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# Hepatitis C Viral Load, Genotype, and Increased Risk of Developing End-stage Renal Disease: REVEAL-HCV Study

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**Lists of Abbreviations** ESRD, end-stage renal disease; DM, diabetes mellitus; CI, confidence interval; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; REVEAL-HCV, Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis C Virus.

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**Author Contributions:**

TSL and CJC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: TSL and CJC. Acquisition, analysis, or interpretation of data: TSL, MHL and HIY. Drafting of the manuscript: TSL. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: TSL. Administrative, technical, or material support: all authors. Study supervision: CJC and KLC.

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**Abstract**

The association between hepatitis C virus (HCV) infection and end-stage renal disease (ESRD) remains controversial without considering the role of HCV viral load and genotype. This study aims to determine whether HCV RNA level and genotype affects the risk of developing ESRD. Between 1991 and 1992, 19,984 participants aged 30–65 years were enrolled in a community-based prospective cohort study in Taiwan. Chronic HCV infection was defined by detectable HCV viral load. ESRD was determined as the need for chronic dialysis or renal transplantation. Conventional Cox proportional hazard and competing risk models were used to determine the hazard ratio (HR) for ESRD. After a median follow-up of 16.8 years, 204 cases were detected during 319,474 person-years. The incidence rates of ESRD for non-chronically-HCV-infected and chronically HCV-infected patients were 60.2 and 194.3 per 100,000 person-years, respectively. The multivariable HR was 2.33 (95% confidence interval [CI], 1.40 to 3.89) when comparing patients with or without chronic HCV infection. Patients with low and high HCV RNA levels were at higher risk of ESRD than those who were non-chronically-HCV-infected (HR [95% CI] 2.11 [1.16 to 3.86] and 3.06 [1.23 to 7.58]; *P*-trend: < 0.001). This association remained robust after taking pre-ESRD death as a competing event for ESRD. Patients with HCV genotype 1 tended to have a higher risk of developing ESRD (HR [95% CI] 3.60 [1.83 to 7.07]) compared with non-chronically-HCV-infected subjects.

***Conclusions:*** This study reveals that chronic HCV infection is associated with an increased risk of developing ESRD and suggests that elevated serum levels of HCV RNA (> 175,000 IU/mL) and HCV genotype 1 are strong predictors of ESRD, indicating clinical implications for the management of chronic HCV.

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

More than 110 million people worldwide have chronic HCV infection and around 80 million people are HCV viremic.(4) Chronic liver disease is common in patients with HCV, but 40% to 74% of patients develop at least one extrahepatic manifestations.(5) HCV is associated with various glomerular diseases, particularly membranous proliferative glomerulonephritis in the context of cryoglobulinemia. The majority of cryoglobulinemic HCV-infected patients have either no or negligible clinical manifestations.(6) In observational studies, the prevalence of HCV infection is much higher in patients undergoing dialysis or in those who are new to dialysis than in normal volunteers.(7, 8) Cross-sectional and retrospective studies have explored the

relationship between HCV infection, proteinuria, and low glomerular filtration rate (GFR), but the results have been conflicting.(9-15) In 2007, a US Veterans retrospective study demonstrated that HCV seropositivity was associated with a greater than 2-fold risk of developing ESRD; however, the HCV diagnosis was based on a positive HCV antibody test, as well as in most previous studies. The impact of the HCV viral load, which represents the degree of active infection, and that of HCV genotypes, which influences the response to anti-viral therapy, on the risk of ESRD remain to be clarified.

Taiwan is known to be an HCV-endemic area and also shares one of the highest prevalence of ESRD worldwide.(16) Unlike HCV-infected patients in other countries are at risk of drug injections, human immunodeficiency virus (HIV) co-infection, or HCV-contaminated vaccinations,(17, 18) the major risk factors of HCV infection in Taiwan were iatrogenic factors.(19) The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL)-HCV study, a large prospective community-based cohort study in Taiwan, provides an excellent opportunity to investigate the natural history of chronic hepatitis C and long-term diseases associated with it.(20) This study aims to assess the risk of developing ESRD in relation to HCV serostatus, HCV RNA level, and HCV genotypes. Accordingly, we conducted a

large-scale community-based cohort study to determine whether chronic HCV infection is an independent risk factor for ESRD.

## Materials and Methods

*Study Cohort Enrollment*

Enrollment and follow-up methods for participants in this community-based prospective study have been described previously.(21) From 1991 to 1992, a total of 23,820 adults aged 30 to 65 years living in seven townships in Taiwan agreed to participate in the REVEAL-HCV study and underwent a health examination that included blood collection. All participants were interviewed in person by trained public health nurses using a structured questionnaire. Information was collected on sociodemographic characteristics, smoking history, alcohol consumption, and presence of chronic diseases such as diabetes mellitus, hypertension, or cardiovascular disease. A 10-mL fasting blood sample was obtained from each participant and samples were fractionated and stored at -70°C until use. All participants were regularly followed up until December 31, 2008.

After the exclusion of 35 samples not available for anti-HCV testing and 38 subjects with liver cirrhosis, there were 23,747 participants recruited who provided informed

consents (Figure 1). We further excluded 3,572 subjects without baseline serum creatinine data, 61 subjects with stage 5 CKD, defined by a baseline estimated glomerular filtration rate (eGFR) of less than 15 mL/min, and 130 anti-HCV-seropositive subjects without available HCV viral load data, yielding a total of 19,984 participants for the longitudinal analysis. This study was approved by the institutional review board of the College of Public Health, National Taiwan University in Taipei.

*Ascertainment of Exposure*

Serum samples were tested for hepatitis C antibody by enzyme immunoassay using a second-generation commercial kit (Abbott HCV EIA, version 2.0; Abbott Laboratories, North Chicago, IL, USA). Samples positive for anti-HCV were further tested for HCV RNA using the COBAS TaqMan HCV test, version 2.0 (Roche Diagnostics Corporation, Indianapolis, IN, USA). The detection limit for the COBAS TaqMan HCV test was 25 IU/mL. We defined chronic HCV-infected subjects as those with detectable serum HCV RNA level. We further categorized HCV RNA levels into low or high HCV viral load group. Since the median detectable HCV RNA level (25,300 IU/mL) at study entry was low, the third quartile of the detectable serum HCV RNA levels was used as a cutoff value (175,000 IU/mL). Detectable HCV RNA

was further examined for HCV genotypes using the LightCycler system (Roche Diagnostics Corporation) for polymerase chain reaction (PCR) and melting curve analysis. HCV genotype was categorized as genotype 1 or genotype 2.

*Ascertainment of Outcome*

We linked the REVEAL-HCV cohort to Taiwan's National Health Insurance Research Database (NHIRD). The NHI is a mandatory program established in 1996 that covers 99% of Taiwan's entire population of 23 million people. The NHIRD provides encrypted patient identification numbers; age; sex; dates of hospital admission and discharge; medical institutions providing services; the International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM) codes of diagnoses and procedures; and outcome at hospital discharge. These claims data are subject to periodic review by the Bureau of NHI to ensure accuracy. ESRD was meant to encompass kidney failure necessitating chronic dialysis or renal transplantation. Using the catastrophic illness registration from the NHIRD, we defined ESRD by ICD-9-CM codes including chronic renal failure (ICD: 585), hypertensive renal disease with renal failure (ICD: 403.01, 403.11, 403.91), hypertensive heart and renal disease with renal failure (ICD: 404.02, 404.03, 404.12, 404.13, 404.92, 404.93), and kidney replaced by transplant (ICD: V42.0).

*Ascertainment of Covariates*

Information collected from the questionnaire included age, sex, smoking (yes/no), alcohol use (yes/no), education status (literate/illiterate), and history of comorbidities. Laboratory examinations included testing for serum levels of triglycerides, total cholesterol, aspartate transaminase (AST), alanine transaminase (ALT), and uric acid. To avoid the potential problems of low awareness of diabetes and hypertension by self-reported history, we reconfirmed the diagnosis in the NHIRD with well-established information. We defined type 2 diabetes if two or more outpatient visits or at least one hospital admission with a diagnostic code of diabetes (ICD-9-CM code 250). This definition of diabetes was validated by a study sampling 9,000 patients with a diagnosis of diabetes in the Taiwan National Health Insurance claims data and the sensitivity and positive predictive value was high (94.8% and 74.6%, respectively)(22). The diagnosis of hypertension followed similar criteria, which included two or more outpatient visit or at least one hospitalization with a diagnosis of hypertension (ICD-9-CM: 401-405). The estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and a low GFR was defined as an estimated GFR of less than 60 mL/min/1.73 $m^2$. Proteinuria was defined as the presence of urinary protein at least grade 1 by the urine dipstick

test.

*Statistical Analysis*

Categorical variables of participants with or without chronic HCV infection were expressed as numbers and percentages and compared using the chi-square test. Continuous variables were expressed as means ± standard deviation (SD) and compared using an unpaired *t*-test. Person-years of each participant were calculated from the date of entry to the date of ESRD, death, or December 31, 2008, the final date of linked data available. The incidence rate of ESRD was calculated by dividing the number of ESRD events by person-years of follow-up. The cumulative incidence of ESRD for chronically HCV-infected and non-chronically-HCV-infected cases was estimated using the Kaplan-Meier method, and the statistical significance of the difference was compared using the log-rank test. Cox proportional hazard models were used to estimate multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of ESRD for HCV viral load and genotypes. The proportionality assumption of Cox models was checked and not violated. The interaction of HCV infection, diabetes, and hypertension was assessed. The statistical significance of the dose-response relationship between serum HCV RNA levels, HCV genotypes, and the incidence of ESRD was assessed using the Cochran-Armitage test

for trend. Statistical significance was determined by a two-tailed test ($P < 0.05$). Statistical analyses were mainly performed using the SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Besides the traditional Cox proportional hazard model, we aimed to further identify the predictors of the cumulative incidence of ESRD via a competing risk analysis, which considers two competing events: the development of ESRD and deaths prior to ESRD. Competing risk analyses were performed using the Cox proportional hazards regression for adjusted cause-specific HRs, and the Fine and Gray method was further used to incorporate rates of competing risks in the cumulative incidence function and subhazard ratios.(23) Statistical analyses for competing risk were performed using the STATA software (version 12; StataCorp, College Station, TX, USA), and the Fine and Gray model was implemented in the Stata statistical software using the "stcrreg" module.

**Results**

Baseline characteristics of the 19,984 study participants according to chronic HCV infection status are shown in Table 1. There were 19,393 non-chronically-HCV-infected subjects and 591 chronically HCV-infected subjects.

The mean age of participants was 47.3 years. Participants who were chronically HCV-infected tended to be older, were more likely to be male, had lower educational levels, and were more likely to have diabetes and hypertension. Patients with chronic HCV infection also had lower GFR values, lower levels of cholesterol and triglycerides, and higher levels of alanine aminotransferase, uric acid, and urinary protein than participants without chronic HCV infection.

The median number of follow-up years was 16.8. A total of 204 ESRD events occurred during the 319,474 person-years. The incidence rate of ESRD was 63.9 per 100,000 person-years (60.2 per 100,000 person-years for non-chronically-HCV infected participants and 194.3 per 100,000 person-years for chronically HCV-infected participants). The incidence rates of ESRD and crude HR by baseline covariates were listed in Table 2. The cumulative incidence of ESRD was 1.1% for non-chronically-HCV-infected subjects and 3.4% for chronically HCV-infected subjects (log-rank $p< 0.001$). Comparing participants with or without chronic HCV infection, the univariate and multivariable-adjusted HRs (95% CI) were 3.31 (2.02-5.45) and 2.33 (1.40-3.89), respectively.

The cumulative risk of developing ESRD was 3.2% for those with low HCV RNA

levels and 3.7% for those with high HCV RNA levels (Figure 2). In model 1, the multivariable-adjusted HRs (95% CI) of those with low or high HCV RNA levels were 2.11 (1.16-3.86), and 3.06 (1.23-7.58), respectively, compared with those non-chronically-HCV-infected participants (*P*-trend: < 0.001) (Table 3). In model 2, the multivariable-adjusted HRs (95% CI) for participants with genotype 1 and genotype 2 compared with those who were not chronically HCV-infected were 3.60 (1.83-7.07) and 1.38 (0.60-3.18), respectively.

A total of 2,416 death events occurred during the follow-up period. After the competing risk of pre-ESRD death is taken into account, predictors of increased cumulative incidence of ESRD were old age; male gender; low educational level; diabetes; hypertension; CKD; and elevated triglycerides, cholesterol, uric acid, and urinary protein levels (see Online Supplementary Table 1). Comparing participants with or without chronic HCV infection, the multivariable-adjusted HR (95% CI) was 2.33 (1.39–3.89) in the cause-specific hazard method and the subhazard ratio was 2.20 (1.24–3.90) in the Fine and Gray method. The multivariable-adjusted hazard ratios and subhazard ratios (95% CI) of those with low, or high HCV RNA levels were listed in Table 4. Cumulative incidence of ESRD increased with increasing HCV RNA levels (see Online Supplementary Figure 1) and the relationship between genotype 1

versus 2 did not change.

## Discussion

Our study demonstrated that chronic HCV infection is an independent risk factor for the development of ESRD. During more than 15 years of follow-up, chronic HCV infection resulted in a 2.2-fold increased risk of ESRD after taking pre-ESRD death as competing risk. Compared with participants who were not chronically-HCV-infected, participants with low and with high HCV RNA levels had a 2.1-fold and 3.1-fold increased risk of developing ESRD, respectively. Patients with HCV genotype 1 had a higher risk of developing ESRD.

Limited studies have examined the association between HCV infection and the risk of ESRD. In a diabetes study, Crook et al. found that patients with diabetes with HCV had worse renal survival, and the effects of HCV were independent of the development of ESRD after adjusting for potential confounders with OR (95% CI): 3.49 (1.27 to 9.57).(24) The first large cohort study was conducted in 2007, in which Tsui et al. retrospectively followed 474,369 US veterans aged 18 to 70 years and

found that HCV seropositivity was associated with a greater than 2-fold risk of developing ESRD (adjusted HR: 2.80; 95% CI 2.43 to 3.23).(25) However, the study was restricted to veterans and the follow-up time (median 3.6 years) was not long enough to observe the natural course of kidney disease progression. The current study is unique in that it utilizes a community-based cohort in an endemic area. The results are generalizable. Furthermore, the study followed HCV infection and renal outcomes for more than 15 years, much longer than previous studies, in which the follow-up periods were less than 4 years.(12, 14, 15)

The most encouraging feature of the current study is that we used serum HCV RNA levels as well as anti-HCV serostatus to define HCV infection. Most studies including Tsui's study only had anti-HCV serotesting data, lacking evidence of whether the infection in the HCV-infected patients was active or not. A retrospective hospital-based study yielded that the number of patients with viral loads above the cutoff value of 600,000 was significantly higher in the group with CKD.(26) In addition, two HIV studies have demonstrated that in HIV-infected patients, HCV viremia is associated with a higher incidence of CKD than HCV seronegative individuals.(27, 28) However, one study found that both HCV viremic and HCV

aviremic HIV-infected individuals were at increased risk for moderate and advanced CKD and another study showed that HCV aviremic patients had a similar incidence rate of CKD compared with anti-HCV-negative patients. The role of HCV aviremia in CKD remains a subject of debate. Our study is the first study to demonstrate that the HCV RNA level increased the risk of ESRD in a dose-dependent relationship among the general population. Patients with undetectable HCV RNA had a similar HR of developing ESRD compared to anti-HCV seronegative patients, suggesting that viral load does play a role in the association between HCV infection and risk of developing ESRD.

HCV genotype has significant clinical importance in relation to the clinical manifestations of the disease and treatment response. In our group, Lee et al. explored the predictive value of HCV genotype for the development of hepatocellular carcinoma and demonstrated that HCV genotype 1 was an independent predictor of hepatocellular carcinoma.(20) In the current study, patients with HCV genotype 1 had a higher HR of developing ESRD than non-HCV-infected patients . This result was consistent across each strata in subgroup analysis (data not shown). High prevalence of HCV genotype 1 was found among previous observational studies in hemodialysis

units among South American, Asian, and European countries.(29-31) The mechanisms between HCV genotype and risk of ESRD needs to be further investigated in the future.

Chronically HCV-infected patients have an increased risk of ESRD and death.(32) These two outcomes have competing effects that potentially interfere with risk samplings in the survival analysis. Thus, competing risk analysis should be performed in the HCV-ESRD association taking pre-ESRD death into consideration. In the current analysis, chronic HCV infection remained associated with a nearly 2-fold risk of developing ESRD after competing risk assessment, either in the cause-specific hazard model or in the Fine and Gray model. The dose-response effect of the HCV RNA level on the risk of incidence of ESRD was even robust and indicated that the HCV viral load is highly predictive of ESRD risk under competing risk consideration.

Recently, new direct-acting antiviral (DAA) drugs that target key components of viral replication have been developed, which allow for more efficient and shortened treatments for HCV than traditional interferon-based one.(33) If so, the use of DAA agents for HCV-infected patients is believed to effectively reduce the morbidity and

mortality of liver-related disease. Our study provided strong evidence that the HCV viral load is predictive of ESRD in a dose-dependent manner; thus, viral eradication therapy might tremendously reduce the incidence of renal disease as well as liver disease. Although the new DAA agents are costly, the potential hepatic and extra-hepatic benefits are valuable.

Our study has several limitations. First, our cohort was built in 1991 to 1992 and the first outcomes that could be traced by linking to the catastrophic illness registration were from 1995. Thus, some incident cases may be missing. The number was speculated to be low because we excluded participants with stage 5 CKD at first, and the remaining population could hardly develop ESRD within a short period and if so, it is unlikely to be caused primarily by HCV. We also did a sub-analysis to exclude individuals with eGFR less than 60 ml/min/1.73m$^2$ at baseline; the deleterious effect of HCV RNA remained robust. Second, the number of cases was small: there were only 17 ESRD cases among the HCV-infected participants; thus, the impact of finer subdivision of HCV viral load and genotypes on ESRD could not be evaluated adequately. Third, we did not consider new HCV infection from enrollment to the date that NHI database could be accessed. The misclassification was non-differential and

the true magnitude of association may be underestimated. Fourth, anti-HCV serostatus HCV RNA levels, genotypes and covariates were measured only at baseline. Though we did not repeat the HCV measurements during follow-up, we did check some of the participants with adequate serum samples at last follow-up. There was a significant correlation between HCV RNA levels at study entry and last follow-up (r=0.76; $P <$ 0.001). Finally, we did not consider the effect of anti-viral therapy in this cohort. In Taiwan, patients with chronic hepatitis C rarely received antiviral treatment until 2004, when patients fulfilling certain criteria could be reimbursed for treatment through the NHI. None of the participants underwent interferon-based therapy after confirmation from linking to the NHIRD database. Hence, our study provided an excellent opportunity to examine serologic markers and kidney disease during the natural course of HCV infection.

**Conclusion**

In conclusion, this study is a reminder that the risk of ESRD among patients with chronic HCV infection may be under-recognized, especially among those with elevated serum levels of HCV RNA (> 175,000 IU/mL) and HCV genotype 1. All patients with chronic HCV infection should undergo a thorough renal survey at diagnosis and receive regular follow-up.

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## Figure Legends

Figure 1. Flow of study participants

Figure 2. Cumulative risk of end-stage renal disease (ESRD) by serum HCV RNA level at study entry

**Table 1. Baseline Characteristics of the Study Participants with or without chronic HCV infection**

| Characteristic | All (N = 19,984) | No chronic HCV infection (N = 19,393) | Chronic HCV infection (N = 591) | *P* value |
|---|---|---|---|---|
| **Age (years)** | 47.3 ± 10.0 | 47.2 ± 10.0 | 50.8 ± 9.1 | < 0.001 |
| **Male sex (n, %)** | 9,804 (49.1) | 9,484 (48.9) | 320 (54.2) | 0.01 |
| **High school education (n, %)** | 7,283 (36.5) | 7,145 (36.9) | 138 (23.4) | < 0.001 |
| **Diabetes (n, %)** | 1,616 (8.1) | 1,523 (7.9) | 93 (15.7) | < 0.001 |
| **Hypertension (n, %)** | 1,294 (6.5) | 1,239 (6.4) | 55 (9.3) | 0.005 |
| **History of heart disease (n, %)** | 329 (1.7) | 314 (1.7) | 17 (1.7) | 0.89 |
| **Alcohol intake (n, %)** | 2,010 (10.1) | 1,948 (10.1) | 62 (10.5) | 0.70 |
| **Cigarette smoking (n, %)** | 5,677 (28.4) | 5,474 (28.3) | 203 (34.4) | 0.001 |
| **Creatinine (mg/dL)** | 1.0 ± 0.3 | 1.0 ± 0.3 | 1.0 ± 0.2 | 0.007 |
| **AST (U/L)** | 15.8 ± 14.4 | 15.2 ± 12.5 | 33.8 ± 39.4 | < 0.001 |
| **ALT (U/L)** | 13.1 ± 17.1 | 12.6 ± 15.8 | 31.0 ± 37.5 | < 0.001 |

| | | | | |
|---|---|---|---|---|
| **Baseline CKD** | 1,412 (7.1) | 1357 (7.0) | 55 (9.3) | 0.03 |
| **Estimated GFR (mL/min/1.73 $m^2$)** | 89.6 ± 20.0 | 89.7 ± 20.0 | 85.0 ± 18.0 | < 0.001 |
| **Triglycerides (mg/dL)** | 136.5 ± 114.8 | 137.3 ± 115.8 | 112.4 ± 70.2 | < 0.001 |
| **Cholesterol (mg/dL)** | 185.5 ± 43.3 | 185.8 ± 43.4 | 175.8 ± 40.4 | 0.005 |
| **Uric acid (mg/dL)** | 5.2 ± 1.8 | 5.2 ± 1.8 | 5.4 ± 1.6 | 0.002 |
| **Urinary protein (n, %)** | 900 (4.5) | 863 (4.5) | 37 (6.3) | 0.04 |
| **HBV surface antigen (n, %)** | 3,301 (16.65) | 3,224 (16.6) | 77 (13.0) | 0.02 |

- Continuous variables are expressed as means ± standard deviations, and the test for statistical significance employed the Student's t-test. Categorical variables are expressed as percentages, and the test for statistical significance employed the chi-square test.
- High school education: junior high school or above
- GFR mL/min/1.73 $m^2$ was estimated in accordance with the Chronic Kidney Disease Epidemiology Collaboration equation.
- Abbreviations: HCV, hepatitis C virus; AST, aspartate transaminase; ALT, alanine transaminase; CKD, chronic kidney disease; GFR, glomerular filtration rate; HBV, hepatitis B virus

**Table 2. Incidence Rates of ESRD and Crude HRs by Baseline Risk Factors**

| Baseline Risk Factors | Cases of ESRD N = 204 | Person-Years | Incidence per 100,000 Person-Years | Crude HR (95% CI) |
|---|---|---|---|---|
| **Chronic HCV infection** | | | | |
| No | 187 | 310724 | 60.2 | 1.00 |
| Yes | 17 | 8750 | 194.3 | 3.31 (2.02-5.45) |
| **Sex** | | | | |
| Female | 98 | 166,272 | 58.9 | 1.00 |
| Male | 106 | 153,202 | 69.2 | 1.19 (0.90-1.57) |
| **Age at recruitment, years** | | | | |
| 30–39 | 25 | 95,177 | 26.3 | 1.00 |
| 40–49 | 45 | 86,980 | 51.7 | 1.98 (1.21-3.23) |
| 50–59 | 93 | 95,682 | 97.2 | 3.77 (2.42-5.86) |
| 60–65 | 41 | 41,635 | 98.5 | 3.92 (2.38–6.45) |
| **Educational level** | | | | |
| No or primary school | 156 | 200,534 | 77.8 | 1.00 |

| | | | | |
|---|---|---|---|---|
| Junior high school or above | 48 | 118,830 | 40.4 | 0.51 (0.37-0.71) |
| **Cigarette smoking** | | | | |
| No | 141 | 231,772 | 60.8 | 1.00 |
| Yes | 63 | 87,342 | 72.1 | 1.21 (0.90-1.62) |
| **Alcohol drinking** | | | | |
| No | 182 | 288,259 | 63.1 | 1.00 |
| Yes | 22 | 30,656 | 71.8 | 1.15 (0.74-1.80) |
| **Diabetes** | | | | |
| No | 117 | 294,741 | 39.7 | 1.00 |
| Yes | 87 | 24,733 | 351.8 | 9.10 (6.90-12.02) |
| **Hypertension** | | | | |
| No | 150 | 299,379 | 50.1 | 1.00 |
| Yes | 54 | 20,095 | 268.7 | 5.46 (4.00-7.45) |
| **HBsAg** | | | | |
| No | 167 | 267,602 | 62.4 | 1.00 |
| Yes | 37 | 51,872 | 71.3 | 1.15 (0.80-1.64) |

| | | | | |
|---|---|---|---|---|
| **Baseline CKD** | | | | |
| No | 136 | 298,894 | 45.5 | 1.00 |
| Yes | 68 | 20,580 | 330.4 | 7.50 (5.61-10.04) |
| **History of heart diseases** | | | | |
| No | 199 | 313,663 | 63.4 | 1.00 |
| Yes | 5 | 4,806 | 104.0 | 1.68 (0.69-4.07) |
| **Urinary protein level (dipstick)** | | | | |
| No | 136 | 306,439 | 44.4 | 1.00 |
| Yes | 68 | 13,035 | 521.7 | 12.17 (9.09-16.28) |
| **Serum triglyceride level, mg/dL** | | | | |
| < 150 | 92 | 227,284 | 40.5 | 1.00 |
| ≥ 150 | 112 | 92,190 | 121.5 | 3.02 (2.29-3.98) |
| **Serum cholesterol level, mg/dL** | | | | |
| < 200 | 101 | 213,876 | 47.2 | 1.00 |
| ≥ 200 | 103 | 105,598 | 97.5 | 2.07 (1.57-2.72) |

| | | | | |
|---|---|---|---|---|
| **Serum uric acid level, mg/dL** | | | | |
| < 8 | 170 | 302,623 | 56.2 | 1.00 |
| ≥ 8 | 34 | 16,851 | 201.8 | 3.64 (2.52-5.26) |

Abbreviations: ESRD, end-stage renal disease; HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; CKD, chronic kidney disease

**Table 3. Crude and Multivariable-adjusted HRs of the Incidence of ESRD by Serum HCV RNA Levels and HCV Genotypes**

| | No. (N = 19,984) | ESRD cases (N = 204) | Person-Years of Follow-up | Incidence per 100,000 Person-Years | Crude HR (95% CI) | Multivariable-Adjusted HR (95% CI) |
|---|---|---|---|---|---|---|
| **Model 1** | | | | | | |
| No chronic HCV infection | 19,393 | 187 | 310,724 | 60.2 | 1.00 (ref) | 1.00 (ref) |
| Low HCV RNA level | 444 | 12 | 6,563 | 182.8 | 3.12 (1.74-5.59) | 2.11 (1.16-3.86) |
| High HCV RNA level | 147 | 5 | 2,187 | 228.6 | 3.90 (1.61-9.48) | 3.06 (1.23-7.58) |
| **Model 2** | | | | | | |
| No chronic HCV infection | 19,393 | 187 | 310,724 | 60.2 | 1.00 (ref) | 1.00 (ref) |
| HCV genotype 1 | 287 | 9 | 4,266 | 211.0 | 3.56 (1.83-6.95) | 3.60 (1.83-7.07) |
| HCV genotype 2 | 246 | 6 | 3,711 | 161.7 | 2.72 (1.21-6.13) | 1.38 (0.60-3.18) |

- Multivariable adjustment included age (per 10-year increments), sex, diabetes, hypertension, baseline CKD, serum cholesterol, triglycerides, uric acid, and urinary protein level
- Cutoff value for low and high HCV RNA levels: third quartile of the HCV RNA (167,000 IU/mL)

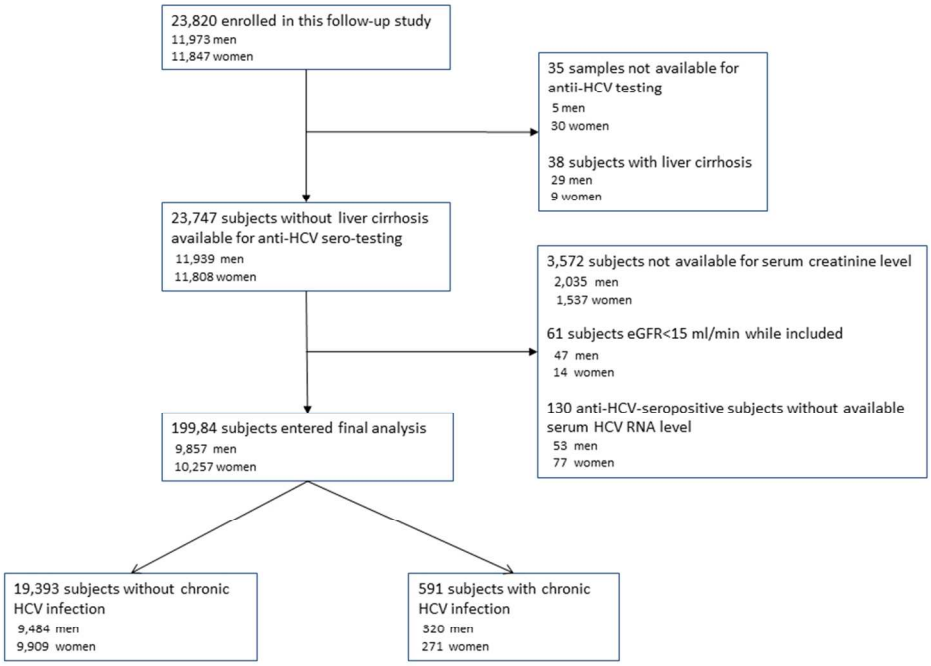
Abbreviations: HR, hazard ratio; ESRD, end-stage renal disease; HCV, hepatitis C virus; CI, confidence interval, CKD, chronic kidney disease

**Table 4. Risk of Serum HCV RNA Level and HCV Genotype in Relation to the Development of ESRD using the Competing Risk Model**

| Baseline Risk Factors | ESRD | | | |
|---|---|---|---|---|
| | Cox Model | | Fine and Gray Model | |
| | Cause-specific HR (95% CI) | *P* for trend | Subhazard ratio (95% CI) | *P* for trend |
| **Model 1** | | | | |
| No chronic HCV infection | 1.00 (ref) | < 0.001 | 1.00 (ref) | < 0.001 |
| Low HCV RNA level | 2.11 (1.15-3.86) | | 1.97 (0.99-3.94) | |
| High HCV RNA level | 3.05 (1.23-7.58) | | 3.03 (1.26-7.27) | |
| **Model 2** | | | | |
| No chronic HCV infection | 1 (ref) | < 0.001 | 1 (ref) | < 0.001 |
| Genotype 1 | 3.60 (1.83-7.07) | | 2.91 (1.43-5.95) | |
| Genotype 2 | 1.38 (0.60-3.18) | | 1.51 (0.58-3.92) | |

● Abbreviations: HCV, hepatitis C virus; ESRD, end-stage renal disease; HR, hazard ratio; CI, confidence interval

- Multivariable adjustment included age (per 10-year increments), sex, diabetes, hypertension, baseline CKD, serum cholesterol, triglycerides, uric acid, and urinary protein level

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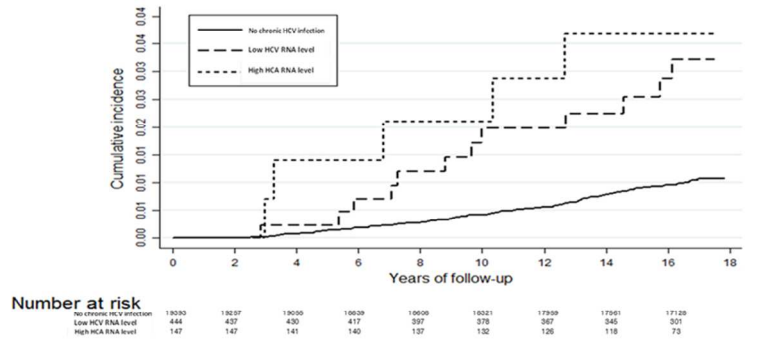


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**Supplementary Table 1.** Risk of Baseline Variables in Relation to the Development of ESRD using the Cox Model and Fine and Gray Model

| Baseline Risk Factors | Outcome: ESRD | | | |
|---|---|---|---|---|
| | Cox Model | | Fine and Gray Model | |
| | Cause-specific HR (95% CI) | *P* value | Subhazard ratio (95% CI) | *P* value |
| Chronic HCV infection (yes versus no) | 2.33 (1.39-3.89) | 0.001 | 2.20 (1.24-3.90) | 0.007 |
| Age (per 10-year increments) | 0.98 (0.84-1.15) | 0.84 | 0.92 (0.79-1.08) | 0.32 |
| Male versus female sex | 0.67 (0.49-0.92) | 0.28 | 0.64 (0.46-0.89) | 0.009 |
| Diabetes (yes versus no) | 4.53 (3.31-6.19) | < 0.005 | 4.58 (3.27-6.42) | < 0.005 |
| Hypertension (yes versus no) | 2.08 (1.48-2.92) | < 0.005 | 2.12 (1.47-3.04) | < 0.005 |
| Baseline CKD (yes versus no) | 5.15 (3.58-7.40) | < 0.005 | 5.05 (3.49-7.30) | < 0.005 |
| Urinary protein (yes versus no) | 6.39 (4.70-8.71) | < 0.005 | 6.09 (4.41-8.42) | < 0.005 |
| Triglycerides (≥ 150 versus < 150 [mg/dL]) | 1.64 (1.21-2.22) | 0.001 | 1.64 (1.19-2.25) | 0.002 |
| Cholesterol (≥ 200 versus < 200 [mg/dL]) | 1.28 (0.96-1.70) | 0.10 | 1.28 (0.95-1.73) | 0.102 |
| Uric acid (≥ 8 versus < 8 [mg/dL]) | 1.23 (0.81-1.85) | 0.33 | 1.25 (0.81-1.93) | 0.32 |

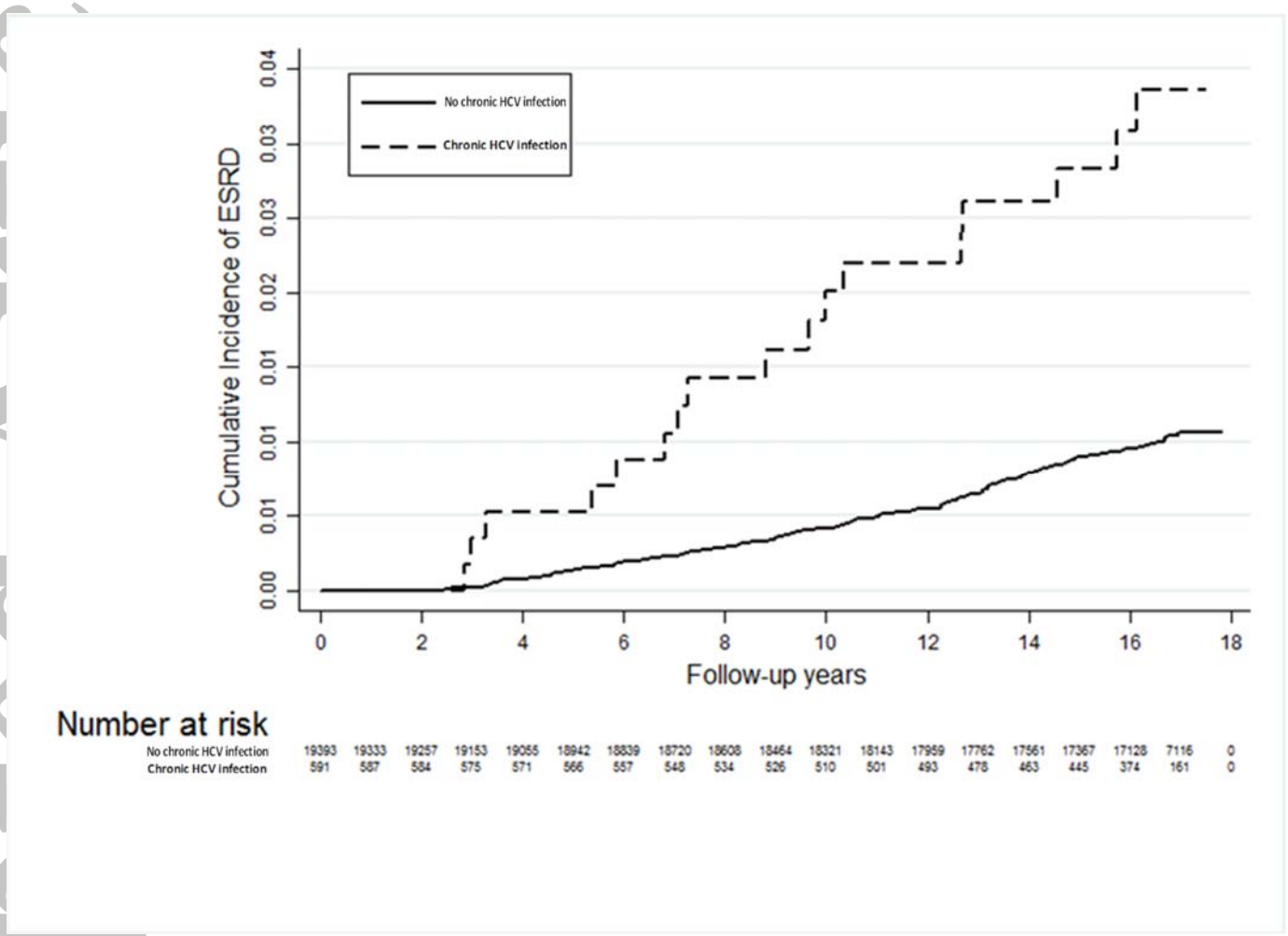
- Abbreviations: ESRD, end-stage renal disease; HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus; CKD, chronic kidney disease

**Supplement Table 2.** Cox Regression Model of HCV Infection and Risk of ESRD and Subgroup Analysis by Possible Effect Modifiers

| | Multivariable-adjusted HR (95% CI) | *P* value | *P* for interaction |
|---|---|---|---|
| **Total cohort** | 2.33 (1.40-3.89) | 0.001 | |
| Not adjusted for DM | 2.76 (1.66-4.59) | < 0.001 | |
| Not adjusted for HTN | 2.51 (1.51-4.17) | < 0.001 | |
| Not adjusted for both DM and HTN | 3.01 (1.81-4.99) | < 0.001 | |
| **Subgroup** | | | |
| DM | 2.64 (1.31-5.33) | 0.007 | 0.64 |
| Non-DM | 2.27 (1.09-4.27) | 0.028 | |
| HTN | 1.98 (0.82-4.80) | 0.13 | 0.72 |
| Non-HTN | 2.79 (1.50-5.21) | 0.001 | |

- The multivariable-adjusted model was adjusted for age, sex, DM, HTN, baseline CKD, serum cholesterol, triglycerides, uric acid, and urinary protein level.
- Abbreviations: HCV, hepatitis C virus; ESRD, end-stage renal disease; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension

**Supplementary Figure 1.** Cumulative Risk of ESRD by chronic HCV Infection



**Supplementary Figure 2.** Cumulative Risk of ESRD by HCV Viral Load in the Competing Risk Regression Analysis