Hepatitis C Virus Infection and the Prevalence of Renal Insufficiency

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Background: Hepatitis C virus (HCV) is associated with pathologic changes in the kidney. However, the association between HCV and renal dysfunction is not well defined.

Design, setting, participants, and measurements: This study estimated the prevalence of renal insufficiency among veterans who received care through the Veterans Affairs Puget Sound Health Care System. The study population consisted of veterans who underwent HCV antibody testing between January 1, 1999, and December 31, 2004, and had at least one primary care or medical subspecialty visit and at least one outpatient creatinine measurement within the 18 mo before antibody testing. Veterans were excluded when they had a history of chronic dialysis, creatinine >5 mg/dl, or renal transplantation. Study data were extracted from the electronic medical record. Renal insufficiency was defined as a creatinine level ≥1.5 mg/dl. Multivariate logistic regression was performed to estimate the risk for renal insufficiency associated with HCV. Among 25,782 eligible veterans, 1928 were HCV antibody positive and 23,854 were HCV antibody negative.

Results: Although the proportion with renal insufficiency was lower for antibody-positive *versus* -negative veterans (4.8 *versus* 6.0%), after adjustment for age, race, gender, diabetes, and hypertension, HCV-positive veterans had a 40% higher odds for renal insufficiency (odds ratio 1.40; 95% confidence interval 1.11 to 1.76) as compared with HCV-negative veterans.

Conclusions: HCV was associated with an increased prevalence of renal insufficiency.

Clin J Am Soc Nephrol 2: 715-721, 2007. doi: 10.2215/CJN.00470107

Between 1999 and 2002, an estimated 4.1 million people in the United States were infected with hepatitis C virus (HCV), and of these, 3.2 million were chronically infected (1). HCV has been associated with extrahepatic manifestations, including cryoglobulinemia (2,3) and pathologic changes in the kidney. The well-recognized renal manifestations of HCV are membranoproliferative glomerulonephritis (MPGN) (4–7) and membranous nephropathy (5,8,9). Although glomerular (4–6,8–14) and tubulointerstitial (15,16) injuries have been described in association with HCV, the causal role of HCV is not clearly established in the majority of renal lesions that are associated with HCV infection. HCV infection has been associated with albuminuria (17,18), and HCV infection may have a broader impact on glomerular and tubulointerstitial function than currently recognized. The primary aim of this study was to examine whether HCV infection was associated with an increased prevalence of renal insufficiency. To address this objective, we studied a cohort of veterans who received their care at the Veterans Affairs Puget Sound Health Care System (VAPSHCS).

Concise Methods

Patient Population

This was a cross-sectional study among veterans who received care at the VAPSHCS (Seattle and American Lake divisions) in Washington State. The study population consisted of veterans who underwent hepatitis C antibody testing between January 1, 1999, and December 31, 2004, in the VAPSHCS and had at least one outpatient primary care or medical subspecialty visit and at least one outpatient serum creatinine measurement within the 18 mo before antibody testing. Veterans were excluded when they had a serum creatinine >5 mg/dl before antibody testing, evidence of chronic dialysis, or renal transplantation. A serum creatinine >5 mg/dl was used to exclude further potentially prevalent dialysis patients who may have been missed by examining dialysis codes alone. Between 1999 and 2000, HCV testing services began to increase throughout US Northwest VA medical centers, and testing included veterans who were at lower risk for HCV infection (19). Subsequently, in 2001, in response to an HCV Performance Measure that was nationally mandated for VA facilities,

Received January 25, 2007. Accepted May 1, 2007.

Published online ahead of print. Publication date available at www.cjasn.org.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

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ISSN: 1555-9041/204–0715

HCV testing was notably expanded in the primary care clinics and mental health clinics within the VAPSHCS such that testing was encouraged for all patients in these clinics (MC Aldassy, HCV Performance Measures, personal communication, February 2007).

Data Source and Data Collection

Demographics, medical conditions, procedures, vital signs, laboratory studies, and medications were collected from the Consumer Health Information and Performance Sets database, which extracts data directly from the electronic medical records of veterans who receive care within eight Northwest region VA medical facilities (Anchorage, Boise, Portland, Puget Sound, Roseburg, Spokane, Walla Walla, and White City). These facilities make up the Northwest Veterans Integrated Service Network (VISN 20).

Ascertainment of Exposure

The exposure of interest was HCV antibody status (positive *versus* negative). The first antibody test that was performed at VAPSHCS between January 1, 1999, and December 31, 2004, was used to determine HCV antibody status. From January 1, 1999, through March 12, 2003, the VAPSHCS used the Abbott HCV EIA 2.0 assay (Abbott Park, IL). From March 12, 2003, through the end of the study, the VAPSHCS used the Ortho-Clinical Diagnostics Vitro Anti-HCV assay (Rochester, NY). These assays have a ≥92% sensitivity and a ≥98% specificity for detection of HCV (20–24).

Ascertainment of Outcome

The primary outcome of interest was prevalent renal insufficiency, defined *a priori* by a serum creatinine measurement ≥1.5 mg/dl. The serum creatinine closest to the antibody test (and within the 18-mo interval before antibody testing) was examined to evaluate renal function; the serum creatinine measured closest to the HCV antibody test was presumed to approximate the serum creatinine at the time of HCV testing. Given that serum creatinine may misclassify renal insufficiency, a second outcome of interest was the estimated GFR (eGFR), calculated from the abbreviated Modification of Diet in Renal Disease (MDRD) equation (25).

Ascertainment of Covariates

Prevalent medical conditions were identified using a combination of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes, laboratory results, and pharmacy data. Medical records were examined from January 1, 1995, until the time of antibody testing. Diabetes was defined on the basis of the presence of any one of the following: (*1*) Two outpatient ICD-9-CM or one inpatient ICD-9-CM code for diabetes; (*2*) two or more outpatient glucose results ≥200 mg/dl; (*3*) an outpatient glycosylated hemoglobin ≥7%; or (*4*) a pharmacy record of dispensed oral hypoglycemic medications, insulin, or testing supplies. Hypertension was defined by any one of the following: (*1*) ICD-9-CM diagnosis code for hypertension, (*2*) two or more outpatient systolic BP ≥140 mmHg, (*3*) two or more outpatient diastolic BP ≥90 mmHg, or (*4*) a filled prescription for an antihypertensive medication (β blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers). Cardiovascular disease was identified using ICD-9-CM diagnosis codes for coronary artery disease or ICD-9-CM procedural codes for cardiac procedures. HIV infection was defined by either of the following: (*1*) ICD-9-CM diagnosis codes for HIV or AIDS or (*2*) serologic evidence of HIV infection (antibody positive or detectable viral load). Hepatitis B virus (HBV) infection was defined by (*1*) ICD-9-CM diagnosis codes for HBV or (*2*) HBV surface antigen positive serologies.

Statistical Analyses

The χ^2 test evaluated the statistical significance of the unadjusted association of renal insufficiency with HCV infection. Logistic regression was used to compare the unadjusted odds of renal insufficiency in HCV-positive patients with HCV-negative patients and to examine the association of covariates with renal insufficiency. Multiple logistic regression was used to estimate the association between HCV infection and renal insufficiency after adjustment for relevant covariates. Covariates included age, gender, race, diabetes, and hypertension. Multiple imputation (26) was used to impute race for 7188 (28%) patients who had missing race data, based on additional covariate information.

Exploratory analyses examined whether the association between HCV infection and renal insufficiency was affected by age, race, gender, hypertension, or diabetes status. Statistical significance was estimated by likelihood ratio tests comparing logistic regression models with and without appropriate interaction terms. In this analysis, age was included as a continuous variable.

Sensitivity analyses were performed to evaluate whether the association between HCV and renal insufficiency was robust. First, renal insufficiency was evaluated using eGFR as opposed to creatinine measurements. Second, serial measurements of creatinine were examined to distinguish whether renal insufficiency was transient or chronic. Among patients with more then one available creatinine measurement in the 18-mo interval before antibody testing, chronic kidney disease was defined by two or more outpatient serum creatinine measurements ≥1.5 mg/dl, at least 90 d apart.

For examination of whether the association between HCV infection and renal insufficiency was influenced by the presence of co-infection with HIV or HBV, a sensitivity analysis was performed in which all patients with evidence of either HIV or HBV were excluded. All data were analyzed using Stata SE-8 and Stata SE-9 MP statistical software (Stata Corp., College Station, TX). The study was approved by the University of Washington institutional review board.

Results

Descriptive Analyses

Between January 1, 1999, and December 31, 2004, 39,574 veterans were tested for antibody to HCV at the VAPSHCS. Among these veterans, 28,908 (73%) had at least one outpatient encounter and 25,946 (66%) had at least one outpatient serum creatinine measurement within the 18 mo before antibody testing. We excluded 124 (0.5%) veterans because of evidence of a dialysis clinic visit or a serum creatinine level >5 mg/dl and 40 (0.2%) because of history of a previous renal transplantation. After exclusions, 25,782 veterans were included in the study. As compared with HCV antibody–negative veterans, HCV antibody–positive veterans were younger; more likely to have abnormal liver function; and less likely to have prevalent diabetes, hypertension, and coronary artery disease (Table 1).

Univariate and Multivariate Analyses

The unadjusted prevalence of renal insufficiency was lower among HCV-positive patients as compared with those who were HCV negative (4.8 *versus* 6.0%; $P = 0.04$). However, the prevalence of renal insufficiency was strongly age related and was generally higher among HCV-positive patients across most age strata (Figure 1). Male gender, diabetes, and hypertension were also associated with renal insufficiency (Table 2). Before adjustment, the odds ratio (OR) of renal insufficiency, comparing HCV-positive

Table 1. Baseline characteristics[a]

Characteristic	HCV Negative (n = 23,854)	HCV Positive (n = 1928)
Age (yr; mean [SD])	58 (14)	53 (9)
Race (n [%])[b]		
white	13,428 (56)	1152 (60)
black	2801 (12)	308 (16)
other	852 (4)	53 (3)
unknown	6773 (28)	415 (22)
Male gender (n [%])	21,620 (91)	1842 (96)
Diabetes (n [%])	5176 (22)	357 (19)
Hypertension (n [%])	16,417 (69)	1175 (61)
Coronary artery disease (n [%])	5462 (23)	286 (15)
SBP (mmHg; n [%])[c]		
<120	1978 (10)	198 (14)
120 to 139	7825 (41)	587 (42)
140 to 159	7086 (37)	467 (33)
≥160 mmHg	2252 (12)	161 (11)
DBP (mmHg; n [%])[d]		
<80	10,793 (56)	662 (47)
80 to 89	6057 (32)	484 (34)
90 to 99	1888 (10)	223 (16)
≥100	402 (2)	45 (3)
BMI (kg/m^2; n [%])[e]		
<18.5	92 (<1)	12 (1)
18.5 to 24.9	3326 (18)	335 (26)
25.0 to 29.9	6677 (37)	502 (38)
≥30.0	8150 (45)	458 (35)
ALT (U/L; mean [SD])	31 (29)	71 (85)
ALT (n [%])[f]		
0 to 39	9036 (80)	424 (40)
≥40	2195 (20)	631 (60)
Albumin (g/dl; n [%])[f]		
<3.5	164 (2)	58 (8)
≥3.5 to 5.2	6785 (98)	712 (92)

[a]BMI, body mass index; DBP, diastolic BP; HCV, hepatitis C virus; SBP, systolic BP.
[b]After multiple imputation, on average, the distribution of race in HCV-negative patients was white 79%, black 16%, and other 5% and in HCV-positive patients was white 76%, black 20%, and other 4%.
[c]Time-averaged outpatient SBP and [d]time-averaged outpatient DBP for 18-mo interval before antibody test for patients with documented BP. Total number reflects number of patients with outpatient BP measured at least once.
[e]BMI defined by time-averaged outpatient weight for 18-mo interval before antibody test divided by height for patients with both height and weight measured.
[f]Time-averaged outpatient laboratory values for 18-mo interval before antibody test for patients. Total number reflects number of patients with specific outpatient laboratory values measured at least once.

veterans with HCV-negative veterans was 0.80 (95% confidence interval [CI] 0.64 to 0.99; $P = 0.041$). After adjustment for age, the OR for renal insufficiency, comparing HCV-positive veterans with HCV-negative veterans was 1.39 (95% CI 1.11 to 1.74; $P = 0.004$). Further adjustment for gender, race, diabetes, and hypertension did not appreciably change the OR for renal insufficiency associated with HCV (OR 1.40; 95% CI 1.11 to 1.76; $P = 0.004$; Table 2). The strength of association of HCV status with renal insufficiency was generally constant across strata of age, race, diabetes, or hypertension ($P = 0.17$, 0.18, 0.81, and 0.87 for interaction, respectively).

Sensitivity Analyses

The relationship of HCV with renal insufficiency was further explored using alternative definitions of abnormal renal function. Positive HCV antibody status was not significantly associated with an eGFR <60 ml/min per 1.73 m^2 (Table 3). However, positive HCV antibody status was associated with lower eGFR for all other dichotomous eGFR cut points. Associations were strongest for the lowest selected cut points of eGFR. After adjustment, HCV-positive veterans had a nearly two-fold increase in risk for renal insufficiency for eGFR of <40 and <30 ml/min per 1.73 m^2.

To evaluate whether the association between HCV-positive sta-

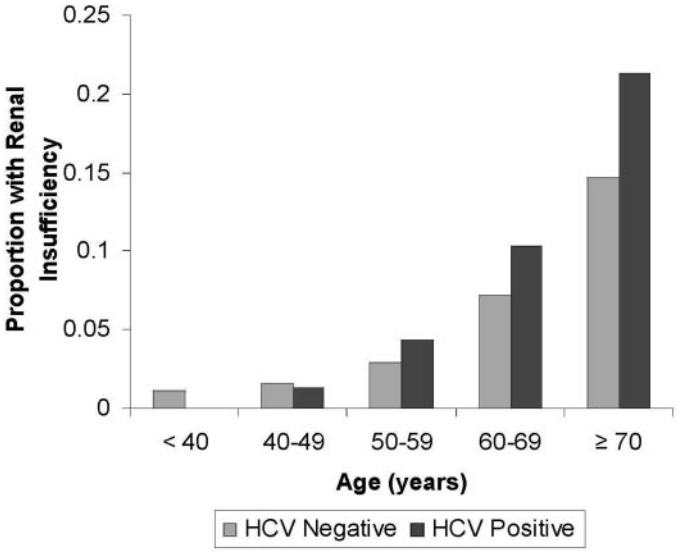

Figure 1. Renal insufficiency stratified by age and hepatitis C virus (HCV) status.

tus and renal insufficiency represented chronic *versus* acute changes in serum creatinine, we examined the risk for a sustained elevation of creatinine. A total of 13,282 (52%) veterans had two or more outpatient serum creatinine measurements, at least 90 d apart, in the 18-mo interval before HCV antibody testing. Of these patients, 12,305 were HCV antibody negative and 977 were HCV antibody positive. After adjustment for age, gender, race, diabetes, and hypertension, the OR for chronic renal insufficiency comparing HCV antibody–positive veterans with HCV antibody–negative veterans was 1.35 (95% CI 0.95 to 1.91; $P = 0.089$).

To examine whether co-infection with HIV or HBV affected the estimated risk for renal disease, we restricted the cohort to those patients without evidence of HIV or HBV infection. Among HCV antibody–negative patients, 132 (0.6%) had evidence of HIV infection, 83 (0.3%) had evidence of HBV infection, and seven (<0.1%) had evidence of both. Among HCV antibody–positive patients, 31 (1.6%) had evidence of HIV infection, 88 (4.6%) had evidence of HBV infection, and four (0.2%) had evidence of both. Removing these 345 patients from the analyses did not appreciably change the association of HCV infection with renal insufficiency (adjusted OR 1.32; 95% CI 1.04 to 1.68; $P = 0.022$).

Discussion

Summary of Findings

Our study found that HCV was associated with an increased prevalence of renal insufficiency, defined by a serum creatinine ≥1.5 mg/dl. The adjusted odds of renal insufficiency was 40% greater among veterans who had a positive HCV antibody test as compared with those who had a negative test. Sensitivity

Table 2. Unadjusted and adjusted odds of renal insufficiency[a]

Parameter	Proportion with Renal Insufficiency (*n* [%])	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b,c]
HCV			
negative	1423 (6)	Reference	Reference
positive	93 (5)	0.80 (0.64 to 0.99)	1.40 (1.11 to 1.76)
Age (yr)			
<40	32 (1)	Reference	Reference
40 to 49	71 (2)	1.46 (0.96 to 2.23)	0.88 (0.58 to 1.36)
50 to 59	244 (3)	2.86 (1.97 to 4.14)	1.40 (0.96 to 2.04)
60 to 69	377 (7)	7.05 (4.90 to 10.15)	3.06 (2.10 to 4.45)
≥70	792 (15)	15.64 (10.95 to 22.34)	7.04 (4.87 to 10.18)
Gender			
male	1504 (6)	Reference	Reference
female	12 (1)	0.08 (0.04 to 0.13)	0.16 (0.09 to 0.28)
Race[c]			
white	1195 (6)	Reference	Reference
black	252 (6)	1.00 (0.86 to 1.15)	1.52 (1.30 to 1.77)
other	69 (6)	0.93 (0.71 to 1.22)	1.18 (0.89 to 1.57)
Diabetes			
absent	859 (4)	Reference	Reference
present	657 (12)	3.04 (2.73 to 3.38)	2.11 (1.89 to 2.36)
Hypertension			
absent	106 (1)	Reference	Reference
present	1410 (8)	6.65 (5.45 to 8.11)	3.31 (2.69 to 4.07)

[a]CI, confidence interval; OR, odds ratio.
[b]Adjusted for all other variables listed.
[c]Analysis using imputed race results.

Table 3. Association between HCV and categories of eGFR[a]

MDRD eGFR (ml/min per 1.73 m^2)	OR[b]	95% CI
<60	1.08	0.88 to 1.33
<50	1.62	1.25 to 2.09
<40	1.83	1.31 to 2.56
<30	1.95	1.23 to 3.11

[a]MDRD eGFR, estimated GFR calculated from the abbreviated Modification of Diet in Renal Disease equation.
[b]Adjusted for age, gender, race, diabetes, and hypertension.

analyses that were restricted to veterans who had at least two available outpatient creatinine measurements demonstrated similar findings to those observed when examining a single measurement, suggesting that HCV is associated with a greater risk for chronic kidney disease.

In our study, the primary outcome of interest was serum creatinine We selected a creatinine cutoff that was consistent with renal dysfunction (27). However, because of the importance of using eGFR in addition to creatinine to assess renal function, we additionally performed sensitivity analyses using eGFR as the outcome of interest. We found associations of HCV infection with renal insufficiency using lower eGFR cut points to define renal dysfunction but did not find a significant association using a definition based on an eGFR <60 ml/min per 1.73 m^2. The association of HCV infection with renal dysfunction at the population level has been examined by Tsui *et al.* (18). Using the Third National Health and Nutrition Examination Survey (NHANES III) data, these authors examined whether HCV infection was associated with an increased risk for renal dysfunction. The investigators did not find an increased risk for renal disease, defined by an eGFR <60 ml/min per 1.73 m^2. Although our study populations differed and we did not calibrate measured serum creatinine levels to the MDRD laboratory, their findings are similar to those observed in our study. In our study, HCV infection was associated with an increased risk for renal insufficiency only when renal insufficiency was defined as an eGFR <50 ml/min per 1.73 m^2. One possible explanation is that HCV infection leads to substantial renal injury rather than mild disease. A second potential explanation is that the abbreviated MDRD equation misclassifies eGFR at lower levels of creatinine, because calculated values separate from those in the original MDRD patient sample (25,28). A third possibility is that the long-standing duration of HCV infection that was likely present in our study population is responsible for greater functional renal impairment. Discordant results according to different definitions of kidney impairment highlight the potential for misclassification of kidney function in observational studies.

Potential mechanisms to explain the observed association of HCV infection with renal insufficiency include direct HCV-related renal injury and HCV-related cirrhosis with subsequent renal impairment. Whether the observed risk for renal dysfunction is secondary to well-described pathologic renal manifestations of HCV or to a spectrum of underrecognized renal disturbances is unknown. In cryoglobulinemic MPGN, the primary hypothesis is that circulating immune complexes (consisting of HCV antigen, IgG directed toward HCV, and IgM with rheumatoid factor activity) deposit in the glomeruli to produce renal injury (7). In people with HCV and cryoglobulinemic MPGN, electron microscopy has demonstrated viral-like particles in the paramesangial regions (4), and HCV-related proteins in the glomerular and tubulointerstitial vascular structures have been isolated (29). In people with membranous nephropathy and HCV infection, potential mechanisms of renal injury include circulating immune complexes with glomerular deposition, formation of immune complexes within glomeruli, or autoantibodies directed toward a renal antigen (8). Immune complexes with HCV core antigen have been isolated in the glomeruli of people with HCV and membranous nephropathy (30). It remains unclear whether HCV RNA represents HCV functioning as a renal pathogen or is simply present in renal cells of infected individuals (31). Finally, HCV may result in renal insufficiency through its effect on the liver. Cirrhosis is associated with alterations in renal blood flow (32,33) and decreased immune complex clearance (34–36), resulting in renal injury.

In addition to numerous studies demonstrating an association between HCV and pathologic renal findings, the clinical course of renal disease after initiation of HCV therapy suggests a direct relationship between HCV and renal disease. Johnson *et al.* (37) observed a significant reduction in proteinuria when patients with HCV infection were treated with IFN-α; the remission of proteinuria corresponded with whether viremia was suppressed during therapy. After discontinuation of therapy, both recurrence of viremia and proteinuria were observed. Other studies (38,39) have demonstrated an improvement in HCV-related renal disease associated with response to treatment, supporting a direct relationship between HCV infection and renal disease.

HIV and/or HBV co-infection is found among some HCV-infected individuals. HBV (40–42) and HIV (43–46) both have been linked with pathologic renal manifestations. Our sensitivity analysis that excluded patients with HIV and/or HBV found a persistent association of HCV with a greater odds of renal insufficiency.

Limitations

There are several limitations to this study. First, the cross-sectional design does not establish whether HCV infection preceded the development of renal impairment. The study population existed primarily of white male veterans, and the findings may not be generalizable to other populations. Neither of the assays that were used during the study interval were 100% sensitive or specific for the detection of hepatitis C, therefore resulting in potential misclassification of the exposure. However, this type of misclassification of the exposure would likely have resulted in an underestimation of the true excess prevalence of renal insufficiency associated with HCV infection. Therefore, the frequency of renal insufficiency in HCV-

infected individuals may be higher than that observed in our study. Another limitation of our study is the ascertainment of renal function; although serum creatinine and equations to estimate GFR are commonly used outcomes in studies of renal function, in patients with cirrhosis, both the serum creatinine and the eGFR based on the MDRD equation may not accurately reflect renal function. Several factors, including decreased muscle mass and decreased creatinine production in patients with cirrhosis, can lead to lower serum creatinine levels and overestimation of GFR in patients with liver disease (47). In this regard, some cases of renal insufficiency may have been missed in the HCV-positive group. The use of ICD-9-CM codes to ascertain comorbidity may misclassify important comorbid conditions. We included additional variables, such as vital signs, dispensed medications, and laboratory results, in our analyses to improve the precision of comorbidity assessment. Furthermore, it is possible that HCV infection is a surrogate for some other factor, such as heroin use, which was not measured in our study and accounts for observed differences in renal function. However, the epidemiology of heroin-associated nephropathy has changed in recent years (48), and a study of renal biopsies in white male heroin users found that all individuals had evidence of HCV infection and the majority of renal pathologic lesions were MPGN (49). Therefore, even in individuals who may have used heroin, HCV is likely to represent an important component of renal dysfunction. Finally, we did not evaluate hepatitis C viremia in our sample. It is possible that the association between HCV and renal insufficiency may depend on the presence of active viremia. However, approximately 78% of antibody-positive individuals have evidence of chronic viremia (1).

Conclusion

We demonstrated that after adjusting for age, gender, race, diabetes, and hypertension, HCV was independently associated with an increased prevalence of renal insufficiency, defined by a serum creatinine $\geq$1.5 mg/dl or eGFR $<$50 ml/min per 1.73 m^2. Our findings identify HCV infection as a potential risk factor for renal impairment and motivate future population-based research regarding HCV infection and kidney disease. Our study extends previous findings, having evaluated different definitions of renal dysfunction and viral co-infections, and identifies prevalent renal insufficiency as a potentially important clinical problem in HCV-infected individuals. Further studies should determine whether HCV infection is a risk factor for incident chronic kidney disease and whether chronic viremia, HCV treatment, or co-infection with HIV influences the risk for renal disease associated with HCV infection.

Acknowledgments

The research reported here was supported by Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service, grant TPA 61-030.

Parts of this article were previously published as an abstract and presented as a poster at the annual meeting of the American Society of Nephrology; November 8 through 13, 2005; Philadelphia, PA.

Disclosures

None.

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