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ORIGINAL ARTICLE

Higher prevalence of chronic kidney disease and shorter renal survival in patients with chronic hepatitis C virus infection

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Abstract
Background The role of hepatitis C virus infection (HCV) in the etiology and progression of chronic kidney disease (CKD) is controversial.
Aim To measure the prevalence of CKD and evaluate its course in patients with chronic HCV infection.
Methods A retrospective analysis was done after excluding patients with nephrolithiasis, structural kidney disease, and those with missing clinical information on 552 anti-HCV-positive patients and 313 patients without known HCV infection matched for age, race, and gender. CKD was defined as estimated glomerular filtration rate value of <60 mL/min/1.73 m^2 and/or persistence of proteinuria (>3 months) on urine analysis by dipstick. Viral load obtained during the initial evaluation was defined as "baseline viral load".
Results The prevalence of CKD in the anti-HCV-positive group was significantly higher compared to control group [53 (9.6%) vs. 16 (5.1%), $P = 0.02$]. On multivariate regression analysis, higher age, hypertension, HCV PCR $> 7 \times 10^5$ cps/mL, and diabetes mellitus were significant independent positive predictors, whereas history of interferon treatment was significant independent negative predictor for CKD. Male gender, human immunodeficiency virus status, body weight, intravenous drug use, and HCV genotype were not predictors of CKD. Analysis of renal survival through Kaplan–Meyer curves revealed significantly shorter time to develop CKD (74 vs. 84 months, $P < 0.001$; log rank) and end-stage renal disease (79.9 vs. 86.5 months, $P = 0.005$; log rank) in the HCV group compared to the control group.
Conclusion Chronic HCV infection was associated with a significantly higher prevalence of CKD compared with controls, as well as significantly shorter renal survival. A higher baseline viral load is an independent predictor of CKD.

Keywords Hepatitis C · Chronic kidney disease · Renal survival

A preliminary version of the study was presented in the plenary session at the annual scientific meeting of the American college of gastroenterology, San Diego, CA and was awarded with the 2009 ACG auxiliary award for the best scientific paper (Trainee). The American Journal of Gastroenterology 2009; 358:S315.

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Introduction

Many studies have implicated a potential role of hepatitis C virus (HCV) infection as a cause of chronic kidney disease (CKD). Chronic infection with HCV is known to cause glomerular diseases [1–3]. Using data from the Third National Health and Nutrition Examination Survey, two studies have found an increased risk of albuminuria in patients with hepatitis C [4, 5], and another study found an increased risk of developing end-stage renal disease (ESRD) [6]. The prevalence of serum positive for antibody to hepatitis C among CKD patients who were never

transfused has been reported to be about ten times higher than that of blood donors [7]. The progression of diabetic nephropathy has been reported to be more rapid when patients were infected with HCV [8, 9], and other studies also found the presence of hepatitis C viral particles or antigens in glomeruli or tubules of kidney biopsy specimens [3, 10, 11]. Although these data support that hepatitis C may also cause CKD, conflicting data also exist [12].

We hypothesized that infection with HCV increases the risk of developing CKD and accelerates the progression to CKD. To test our hypothesis, we compared a cross section of hepatitis C positive patients with age-, race-, and sex-matched controls without known HCV infection. We retrospectively followed these populations from their first hospital visit until their last follow-up visit to assess the risk of developing CKD.

Subjects and methods

Study groups

Patients and definitions

The study was conducted at the Metropolitan Hospital Center. All consecutive patients with serum positive for antibody to hepatitis C, seen at the outpatient gastroenterology as well as medicine clinic between January 2003 and October 2006 were enrolled into this study. Controls were selected from a list of 1,847 consecutive patients after filtering out HCV-infected patients (hepatitis C diagnosis based on the ICD code) seen at the outpatient gastroenterology clinic over a period of 1 year from October 2005 to October 2006. Charts and electronic medical records were further reviewed for any documented serum positive for antibody to HCV and were excluded if found positive from the primary control list. Patients were then sorted out based on their age, race, and gender in that order. The best possible match for each HCV-infected patient was then selected from the control list with the clinician having been blinded to the clinical information of the patients. For this study, data were reviewed from patient's first visit on or after 1 June 1999 when the electronic record came into effect at our institution. Follow-up data of renal functions were longitudinally reviewed until October 2006, which included all inpatient and outpatient visits.

All patients with at least one measurement of serum creatinine were included in the study. Charts and electronic medical records of 568 patients with chronic HCV infection based on anti-HCV-positive status were reviewed. Of the 568 patients with anti-HCV-positive status, 9 patients were lacking serum creatinine measurements and were excluded. A total of 349 age-, race-, and sex-matched controls were identified, 26 of these were further excluded due to lack of data on serum creatinine measurements. Subsequently, 5 of the remaining 559 anti-HCV-positive patients, and 9 of the remaining 323 control group of patients were excluded due to missing clinical information, duplicate charts, or inability to retrieve old records for review. Two further patients from the HCV group and one from the control group were excluded due to presence of structural kidney disease and nephrolithiasis in them, respectively. Thus, 552 patients with anti-HCV-positive status were compared with 313 age-, race-, and gender-matched controls. HCV PCR was negative on initial evaluation of 50 (9.1%) subjects from the anti-HCV-positive group, and HCV viral load was not available in another 51 (9.2%) subjects. Of the 313 controls, 154 patients were confirmed negative for anti-HCV and the rest had no suspicion for the same and had normal liver function tests (LFTs). Reason for their visit to the gastroenterology and hepatology clinic is summarized in Table 1.

Data on liver biopsy were available for 45 (8.2%) of the 552 anti-HCV-positive patients, 11 of them had advanced liver disease (stage $\geq$3). An additional 22 (4%) patients had imaging evidence of cirrhosis (surface nodularity in the liver and/or esophageal varices or ascites).

CKD was defined by two differing definitions as described below.

CKD by serum creatinine methods

CKD was defined by either persistence of proteinuria on urine analysis by dipstick and/or a serum creatinine of >1.5 mg/dL in men and >1.3 mg/dL in women for >3 months.

CKD as defined by kidney disease outcomes quality initiative guidelines

According to Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, the criteria for definition of CKD are the presence of glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for $\geq$3 months, with or without kidney damage, or the presence of kidney damage for $\geq$3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by either pathological abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging test [13].

GFR was estimated with the simplified version of the modification of diet in renal disease (MDRD) equation including four variables (age, gender, creatinine, and race). According to MDRD equation, GFR (mL/min/1.73 m^2) is calculated as $186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742, \text{if female}) \times (1.210, \text{if black})$. Subsequent to GFR

Table 1 Disease entity or reason for visit to the outpatient gastroenterology clinic in the control group

Disease entity/reason for visit	*N* (%)
Abdominal pain	27 (8.6)
Abnormal LFT	35 (11.2)
Anemia	41 (13.1)
Gastroesophageal reflux disease	41 (13.1)
Colon cancer	3 (1)
Gastric cancer	2 (0.6)
Colitis (unspecified)	5 (1.6)
Inflammatory bowel disease	2 (0.6)
Dysphagia	1 (0.3)
Fatty liver	7 (2.2)
Helicobacter pylori gastritis	4 (1.3)
Rectal bleed	1 (0.3)
Hepatitis B	19 (6.1)
Hemangioma liver	2 (0.6)
Irritable bowel syndrome	3 (1)
Liver mass	2 (0.6)
Malabsorption	2 (0.6)
Nonalcoholic steatohepatitis	6 (1.9)
Nausea	1 (0.3)
Primary biliary cirrhosis	1 (0.3)
Sarcoidosis	1 (0.3)
Ulcerative colitis	10 (3.2)
Unspecified diagnosis[a]	97 (31)

[a] Majority patients in the control group with unspecified gastrointestinal diagnosis were referred for screening colonoscopy and were otherwise healthy

estimation, patients were classified according to CKD stage, as indicated in the K/DOQI guidelines: stage 1 (GFR $>$ 90 mL/min/1.73 m^2); stage 2 (GFR = 60–90 mL/min/1.73 m^2); stage 3 (GFR = 30–59 mL/min/1.73 m^2); stage 4 (GFR = 15–29 mL/min/1.73 m^2); and stage 5 (GFR $<$ 15 mL/min/1.73 m^2).

In the present study, patients with GFR $\geq$ 60 mL/min were classified as having CKD stage 1 or 2 only when renal damage was observed, and it was defined as: urine positive for protein in two or more consecutive tests conducted 3 months apart. Proteinuria was defined in the current study as a urinary protein excretion of $\geq$30 mg/dl by dipstick test.

For the purpose of this study, patients with single available creatinine measurement with GFR $>$ 60 mL/min/1.73 m^2 were classified as not having CKD. However, patients with a single abnormal creatinine value with GFR $<$ 60 mL/min/1.73 m^2 were omitted from the CKD group during the analysis. Diagnosis of CKD was based only on estimates of GFR derived from at least two available serial serum creatinine measurements 3 months apart for each outpatient visit for the period until October 2006. The last available serum creatinine measurement was used for CKD staging. If this measurement was abnormal, the preceding serum creatinine value was further scrutinized for evidence of any acute rise to rule out acute renal failure. Acute renal failure was defined as an increase in serum creatinine ($\leq$2 days) of (1) 0.5 mg/dL for patients with baseline serum creatinine level of $<$2.0 mg/dL, (2) 1.0 mg/dL with baseline 2.0–5.0 mg/dL, and (3) 1.5 mg/dL with baseline $\geq$5.0 mg/dL. For the purpose of CKD staging, the value of serum creatinine prior to the acute rise was used.

Etiologies of the CKD were looked for based on the evaluations available from the medical chart review. We used the primary renal diagnosis as determined by the treating nephrologist. When no primary renal diagnosis was given, diabetic nephropathy was defined if there was presence of retinopathy, micro- or macro-albuminuria, and diagnosis of DM for $\leq$5 years, and there was no other obvious renal cause to attribute for the CKD.

Serological methods

A positive hepatitis C test result was defined as a positive antibody result by means of first-, second-, or third-generation enzyme-linked immunosorbent assay with or without immunoblot assay confirmation. Patients with serum positive for antibody to hepatitis C were further scrutinized for detectable HCV-RNA (RT-PCR) if available from review of the medical records. HCV genotypes were recorded whenever available. Baseline viral load was defined as the date of the first test result if viral loads were negative prior or the initial viral load available in the medical records on or after June 1999 before initiation of any antiviral therapy.

Comorbidities definitions and laboratory data

We looked for potential confounders of the relationship between hepatitis C status and CKD, including age, race, gender, body weight, and comorbidities such as: diabetes mellitus (DM), hypertension, human immunodeficiency virus (HIV), hepatitis C viral load at baseline, presence or absence of decompensated liver disease, and history of intravenous drug abuse (IVDU). Hypertension was defined as a blood pressure of $\geq$140/90 mmHg and/or on antihypertensive medication. Patients were designated as having DM if history of the diagnosis was recorded in the chart, or the patient was on glucose-lowering medications.

Statistical analysis

Data are expressed as mean $\pm$ standard deviation. Non-parametric data are expressed as median with respective ranges. Group comparisons were made by Mann–Whitney

test for continuous data. Chi-square test (with Yates correction if indicated) and Fisher's exact test were used for nominal or categorical data. Both univariate and multivariate logistic regression analyses were conducted with chronic renal failure as the dependent variable, with age, gender, presence or absence of DM, hypertension, HIV, history of IVDU, and HCV viral load as covariates. A P value of 0.05 was used to indicate statistical significance. Renal survival was estimated by Kaplan–Meyer survival analysis using log rank (Mantel–Cox) test, and the end point for renal survival was calculated as time to develop CKD and ESRD. For estimation of time to develop CKD, duration of follow-up was censored at the date on follow-up when the GFR started remaining persistently <60 mL/min/1.73 m^2. For patients with GFR > 60 mL/min/1.73 m^2 but with persistent proteinuria, the last date of follow-up was utilized as the date for CKD. ESRD was defined as the time when patient needed renal replacement therapy. For estimation of time to develop ESRD the last GFR value prior to initiation of renal replacement therapy was used for the comparison of renal survival by Kaplan–Meyer survival analysis using log rank (Mantel–Cox) test. Statistical analysis was performed using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL).

Results

Baseline characteristics and demographics

The prevalence, severity, and characteristics of CKD were compared among 552 patients with chronic HCV infections and 313 controls without known HCV infection. As summarized in Table 2, HCV group and the controls were well matched in relationship to age, race, and gender at baseline. Majority of the included patients were of Hispanic and African–American origin. However, a significant number of the patients in the HCV group had history of IVDU [128 (23.2%) vs. 6 (1.9%), $P < 0.0005$] and positive HIV status [42 (7.6%) vs. 4 (1.3%), $P < 0.0005$].

Prevalence of CKD in the study population

Estimation of CKD by creatinine method revealed 37 (6.7%) patients in the HCV group developed CKD compared to 11 (3.5%) in the control group without known HCV infection (Pearson Chi-square, $P = 0.05$). When patients with proteinuria were also added to the patients with CKD by creatinine estimation method, 43 (7.8%) patients with serum positive for anti-HCV antibody could be categorized as having CKD compared to 13 (4.2%) controls ($P = 0.04$) (Fig. 1).

Table 2 Demographic characteristics of patients with chronic hepatitis C compared with controls

Characteristics	HCV group ($N = 552$)	Control group ($N = 313$)	P value
Male (%)	377 (68.3)	201 (64.2)	0.25
Weight (kg)	79.6 ± 18.6	78.2 ± 17.2	0.47
Mean age ± SD	50 ± 10.6	50 ± 11.4	0.37
Race, N (%)			
Blacks	154 (27.9)	90 (28.8)	0.85
Hispanics	344 (62.3)	198 (63.3)	0.84
Whites	22 (4)	11 (3.5)	0.87
Others	32 (5.8)	14 (4.5)	0.45
DM, N (%)	105 (19)	51 (16.3)	0.36
Hypertension, N (%)	217 (39.3)	117 (37.4)	0.63
HIV, N (%)	42 (7.6)	4 (1.3)	<0.0005
History of IVDU, N (%)	128 (23.2)	6 (1.9)	<0.0005
History of alcohol abuse, N (%)	109 (19.7)	59 (18.8)	0.82

Data are presented as mean ± SD and number (%)

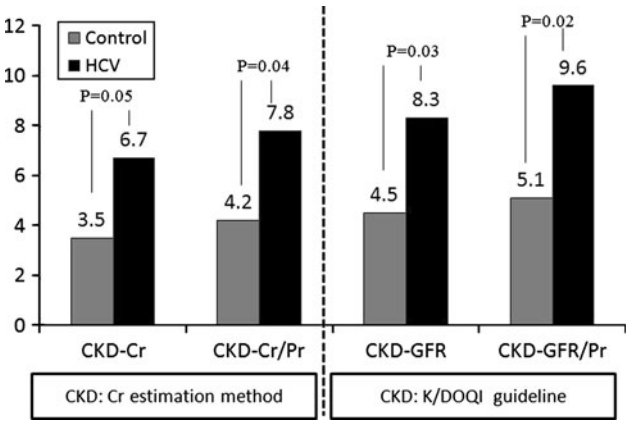

Fig. 1 Prevalence of CKD in patients with HCV infection compared with controls. (CKD-Cr indicates CKD defined by serial creatinine measurement, CKD-Cr/Pr indicates CKD defined by serial creatinine measurement and proteinuria, CKD–GFR indicates CKD defined by serial eGFR estimation, CKD-GFR/Pr indicates CKD defined by serial eGFR and proteinuria)

On a cross-sectional analysis based on the initial evaluation (first visit to the hospital), GFR < 60 mL/min/1.73 m^2 was noted in 16 (5.1%) of 314 controls compared to 26 (4.7%) of 552 anti-HCV-positive patients ($P = 0.79$). Nonspecific isolated elevation or acute renal failure accounted for the decline in GFR in 6 patients in the control group and 8 patients in the HCV group. Thus at the baseline, 10 (3.2%) of 314 controls compared to 18 (3.3%) of 554 had CKD by four-variable MDRD method ($P = 0.96$). Longitudinal analysis of serial GFR values until the last available follow-up or until the defined time

period (whichever was last), as noted in the method section CKD (stage ≥3 by four-variable MDRD GFR estimation), revealed a significantly higher prevalence of CKD in the HCV group compared to the controls [46 (8.3%) vs. 14 (4.5%), $P = 0.03$]. When patients with proteinuria were also added to the estimated GFR (eGFR) group as defined by the modified K/DOQI guidelines, 53 (9.6%) of the anti-HCV-positive group patients could be categorized as having CKD compared to 16 (5.1%) patients in the control group ($P = 0.02$). After exclusion of the 50 (9.1%) HCV PCR negative subjects and 51 (9.2%) without an available viral load, the prevalence of CKD in the 451 HCV RNA positive patients was 9.1% ($N = 41$). On a comparative note, the prevalence of CKD in the HCV RNA positive patients was still significantly higher compared to the controls [41 (9.1%) vs. 16 (5.1%), $P = 0.04$].

As serial serum creatinine measurements underestimated the true prevalence of CKD compared to K/DOQI guidelines, we made the latter as the basis for eGFR estimation by four-variable MDRD equations in all our further evaluations. Age-specific prevalence of CKD in the HCV group and the control group is shown in Fig. 2. As represented in Fig. 2, there was trend for higher prevalence of CKD with increasing age in both HCV and control populations, although this trend was higher in the HCV group and was more pronounced after the age of 60 years.

Advanced liver disease (defined as stage ≥3 or imaging evidence of cirrhosis) was present in 33 (6%) patients with chronic hepatitis C infection. A significantly higher prevalence of CKD was noted in these groups of patients with documented advanced liver disease compared to patients who had a liver biopsy and had less severe liver disease (stage <3) [10 (30.3%) of 33 vs. 3 (8.8%) of 34, $P = 0.02$]. After exclusion of the patients with advanced liver disease as defined above, a trend for numerically higher prevalence of CKD persisted in the anti-HCV-positive patients [43 (8.3%) vs. 16 (5.1%), $P = 0.08$].

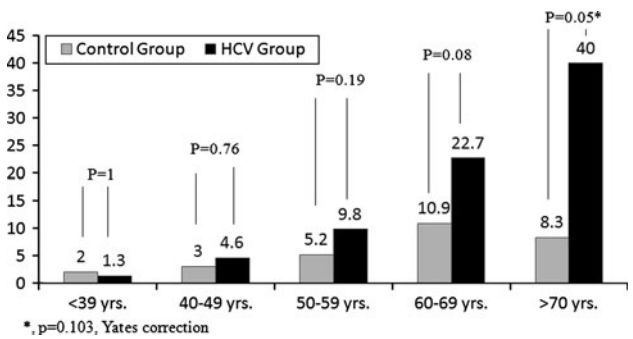

Fig. 2 Age-specific prevalence of CKD in patients with HCV infection compared with controls without known HCV infection. (*$P = 0.103$, Yates correction)

We then tried to look for any additive effect of DM, hypertension, and body weight on the prevalence of CKD in the HCV group, and further compared this with the control group. Prevalence of CKD was comparable in the HCV group with DM and controls with DM [23 (21.9%) vs. 7 (13.7%), $P = 0.22$]. When patients with DM were excluded from the HCV and the control group and the prevalence of CKD was compared again, a trend for higher prevalence of CKD was noted in the HCV group than in the control group which did not reach statistical significance [30 (6.7%) vs. 9 (3.4%), $P = 0.06$]. Also when HCV group with hypertension was compared with control group with hypertension, no significant difference was noted in the prevalence of CKD [40 (18.4%) vs. 14 (12%), $P = 0.12$]. When patients were categorized into higher (>75 kg) and lower (<75 kg) body weight, no significant difference was noted between HCV group and control group with higher body weight [20 (7.9%) vs. 9 (5.7%), $P = 0.39$].

Baseline variables were further compared between HCV patients with CKD and controls with CKD. No specific variables could be identified to be significantly prevalent in any specific group, although mean weight appeared to be higher in the control group with CKD. Results are summarized in Table 3.

Prevalence of proteinuria in HCV group and controls

Urine analysis for proteinuria was available in 425 (77%) patients from the anti-HCV-positive group and 274 (87.5%) from the control group. Proteinuria was noted in a significantly higher number of patients with chronic HCV infection

Table 3 Demographic characteristics of patients with chronic hepatitis C with CKD compared to controls with CKD

Characteristics	HCV patients with CKD ($N = 53$)	Controls with CKD ($N = 16$)	p-value
Male (%)	35 (66%)	10 (62.5%)	0.79
Weight (kg)	74.2 ± 17.5	88 ± 24	0.06
Mean age ± SD	58.7 ± 9.1	56.7 ± 11.8	0.48
Race, *N* (%)			
Blacks	15 (28.3)	7 (43.8)	0.24
Hispanics	34 (64.2)	7 (43.8)	0.14
Whites	3 (5.7)	1 (6.3)	1
Others	2 (3.8)	1 (6.3)	0.55
DM, *N* (%)	23 (43.4)	7 (43.8)	0.98
Hypertension, *N* (%)	40 (75.5)	14 (87.5)	0.49
HIV, *N* (%)	7 (13.2)	1 (6.3)	0.67
History of IVDU, *N* (%)	12 (22.6)	1 (6.3)	0.27
History of alcohol abuse, *N* (%)	7 (13.2)	6 (37.5)	0.06

Data are presented as mean ± SD and number (%)

Table 4 Potential etiology of CKD in hepatitis C patients and controls with various range of proteinuria

Proteinuria	Control patients $N = 8$			HCV patients $N = 29$		
	Total (*N*)	Etiology	*N*	Total (*N*)	Etiology	*N*
Nephrotic range	3	DM	2	9	NS	5
		Amyloidosis	1		DM	1
					HIV	1
					Unknown	2
Non-nephrotic range	5	Unknown	3	20	Unknown	8
		DM	1		DM	7
		HIV	1		HIV	2
					Recurrent ARF	1
					HTN	1
					Cryoglobulinemia	1

NS nephrotic syndrome, *ARF* acute renal failure, *HTN* hypertension

[29 (6.8%) vs. 7 (2.9%), $P = 0.02$]. Among the patients with proteinuria, nephrotic range of proteinuria was noted in 9 (2.1%) HCV-infected patients compared to 3 (1.1%) in the control group ($P = 0.39$). However, a significantly higher number of patients with non-nephrotic range of proteinuria was noted in HCV-infected patients compared to CKD patients in the control group [20 (4.7%) vs. 5 (1.8%), $P = 0.04$]. When only patients with DM of both groups were compared no significant difference in the proteinuria was noted [14 (14.6%) of 96 vs. 4 (8.2%) of 49, $P = 0.27$], however upon exclusion of the diabetic patients there was a trend for higher prevalence of proteinuria in the HCV group [15 (4.6%) of 329 vs. 4 (1.8%) of 225, $P = 0.07$].

Potential etiologies of the CKD patients with various range of proteinuria are shown in Table 4. Proteinuria was noted in 29 of the 53 HCV patients with CKD and 8 of the 16 controls. Etiology of the CKD was unknown in 24 (45.3%) of the 53 patients with serum positive for anti-HCV. Nephrotic range of proteinuria was noted in 9 (17%) of the 53 CKD cases; 5 of the 9 had no potential etiology other than HCV. Renal biopsy was available in 4 of the 5 cases without any clear etiology for the nephrotic syndrome. Most common lesion on renal biopsy was focal and segmental glomerulosclerosis (FSGS), which was noted in 3 cases, and in one case, FSGS variant membrano-proliferative glomerulonephritis was noted. Among the 20 (37.7%) of the 53 CKD patients with non-nephrotic range of proteinuria no potential etiology could be identified in 8. Of the 16 CKD cases in the control group only 3 (18.7%) had nephrotic range of protenuria, and 5 had non-nephrotic range of proteinuria.

Viral load and effects of interferon-based therapy

Data on HCV viral load at baseline were available in 451 (81.7%) of the patients. The mean viral load was not significantly different at baseline in the group that developed CKD compared to those who never developed CKD [(4.64 ± 3.32) vs. $(4.58 \pm 5.56) \times 10^5$ cps/mL; $P = 0.24$]. However, when we performed a sensitivity analysis using a series of cut-offs for viral loads ranging from 4×10^5 cps/mL through 8×10^5 cps/mL, the frequency of patients having viral load above the specific cut-off level of 6×10^5 was significantly high in those with CKD compared to those without CKD. This trend persisted with higher cut-off levels as well (Fig. 3). Only 4 (7.5%) of the 53 patients with CKD received interferon (IFN) therapy compared to 155 (31.1%) of 499 without CKD ($P < 0.0005$) during the observation period. Total 9 (17%) of the 53 patients did not receive treatment secondary to decompensated liver disease. None of the 3 patients who received IFN-based therapy in the CKD group had a sustained virologic response. Genotype was available in only 34 of the 55 patients who developed CKD, 27 (79.4%) of the 34 had genotype-1 infection.

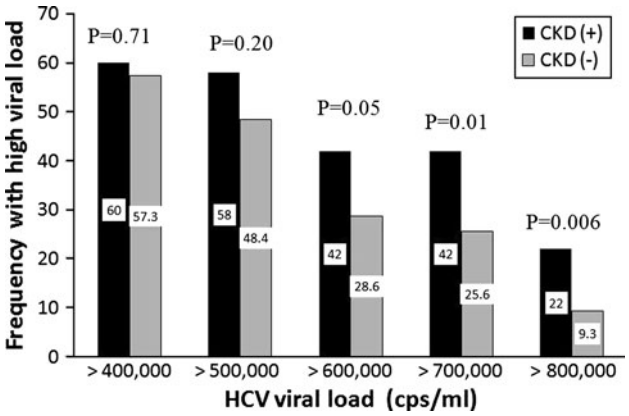

Fig. 3 Frequency of high viral load at various cut-off levels ranging from 4×10^5 to 8×10^5 with and without CKD in patients with chronic HCV infections

Predictors of CKD

Both univariate and multivariate logistic regression analyses were performed to determine the predictors for CKD

Table 5 Univariate and multivariate logistic regression analyses for predictors of CKD in patients with serum positive for antibody for HCV

	Univariate regression analysis					Multivariate regression analysis				
	Regression estimate	*P* value	OR	95% CI		Regression estimate	*P* value	OR	95% CI	
				Lower	Upper				Lower	Upper
Hypertension	1.72	<0.001	5.60	2.92	10.74	0.98	0.02	2.68	1.15	6.22
Body weight	–0.02	0.03	0.98	0.96	0.99	–0.01	0.15	0.98	0.96	1.01
HCV PCR (>700,000) cps/mL (Baseline)	0.74	0.01	2.10	1.16	3.83	0.90	0.01	2.45	1.21	4.98
Age	0.09	<0.001	1.09	1.06	1.13	0.05	0.004	1.06	1.01	1.10
Gender (being male)	–0.11	0.71	0.89	0.49	1.62					
HIV status	0.70	0.11	2.11	0.85	4.80					
DM	1.36	<0.001	3.90	2.16	7.05	0.86	0.02	2.37	1.14	4.91
Hx of Etoh abuse	–0.52	0.21	0.59	0.26	1.35					
Intravenous drug abuse	0.03	0.92	0.97	0.49	1.90					
Race (being Black)	0.02	0.94	1.02	0.54	1.92					
Race (being Hispanic)	0.09	0.77	1.09	0.60	1.97					
Race (being White)	0.42	0.51	1.52	0.43	5.30					
HCV genotype 1	–0.22	0.45	0.80	0.45	1.42					
Received IFN therapy	–1.70	0.001	0.18	0.06	0.51	–1.69	0.003	0.18	0.06	0.56

(Table 5). Of all the factors analyzed in the univariate model, higher age ($P < 0.001$; OR 1.09; 95% CI 1.06–1.13), hypertension ($P < 0.001$; OR 5.60; 95% CI 2.92–10.74), DM ($P < 0.001$; OR 3.90; 95% CI 2.16–7.05), and viral load ($>7 \times 10^5$ cps/mL) at baseline ($P = 0.01$; OR 2.10; 95% CI 1.16–3.83) were noted as significant independent positive predictors for CKD. On the contrary, body weight ($P = 0.03$; OR 0.98; 95% CI 0.96–0.99) and history of IFN treatment ($P = 0.001$; OR 0.18; 95% CI 0.06–0.51) were noted as significant independent negative predictors for CKD.

On multivariate regression analysis, only higher age ($P = 0.004$; OR 1.06; 95% CI 1.01–1.10), hypertension ($P = 0.02$; OR 2.68; 95% CI 1.15–6.22), HCV PCR $> 7 \times 10^5$ cps/mL ($P = 0.01$, OR 2.45; 95% CI 1.21–4.98), and DM ($P = 0.02$, OR 2.37; CI 1.14–4.91) were noted as significant independent positive predictors for CKD, whereas history of IFN treatment ($P = 0.003$; OR 0.18; 95% CI 0.06–0.56) was noted as significant independent negative predictor for CKD. Age, gender, HIV status, DM, IVDU, and HCV genotype were not predictors for CKD in this study.

Prognosis in patients with CKD

The mean estimated time to develop CKD was significantly shorter in the HCV group compared to the control group (74 vs. 84 months, $P < 0.001$; log rank) by Kaplan–Meyer survival analysis (Fig. 4a). A total of 15 patients in the HCV group developed ESRD compared to only 2 in the control group during the observation period. Of the 15 patients in HCV group 5 had DM, 12 had hypertension, and 2 had HIV. On the contrary, HIV and hypertension were co-prevalent in the two ESRD patients from the control group, one of them had DM in addition. Time to develop ESRD was also significantly shorter in patients with chronic HCV infection compared to control population by Kaplan–Meyer (Fig. 4b) survival analysis (estimated mean; 79.9 vs. 86.5 months, $P = 0.005$; log rank). To further investigate any independent role of HCV infection on the progression CKD, we compared the control and the HCV group without DM. Kaplan–Meyer survival analysis revealed a significantly shorter (Fig. 4c) time for development of CKD in patients with HCV infections without DM compared to controls without DM (estimated mean of 75.9 vs. 84.3 months, $P = 0.001$; log rank).

Discussion

In this large retrospective analysis, we have tried to analyze the prevalence, etiologies, predictive factors, and prognosis of CKD in patients with chronic HCV infection by two differing definitions and compared them with an age-, race-, and gender-matched control population without known HCV infection. Based on modified K/DOQI guidelines proposed by the National Kidney Foundation, we found a significantly higher prevalence of CKD in patients with chronic HCV infection compared to the control population by serial estimation of GFR and proteinuria (9.6 vs. 5.1%,

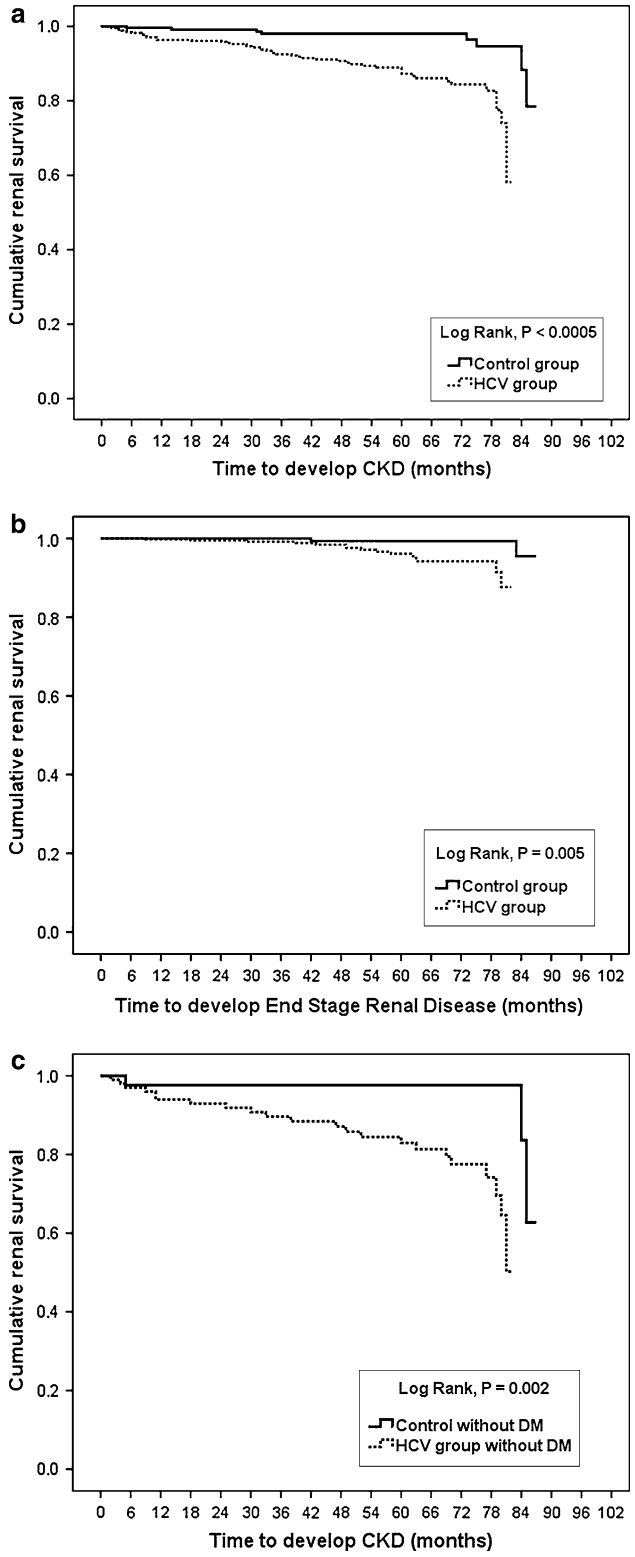

Fig. 4 Renal survival in HCV patients and controls compared by Kaplan–Meyer survival analysis. **a** Time to develop CKD. **b** Time to develop ESRD. **c** Time to develop CKD in patients without DM

$P = 0.02$). Further, the prevalence of CKD remained significant in HCV-infected patients regardless of whether CKD was defined in terms of creatinine measurements, proteinuria, GFR, or a combination of the parameters. Thus, the study further strengthens the potential positive association of HCV infection and development of CKD as reported previously [4–6].

Analysis of the data by age groups showed that 1–2% of patients aged <40 years had CKD in both the control and HCV groups. With increasing age, more patients in the HCV group had CKD compared with the control group, although the differences did not reach statistical significance. The disparity of developing CKD between patients who have HCV infection and those who do not reach almost fivefold in patients aged >70 years. An age-dependent association also has been reported for HCV and diabetes [14, 15]. It is plausible that nonhepatic manifestations of HCV, such as development of CKD and diabetes, develop after many years of chronic infection. Case series of patients with membranoproliferative glomerulonephritis (MPGN) and HCV describe the average age to be ≥50 years [16, 17].

In the HCV group, components of metabolic syndrome such as hypertension and DM emerged as independent positive predictors for development of CKD, although body weight was negatively associated. The negative association of higher body weight with CKD could be a "time effect", since this piece of information was collected at the last follow-up visit. The diet restriction imposed on patients with CKD more so in patients with ESRD, chronic liver disease, and other associated comorbid illnesses may have caused significant weight loss in this population. Hence, the negative association with higher body weight should be interpreted cautiously. Earlier studies have reported a rapid progression of diabetic nephropathy in patients infected with HCV [9]. We found significantly shorter time to develop CKD in HCV-infected patients compared to controls without HCV infection irrespective of the presence or absence of DM. Although the mechanism of HCV-related renal disease is uncertain, research suggests that glomerular injury results from deposition of circulating immune complexes that contain hepatitis C antibody, antigens, and complement [18]. It also could be a result of accelerated atherosclerosis among individuals with HCV, which has been suggested in some studies [19–21]. Thus, although the current study further supports a casual role of HCV in the pathogenesis of CKD, the mechanism for progression to CKD may not necessarily be related to HCV alone; a potential role of metabolic syndrome related to chronic HCV infection leading to accelerated atherosclerosis may also be implicated.

Earlier studies have reported significantly higher prevalence of anti-HCV-positive status in ESRD patients undergoing hemodialysis. Whether HCV infections in these patients are acquired nosocomially in the hemodialysis unit [22], or are acquired prior to initiation of hemodialysis potentially leading to CKD/ESRD in the long run is a matter still to be resolved [23]. Nonetheless, in the present study only a single patient from the HCV group was on hemodialysis at the first visit. It is thus seemingly unlikely that the higher prevalence of CKD in the HCV-infected patients in the current study can be explained on the basis of nosocomially acquired HCV infection during hemodialysis.

Higher viral load has been reported in patients with chronic HCV infections and ESRD compared to controls [24]. Although in the current study, the mean viral loads in the HCV group with and without CKD were not significantly different on their first evaluations, baseline viral load $>7 \times 10^5$ cps/mL significantly predicted the development of CKD. Similar relationship was observed in a recent smaller study that involved 19 HCV-positive patients who had a persistently elevated viral load (>1 million cps/mL) during follow-up for >1.5 years, and 17 HCV patients who had a persistently low viral load (<10,000 cps/mL) during follow-up [25]. At the beginning of follow-up, patients in the two groups had similar kidney function. During 2.6 years of follow-up none of the patients received treatment for HCV, mean GFR decreased significantly with a persistently elevated viral load ($P = 0.003$). Based on these findings, we hypothesize a direct role of "high viral load" in causing glomerular injury in patients with chronic HCV infection and in the development of CKD. Although the current study is not designed to prove or disprove such a fact, it definitely opens the gate for more research on this intriguing finding.

Proteinuria was noted in a significantly higher number of patients with chronic HCV infection [6.8 vs. 2.9%, $P = 0.024$]. A significant proportion of the HCV-infected patients with proteinuria had non-nephrotic range of proteinuria (4.7 vs. 1.8%, $P = 0.04$). Nephrotic-range proteinuria was noted in 9 (2.1%) patients who developed CKD in the HCV group compared to 3 (1.1%) in the control group ($P = 0.39$). In the current study, it is not entirely clear whether HCV is primarily responsible for the range of observed proteinuria, or whether associated comorbid conditions such as DM, hypertension, and HIV (which are known risk factors for the development of CKD) also played an etiologic role (Table 4). Besides, in a logistic regression analysis DM and hypertension were significantly associated with CKD in hepatitis C infected patients. However, except for HIV infection and history of IVDU, these comorbid conditions are not significantly different in the HCV group and the controls, thus does not entirely negate a direct pathogenetic role of HCV infection.

The most common form of renal disease reported in patients with HCV infections is cryoglobulinemic membranoproliferative glomerulonephritis (MPGN type I) [2]. Other types include noncryoglobulinemic MPGN, membranous glomerulonephritis, MPGN type III, FSGS, and mesangial proliferative glomerulonephritis. Information on cryoglobulinemia was limited and was tested only rarely in patients with overt renal failure. Due to limited data and lack of renal biopsy in all the patients with CKD we are unable to say if worse renal survival was due specifically to HCV-related glomerular disease. HCV-NS3 antigens have been detected in kidney tissue of HCV-infected patients with various glomerulonephritis, but mainly in those with MPGN and HCV-RNA positive [3].

There are several limitations to this study. The major potential limitation in the current study is its retrospective design and use of a clinical database with incomplete data for creatinine in both cross-sectional and longitudinal data, and with limited data for proteinuria because our hospital system relies predominately on dipstick testing for screening. However, we believe that any resulting inaccuracy would be in the direction of underdiagnosis, specifically CKD, because proteinuria generally precedes the development of an abnormal eGFR. Second, the diagnosis of hepatitis C positivity was based on different assays because of the 7-year span in which these data were collected. Also almost 20% of the anti-HCV-seropositive patients were either HCV PCR negative or data on their viral load were not available. Third, not all patients included in the control group had their serum tested for anti-HCV antibody and the study assumed that subjects were anti-HCV negative if they were either "tested negative for anti-HCV" or "assumed negative", if they were never tested because of no suspicion for HCV infection. Although this can be interpreted as a limitation, we noted that subjects in the control group who were documented negative for anti-HCV had a numerically higher prevalence of CKD compared to those who were never tested for anti-HCV (7.1 vs 3.1%, $P = 0.10$). A significant number of the patients in the control group who were tested for anti-HCV had their test done either because of abnormal LFT or as a part of the diagnostic workup for CKD. We thus believe that a retrospective study design including only those patients who were tested negative for anti-HCV could potentially skew the data for higher prevalence of CKD in the control population. Therefore by including those who were tested negative for anti-HCV and those with low suspicion for HCV infection in the control group, our study likely represents a more homogenous population. Also, we were unable to get data on BMI due to unavailability of height measurements in a large proportion of the patients and hence presented the body weight data as surrogate for BMI. Another limitation of the study is the limited

information on liver biopsy to stage the severity of liver disease, which relied mostly on the clinical presentation and imaging modalities. Last, this study evaluated predominantly African–American and Hispanic patients in the USA, a cohort with a high prevalence of HIV, suggesting IVDU or multiple sexual partners as the major cause for the high prevalence of hepatitis C. Thus, results may not be generalizable to other races and geographic areas.

Despite its limitations this study provides a number of relevant and novel observations. We focused on determining the prevalence of CKD in a large cohort of chronic HCV-infected ambulatory patients and highlighted the significantly increased prevalence. The study further confirmed that the progression to CKD and ESRD is more rapid in HCV-infected patients, and the progression to CKD is independent of the effect of the presence or absence of DM. In addition to conventional metabolic risk factors such as DM and presence of hypertension, a baseline viral load $>7 \times 10^5$ emerged as an important predictor of CKD. Although the current study also emphasized that history of IFN treatment may have a protective effect, this fact needs to be further verified in larger prospectively designed study with ample statistical power including patients with sustained and those without sustained virologic response. Since many of the patients who were not selected for treatment, they were simply not candidates for antiviral therapy. In summary, chronic HCV infection is associated with development of CKD and shorter renal survival. The mechanism of this association appears to be complex, with both viral and nonviral processes being implicated. Clearly, prospectively designed controlled study with histologic evaluation of liver disease and renal lesion is warranted to better understand this association.

Conflict of interest None.

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