associated with CKD[24,25] and is more common in HCV-infected persons.[26,27] Whether nonalcoholic fatty liver disease was more prevalent in HCV-infected persons in our study is not known because both nonalcoholic fatty liver disease and chronic HCV infection itself may present as increased alanine/aspartate aminotransfer-

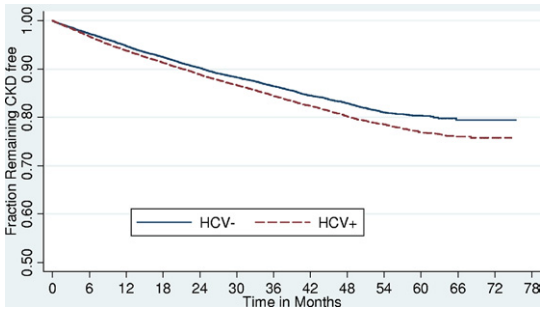

Figure 2. Kaplan-Meier plots show time to onset of chronic kidney disease (stages 3-5) by hepatitis C virus (HCV) status, adjusted for age, race, and sex ($P < 0.001$).

ase levels. Because treatment of HCV has improved steatosis, this presents an attractive strategy for future studies to determine whether such treatment also will improve renal outcomes.

Our study has the advantage of a large national sample and having the availability of information for HCV RNA and ACE-inhibitor/ARB use. The VA has a national screening program for HCV, which decreases the risk of underascertainment. Limitations include the absence of accurate data for proteinuria in the national data set. Proteinuria is a strong predictor of progression of kidney disease, although if HCV contributes to the development of proteinuria, controlling for proteinuria in a model might be overadjusting. We

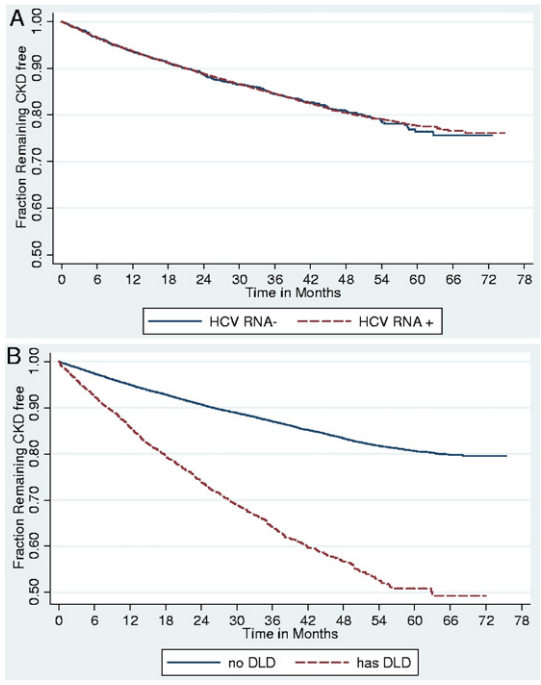

Figure 3. Kaplan-Meier plots show time to onset of chronic kidney disease in the hepatitis C virus (HCV)-infected group, adjusted for age, race, and sex in those (A) with and without detectable HCV RNA ($P = 0.8$) and (B) with and without baseline decompensated liver disease (DLD; $P < 0.001$).

did not analyze the association of individual HCV genotypes on the risk of CKD. We also did not study the effect of other renal insults, for example, nonsteroidal anti-inflammatory drug use, on the risk of CKD. We also did not study the effect of HCV treatment on such risk. However, only ~11% of veterans overall are treated for HCV infection, and for those who develop CKD, treatment with ribavirin is contraindicated.[15]

Some differences between the HCV-infected and -uninfected groups are small in absolute terms, but statistically significant. This is due to the large sample size, and readers should be cautious in making inferences about clinical differences based solely on statistical significance. Additionally, our participants were mostly male veterans, and results should not be generalized to the female nonveteran population without further study.

In conclusion, HCV infection is associated with a higher incidence of and shorter time to the development of stages 3-5 CKD, although many CKD risk factors were less prevalent in the HCV-infected group. This association is not explained fully by HCV infection itself, and the presence of decompensated liver disease, which may be a marker of hepatorenal syndrome, may have a role in this regard. HCV-infected persons should be monitored closely for the development and progression of CKD. Further studies are required to determine the pathogenic mechanism of this association and whether treatment for HCV infection may decrease the risk of CKD.

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SUPPLEMENTARY MATERIALS

Table S1: Multivariable factors associated with incident CKD in all participants, after excluding those with decompensated liver disease at or before baseline.

Table S2. Multivariable factors associated with incident CKD in all participants, using CKD-EPI equation to define CKD.

Table S3. Multivariable factors associated with incident CKD in all participants, using MDRD Study equation to define CKD but decreasing serum creatinine by 5%.

Figure S1. Study flow sheet using CKD-EPI equation to estimate GFR in defining CKD.

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2010.09.023) is available at www.ajkd.org.

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