High hepatitis C viral load and genotype 2 are strong predictors of chronic kidney disease

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Associations between chronic hepatitis C virus (HCV) infection and chronic kidney disease (CKD) remain controversial. Here we aimed to clarify the association between HCV viral load, genotype, and CKD in 13,805 participants aged 30-65 years enrolled in the REVEAL-HCV Study, a community-based prospective study conducted in 1991-1992. CKD was defined by consecutive proteinuria or an estimated glomerular filtration rate (eGFR) under 60 mL/min/1.73 m^2. Chronic HCV infection was defined by detectable HCV viral load. Logistic regression models were used to estimate prevalence odds ratio of CKD for chronic HCV infection after adjusting for other risk factors. Compared to non-chronically HCV-infected participants, the adjusted prevalence odds ratio (95% confidence interval) for CKD was significantly increased to 1.91 (1.27–2.88) for chronically HCV-infected participants. Compared to non-chronically HCV-infected participants, the adjusted prevalence odds ratio of CKD was 1.21 (0.54-2.70), 1.40 (0.66-3.00) and 3.44 (1.92-6.14) for chronically HCV-infected participants with low to high tertiles of serum HCV RNA, respectively. The adjusted prevalence odds ratios of CKD were 0.54 (0.17-1.75) for participants with low HCV RNA and genotype 1, 1.80 (0.84-3.87) for those with low HCV RNA and genotype 2, 2.62 (1.11-6.17) for those with high HCV RNA and genotype 1 and 4.99 (2.25-11.06) for those with high HCV RNA and genotype 2, compared with non-chronically HCV-infected participants. Thus, chronic HCV infection is associated with an increased risk of CKD. High HCV viral load and HCV genotype 2 are strong CKD predictors.

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Chronic kidney disease (CKD) with subsequent end-stage renal disease (ESRD) is a global health challenge with high medical costs and poor treatment outcomes.[1] Conventional risk factors for developing chronic renal disease include increasing age, male gender, a history of smoking, diabetes, and hypertension; however, these risk factors cannot fully account for the occurrence of the disease, and new risk factors and markers have been identified.[2] The role of chronic infectious disease, which is 1 of the new risk factors for CKD, may be underestimated. Previous research has documented the association between hepatitis C virus (HCV) infection and glomerulonephritis.[3] However, the causal relationship between chronic HCV infection and CKD remains controversial.

More than 170 million people worldwide are chronically infected with HCV, and 3 to 4 million people are newly infected with HCV annually.[4] Chronic liver disease is common in HCV patients, but 40% to 74% of patients develop at least 1 extrahepatic manifestation, including glomerulonephropathy.[5] In observational studies, the prevalence of HCV infection is much higher in patients undergoing or new to dialysis than in healthy volunteers.[6,7] Cross-sectional and retrospective studies have explored the relationship between hepatitis C infection, proteinuria, and low glomerular filtration rate (GFR).[8–14] A meta-analysis of 9 clinical studies showed that HCV is independently associated with proteinuria but not with reduced GFR, although a substantial heterogeneity cannot be ignored among these studies.[15] The discrepancy may stem from the definition of HCV infection. Most previous studies lacked HCV RNA data and used anti-HCV serostatus to define HCV infection. However, it is the HCV viral load that determines active infection, not anti-HCV serostatus. Moreover, HCV genotypes influence the

treatment response and the prognosis of HCV-related liver diseases. The impact of HCV genotype on HCV-related renal outcome has been lacking.

Taiwan is known to be an HCV-endemic area and also shares the highest prevalence of ESRD worldwide.[16] Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL)-HCV, a large prospective community-based cohort study in Taiwan, provides an excellent opportunity to investigate the effect of chronic hepatitis C and other associated chronic diseases.[17] This study aims to assess the risk of CKD prevalence of HCV viral load and genotypes. Accordingly, we conducted a large-scale community-based cohort study to demonstrate whether chronic HCV infection is an independent risk factor for CKD.

RESULTS

Baseline characteristics of the 13,805 study participants according to chronic HCV infection status are shown in Table 1. The mean age was 47.5 years. The prevalence of chronic HCV infection was 0.3%. Participants with chronic HCV infection tended to be older, male, and more likely to have a history of diabetes and hypertension. The overall prevalence of low GFR and CKD was 2.3% and 3.3%, respectively. Compared with anti-HCV-seronegative participants, the prevalence odds ratios (POR_{adj}) of CKD were 1.32 (0.68–2.56, $P = 0.41$) and 1.74 (1.08–2.82, $P = 0.02$) for anti-HCV-seropositive participants with undetectable and detectable HCV RNA levels, respectively, after adjusting for demographic factors. Patients with undetectable HCV viral load had a risk similar to those who were anti-HCV seronegative; therefore, we defined these 2 groups as nonchronic HCV infection, while chronic HCV infection was defined by detectable HCV viral load.

HCV viremia was present in 65.4% (431 of 660) of anti-HCV-seropositive participants. The detectable HCV RNA ranged from 26 to 8,450,000 IU/ml, and the cutoff values of tertiles of HCV RNA level were 9,000 IU/ml and 107,000 IU/ml. Taking nonchronically HCV-infected participants as a reference group, the POR_{adj} of CKD was 1.91 (1.27–2.88) for chronically HCV-infected participants ($P = 0.002$, Table 2). Compared with nonchronically HCV-infected participants, the POR_{adj} values were 1.21 (0.54-2.70), 1.40 (0.66–3.00), and 3.44 (1.92–6.14) for chronically HCV-infected participants with low to high tertiles of serum HCV RNA levels (P for this trend < 0.001). The dose-dependent trend of HCV RNA levels was also significant for increased risk of CKD components, either low GFR or proteinuria (Table 3).

Among 393 HCV-viremic participants with available genotyping, 215 had HCV genotype 1 and 178 had genotype 2. For those with subtype analysis, the distributions were genotype 1a: 18 (4.6%), 1b: 174 (44.3%), 2a: 87 (22.1%), and 2b: 38 (9.7%). We further used the second tertile of serum HCV RNA (107,000 IU/ml) as a cutoff to define low and high serum HCV RNA. Compared with nonchronically HCV-infected participants, the POR_{adj} values of CKD were 0.54 (0.17–1.75) for participants with low HCV RNA and genotype 1, 1.80 (0.84–3.87) for participants with low HCV RNA and genotype 2, 2.62 (1.11–6.17) for participants with high HCV RNA and genotype 1, and 4.99 (2.25–11.06) for participants with high HCV RNA and genotype 2 (Table 4). In a subanalysis that included only participants with detectable serum HCV RNA levels, the POR_{adj} for participants with genotype 2 was 2.98 (1.77–5.03) with $P < 0.001$ in comparison with participants with genotype 1.

Table 1 | Baseline characteristics of study participants by chronic HCV infection status

Characteristic	All (n = 13,805)	No chronic HCV infection (n = 13,374)	Chronic HCV infection[a] (n = 431)	P value
Age (yr)	47.5 ± 10.0	47.4 ± 10.0	51.1 ± 9.0	<0.001
Sex (M)	6,601 (47.8)	6365 (47.6)	236 (54.8)	0.003
Education (literate)	5,258 (38.1)	5158 (38.6)	100 (23.2)	<0.001
Cigarette smoking	3,582 (26.0)	3442 (25.8)	140 (32.5)	0.002
Alcohol intake	1,241 (9.0)	1199 (9.0)	42 (9.8)	0.56
History of diabetes	335 (2.4)	314 (2.4)	21 (4.9)	<0.001
History of hypertension	821 (6.0)	787 (5.9)	34 (7.9)	0.08
History of cardiovascular disease	237 (1.7)	231 (1.7)	6 (1.4)	0.60
HBsAg	2,318 (16.8)	2250 (16.8)	68 (15.8)	0.57
Creatinine (mg/dl)	1.0 ± 0.8	1.0 ± 0.8	1.1 ± 0.7	0.07
GFR (CKD-EPI) (ml/min/1.73 m^2)	79.6 ± 17.7	79.7 ± 17.7	75.8 ± 17.2	<0.001
AST (U/l)	15.8 ± 13.4	15.2 ± 11.9	33.4 ± 32.1	<0.001
ALT (U/l)	13.4 ± 17.1	12.8 ± 15.9	30.3 ± 35.1	<0.001
Urine protein (dipstick)	1072 (7.8)	1017 (7.6)	55 (12.8)	<0.001
Triglyceride (mg/dl)	133.7 ± 109.0	134.4 ± 110.0	110.8 ± 66.2	<0.001
Cholesterol (mg/dl)	185.2 ± 43.2	185.5 ± 43.2	176.2 ± 41.3	<0.001
Uric acid (mg/dl)	5.2 ± 1.8	5.2 ± 1.8	5.4 ± 1.6	0.004

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; DM, diabetes mellitus; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; M, male.
Continuous variables are expressed as mean ± SD; tests for statistical significance employed the Student t-test. Categorical variables are expressed as number and percentage; tests for statistical significance employed the chi-square test.
Urine protein positive: defined by urine dipstick test value of at least 1+.
[a]Chronic HCV infection was defined by detectable serum HCV RNA level.