Hepatitis C Virus Infection and Increased Risk of Cerebrovascular Disease

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Background and Purpose—The association between hepatitis C virus (HCV) infection and cerebrovascular disease remains controversial. This study aimed to assess the risk of lethal cerebrovascular diseases associated with chronic HCV infection.

Methods—In this community-based prospective cohort study, 23 665 residents (aged 30 to 65 years) were enrolled in 1991 to 1992. They were personally interviewed using structured questionnaires and provided blood samples for various serological and biochemical tests at study entry. Serum HCV RNA level and HCV genotype were tested for participants seropositive for antibodies against HCV (anti-HCV). Deaths from cerebrovascular disease during follow-up were ascertained by computerized linkage with National Death Certification profiles from 1991 to 2008 (International Classification of Diseases, 9th Revision 430 to 438). Multivariate-adjusted hazard ratio with 95% CI was estimated for each risk predictor.

Results—There were 255 cerebrovascular deaths during 382 011 person-years of follow-up. The cumulative risk of cerebrovascular deaths was 1.0% and 2.7% for seronegatives and seropositives of anti-HCV, respectively ($P<0.001$). The hazard ratio (95% CI) of cerebrovascular death was 2.18 (1.50 to 3.16) for anti-HCV seropositives after adjustment for several conventional risk factors of cerebrovascular disease. Compared with participants seronegative for anti-HCV as the referent, the multivariate-adjusted hazard ratio (95% CI) was 1.40 (0.62 to 3.16), 2.36 (1.42 to 3.93), and 2.82 (1.25 to 6.37), respectively, for anti-HCV-seropositive participants with undetectable, low, and high serum levels of HCV RNA ($P<0.001$ for trend). However, no significant association was observed between HCV genotype and cerebrovascular death.

Conclusions—Chronic HCV infection is an independent risk predictor of cerebrovascular deaths showing a biological gradient of cerebrovascular mortality with increasing serum HCV RNA level. **(*Stroke*. 2010;41:2894-2900.)**

Key Words: cerebrovascular disease ■ hepatitis C virus ■ prospective study

There are 170 million people affected with chronic hepatitis C virus (HCV) infection, which may cause liver cirrhosis and hepatocellular carcinoma, worldwide.[1] In addition to hepatic complications, chronic HCV infection has been suggested to cause extrahepatic disorders.[2] Antiviral therapy has successfully decreased the rate of fibrosis progression in patients with chronic HCV infection,[3] and a large community-based study in Australia found declined standardized mortality ratios for liver-related deaths in HCV-infected patients from 1995 to 2002.[4]

Cerebrovascular disease is the second leading cause of death worldwide. It is becoming a great health burden in most industrialized countries in future decades.[5] Conventional risk factors for cerebrovascular disease include cigarette smoking, alcohol consumption, obesity, hyperlipidemia, hypertension, and diabetes.[6] These risk factors cannot completely explain the occurrence of the disease, and new risk factors including infectious agents have been documented.[7,8]

Chronic HCV infection has been found to increase the risk of ultrasonographically defined carotid intima-media thickness and/or plaque,[9–11] which are predictors for cerebrovascular disease.[12] However, these cross-sectional studies could not verify the causal temporality between HCV infection and cerebrovascular disease. Serum HCV RNA level is a biomarker of active HCV replication, and HCV genotype determines the severity of liver diseases associated with HCV infection.[13] To further elucidate the rela-

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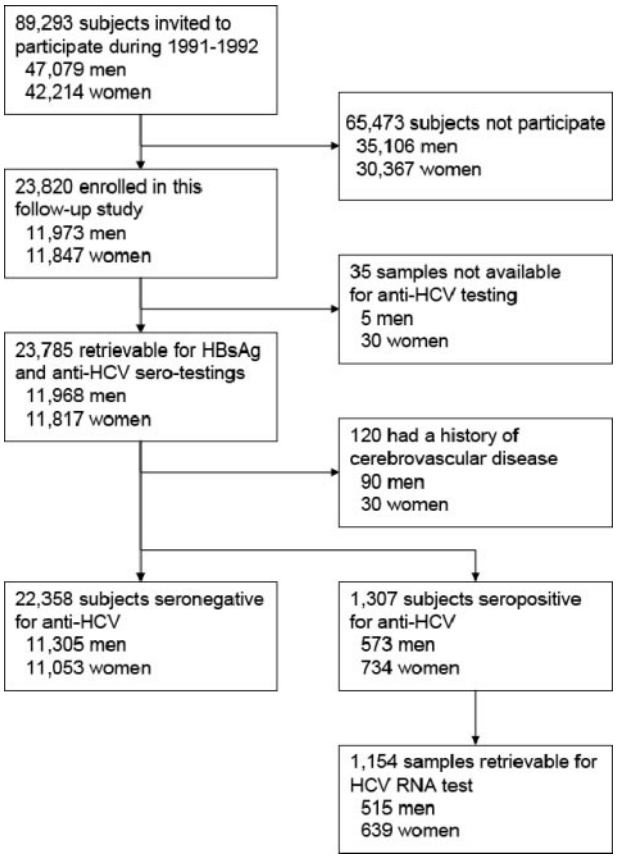


Figure 1. Flows of study participants.

tionship between HCV infection and cerebrovascular deaths, we conducted this population-based, long-term prospective study to (1) estimate mortality rates of cerebrovascular diseases in participants with and without HCV infection; (2) assess the independent effect of HCV infection on cerebrovascular deaths after adjustment for conventional risk factors; and (3) evaluate the importance of serum HCV RNA level and HCV genotype in the risk prediction of cerebrovascular death.

Methods

Study Cohort Enrollment

Methods of enrollment and follow-up of this community-based prospective study have been described previously.[14,15] The flow of study participants is shown in Figure 1. Totally 89 293 adult residents living in 7 townships in Taiwan were invited to participate in 1991 to 1992, 23 820 of them provided written informed consent for interview, health examination, and blood collection. Participants seropositive for either antibodies against HCV (anti-HCV) or hepatitis B surface antigen at study entry were followed up by abdominal ultrasonography and serological tests until the end of 2005. A total of 120 participants with a history of cerebrovascular disease were excluded in this study, giving a total of 23 665 participants in the analysis. This study was approved by the Institutional Review Board of the College of Public Health, National Taiwan University in Taipei.

Interview and Blood Collection

All participants were personally interviewed by public health nurses using structured questionnaires to collect information on demographic characteristics (age, sex, educational levels, occupation, etc), habits of cigarette smoking and alcohol consumption, and personal history of diseases (previous diagnosis of diabetes, hypertension, heart diseases, or cerebrovascular diseases). Body weight and height were measured. Blood samples were obtained from each participant using disposable needles and vacuum syringes. The serum samples were fractionated within 6 hours after collection and stored at −70°C until assay.

Laboratory Examinations

Serum samples for HBsAg and anti-HCV were tested using commercial kits as described previously.[14] Serum samples positive for anti-HCV were further tested for HCV RNA by the COBAS TaqMan HCV test, Version 2.0 (Roche Diagnostics, Indianapolis, NJ) with a linear range from 25 to 3.9×10^8 IU/mL. Serum samples with detectable HCV RNA were examined for HCV genotypes by LightCycler-based polymerase chain reaction and melting curve analysis, which could effectively differentiate HCV genotypes by different melting temperatures. In our test, the genotype calling for genotype 1 and nongenotype 1 achieved 100% accuracy by the method.[16,17] The third quartile of serum HCV RNA levels (ie, 1.6×10^5 IU/mL) at study entry was used to stratify participants with detectable HCV RNA into low and high HCV RNA levels. Serum levels of triglycerides and total cholesterol were measured using commercial kits and an automated analyzer.[18]

Ascertainment of Cerebrovascular Disease Deaths

In Taiwan, it is mandatory to register all death certificates within 1 month after deaths. The computerized National Death Certification Registry profile contains updated and accurate information on the date and causes of deaths.[15,19] The national identification number, date of birth, and sex were used as the linking variables to double-check the vital status and causes of death of study participants from the national death certification system. All deaths occurring between study entry and December 31, 2008, were included. The underlying cause of death was coded according to the International Classification of Disease, 9th Revision, and 430 to 438 coded as cerebrovascular disease.

Statistical Analysis

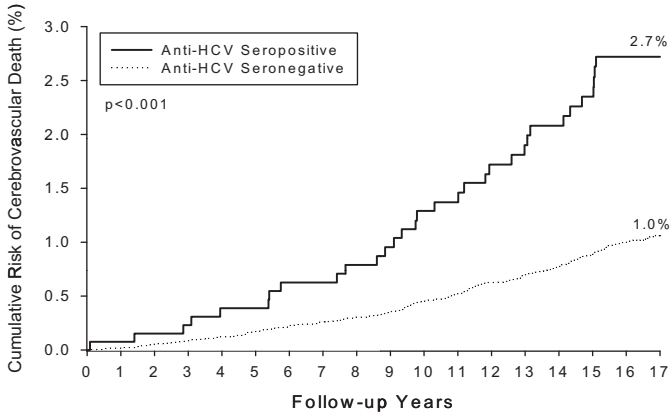
Baseline characteristics of participants seronegative and seropositive for anti-HCV were compared with χ^2 tests. The person-years of follow-up were calculated for each participant as the time from the enrollment to the date at death or December 31, 2008, for those still alive then. Mortality rates of cerebrovascular disease per 100 000 person-years were calculated by dividing the number of cerebrovascular deaths by person-years of follow-up. The cumulative risk of dying from cerebrovascular diseases in anti-HCV seronegatives and seropositives was estimated by Kaplan-Meier method and the statistical significance of the difference was examined by log-rank test.

Potential confounding factors examined in the analyses included entry age, sex, cigarette smoking status (never/current/past), habitual alcohol consumption (no/yes), serum levels of triglycerides and total cholesterol, body mass index (in kg/m^2), and history of diabetes, hypertension, and heart disease. Metabolic factors including body mass index and serum levels of triglycerides and total cholesterol were categorized based on guidelines for adult Asians.[20] In multivariate models, 3 metabolic factors were included as continuous variables.

Cox proportional hazards models were used to estimate multivariate-adjusted hazard ratio (HR) with 95% 95% CIs of cerebrovascular deaths for anti-HCV serostatus and other risk factors. Statistical significance levels were determined by 2-sided probability values of 0.05. The proportionality assumption (nonchanging HRs over time) of Cox models was examined, and the assumption was not violated. The statistical significance of the dose–response relationship between serum HCV RNA levels and risk of cerebrovascular death was assessed by a test for trend. Sensitivity analyses were examined to test anti-HCV seropositivity and serum HCV RNA levels and risk

Table 1. Baseline Characteristics of Study Participants by Serostatus of Antibodies Against HCV

Baseline Characteristics	Anti-HCV Seronegatives, No. (%) (n=22 358)	Anti-HCV Seropositives, No. (%) (n=1307)	*P*
Sex			
Females	11 053 (49)	734 (56)	<0.001
Males	11 305 (51)	573 (44)	
Age at recruitment, years			
Mean±SD	47.1±10.0	50.6±9.3	<0.001
30–39	6589 (30)	226 (17)	<0.001
40–49	5927 (27)	297 (23)	
50–59	6716 (30)	525 (40)	
60–65	3126 (14)	259 (20)	
Cigarette smoking			
Never	15 852 (71)	951 (73)	0.34
Past	765 (3)	42 (3)	
Current	5663 (25)	309 (24)	
Unknown	78	5	
Alcohol consumption			
No	19 908 (89)	1202 (92)	<0.001
Yes	2399 (11)	102 (8)	
Unknown	51	3	
Body mass index, kg/m^2			
Mean±SD	24.0±3.4	24.2±3.5	0.09
<23	9022 (40)	525 (40)	0.044
23–24.9	5289 (24)	274 (21)	
25–29.9	6933 (31)	430 (33)	
≥30	1063 (5)	76 (6)	
Unknown	51	2	
Serum triglycerides level, mmol/L			
Mean±SD	1.5±1.3	1.4±1.1	<0.001
<1.69	15 889 (71)	1008 (78)	<0.001
≥1.69	6372 (29)	289 (22)	
Unknown	97	10	
Serum total cholesterol level, mmol/L			
Mean±SD	4.8±1.1	4.6±1.1	<0.001
<5	13 920 (62.5)	875 (67.5)	<0.001
≥5	8347 (37.5)	421 (32.5)	
Unknown	91	11	
History of diabetes			
No	21 772 (98)	1248 (96)	<0.001
Yes	526 (2)	54 (4)	
Unknown	60	5	
History of heart disease			
No	21 891 (98)	1271 (98)	0.13
Yes	403 (2)	31 (2)	
Unknown	64	5	
History of hypertension			
No	21 028 (94)	1201 (92)	0.002
Yes	1266 (6)	101 (8)	
Unknown	64	5	



No. at Risk

Anti-HCV Seropositives	1307	1304	1297	1281	1268	1259	1245	1231	1213	1198	1171	1148	1126	1107	1080	1054	1029	577
Anti-HCV Seronegatives	22358	22291	22197	22088	21987	21869	21750	21614	21498	21338	21182	20991	20789	20589	20380	20170	19923	9940

Figure 2. Cumulative risk of cerebrovascular death by anti-HCV seropositivity.

of cerebrovascular deaths described previously by excluding those positive for HBsAg. All analyses were performed by using the SAS statistical software package (Release 9.1; SAS Institute Inc, Cary, NC).

Results

There were 22 358 participants seronegative for anti-HCV and 1307 seropositive for anti-HCV in this study (Figure 1). Baseline characteristics of study participants stratified by serostatus of anti-HCV are compared in Table 1. Anti-HCV seropositives had higher proportions of females, older ages, low educational level, no alcohol consumption, high body mass index, low serum triglycerides level, diabetes, and hypertension history than seronegatives ($P<0.05$).

All participants were followed for a median of 16.9 years. There were 255 cerebrovascular deaths occurred during 382 001 person-years of follow-up, giving a cerebrovascular mortality rate of 66.8 per 100 000 person-years. The cumulative risk of cerebrovascular deaths was 1.0% for anti-HCV seronegatives and 2.7% for anti-HCV seropositives (Figure 2, $P<0.001$). As shown in Table 2, increased cerebrovascular mortality rates were found for anti-HCV seropositives. The crude HR (95% CI) of cerebrovascular death was 2.61 (1.80 to 3.78) for seropositivity of anti-HCV. In multivariate model, the risk of cerebrovascular death for anti-HCV seropositives was 2.18 (1.50 to 3.16) compared with anti-HCV seronegatives (Table 3).

Among 1307 anti-HCV seropositives, 1154 had retrievable serum samples for the test of HCV RNA. Among 785 participants with detectable HCV RNA levels, 587 and 198 participants had low and high serum HCV RNA levels, respectively. Elevated serum HCV RNA levels were associated with an increasing the risk of cerebrovascular death with a dose–response relationship ($P<0.001$; Table 4). The multivariate-adjusted HR (95% CI) of cerebrovascular death was 1.40 (0.62 to 3.16), 2.36 (1.42 to 3.93), and 2.82 (1.25 to 6.37), respectively, for anti-HCV-seropositives with undetectable, low, and high serum HCV RNA levels compared with anti-HCV-seronegatives. The multivariate-adjusted HR (95% CI) of cerebrovascular death was 1.92 (0.98 to 3.75) and 3.48 (1.94 to 6.23) for anti-HCV-seropositive participants infected with genotype 1 and nongenotype 1 HCV, respectively, in another analysis. The risk of cerebrovascular death was 1.89 (0.79 to 4.53) for those infected with HCV nongenotype 1 compared with genotype 1 as the reference group.

By excluding 4129 (17.4%) participants seropositive for HBsAg, the associations between HCV infection and cerebrovascular death remained statistically significant. The multivariate-adjusted HR for anti-HCV seropositives was 2.14 (1.43 to 3.21) compared with seronegatives. The multivariate HR (95% CI) was 1.64 (0.73 to 3.71), 2.01 (1.12 to 3.61), and 2.78 (1.14 to 6.78), respectively, for anti-HCV seropositives with undetectable, low, and high serum HCV RNA level compared with anti-HCV seronegatives ($P<0.001$ for trend).

Discussion

Previous clinical studies found that HCV-infected transplant recipients had an increased risk of accelerated coronary stenosis.[21,22] Similar to our findings, a large-scale study in Australia found an excess mortality from circulatory diseases in a population with HCV infection showing a standardized mortality ratio of 1.3 (1.2 to 1.5) compared with the general population in Australia.[4] In another study of 10 259 anti-HCV seropositive and other 10 259 matched anti-HCV seronegative blood donors in the United States, the HR of death from stroke was 2.20 (0.84 to 5.79) for HCV infection.[23] The blood donor study essentially supported our findings with similar HR, but it was limited by the low statistical power to detect a significant association because of the small number (n=19) of cerebrovascular deaths in younger and generally healthier blood donors. Both studies may potentially be confounded by the inadequate adjustment of risk factors, including lifestyle habits, serum lipid profiles, and history of diseases.

There have been negative findings that failed to show the association between HCV infection and cardiovascular-

Table 2. Cerebrovascular Mortality Rates and Crude HRs by Baseline Risk Factors

Baseline Risk Factors	No. of Deaths (n=255)	Mortality per 100 000 Person-Years)	Crude HR (95% CI)
Anti-HCV			
Seronegative	223	62	1.00
Seropositive	32	158	2.61 (1.80–3.78)
Sex			
Female	97	50	1.00
Male	158	84	1.70 (1.32–2.19)
Age at recruitment, years			
30–39	11	10	1.00
40–49	30	29	3.05 (1.53–6.08)
50–59	116	101	10.64 (5.73–19.74)
60–65	98	197	21.29 (11.41–39.71)
Cigarette smoking			
Never	140	51	1.0
Exsmoker	10	79	1.58 (0.83–3.00)
Current smoker	105	113	2.26 (1.75–2.91)
Alcohol consumption			
No	216	63	1.00
Yes	39	101	1.62 (1.15–2.28)
Body mass index, kg/m^2			
<23	72	47	1.00
23–24.9	56	62	1.33 (0.94–1.89)
25–29.9	103	87	1.88 (1.39–2.54)
≥30	22	123	2.66 (1.65–4.29)
Serum triglycerides level, mmol/L			
<1.69	154	56	1.00
≥1.69	100	94	1.69 (1.32–2.18)
Serum total cholesterol level, mmol/L			
<5	134	56	1.00
≥5	120	86	1.53 (1.20–1.96)
History of diabetes			
No	231	62	1.00
Yes	24	306	5.25 (3.45–7.99)
History of heart diseases			
No	246	66	1.00
Yes	9	138	2.16 (1.11–4.19)
History of hypertension			
No	211	59	1.00
Yes	44	213	3.71 (2.68–5.13)

related disease. A case–control study enrolling men suggested no evidence to show HCV seropositivity and acute myocardial infarction.[24] HCV infection was found to have no significant impact on stroke, myocardial infarction, and carotid atherosclerosis after controlling risk factors.[25] In a follow-up study on atherosclerotic lesion through ultrasound scanning, chronic active hepatitis B/C was not associated with carotid plaques.[26] Unfortunately, the diagnostic of serostatus in that study was ill-defined.[26] The discrepancy in the findings of these previous studies and our study might have resulted from different characteristics of the study population and different prevalence of HCV infection. Moreover, it is probable that HCV infection may only play a role during particular stages of the natural history of atherosclerosis. In this study, there were 53 deaths from all vascular diseases among anti-HCV seropositives. Among them, 32 died from cerebrovascular diseases and 12 from ischemic heart diseases. There was no significant association between HCV infection and ischemic heart diseases showing an age- and sex-adjusted HR (95% CI) of 1.19 (0.66 to 2.14). However, the number of deaths from ischemic heart diseases among anti-HCV seropositives was too small to draw a confident conclusion for ischemic heart diseases.

The frequency and intensity of infection might be associated with the progression of atherosclerosis. A 2.5-year follow-up study on several serological markers of infectious agents showed that individuals who had been exposed to an increased number of infectious pathogens had an elevated risk of atherosclerosis.[27] Individuals seropositive for HCV core protein, 1 of the seromarkers of HCV replication, had 5.6 times risk of developing carotid plaque.[11] In our study, the increasing risk of cerebrovascular death across the biological gradient of serum HCV RNA levels was found and this dose–response relationship further supports the causal association.

Infectious agents may play as a stimulus for atherothrombosis.[7,27,28] Infection affects atherothrombosis by triggering a cascade of immune responses and inflammatory stimuli either locally within vascular tissue or systemically through inflammatory mediators.[29] It has been found that HCV infection is associated with an increased risk of cryoglobulinemia,[30] which is thought to participate in the formation of immune complexes precipitating in vessel walls then leads to vasculitis.[31] Elevated serum HCV RNA level was associated with an increased risk of cerebrovascular death, suggesting that individuals with an active HCV infection may trigger a stronger inflammation response by host–virus interaction leading to atherothrombosis. Whether patients with persistent HCV infection had increased circulating levels of inflammation markers such as C-reactive protein or endothelial progenitor cells may provide insights on the mechanisms of HCV infection and cerebrovascular disease.[32,33]

This study was limited to small number of cerebrovascular deaths (32 in anti-HCV seropositives); thus, the impacts of HCV infection on subtypes of stroke could not be evaluated adequately. Moreover, by using mortality data, whether HCV infection increased the incidence of cerebrovascular events or amplified the risk of cerebrovascular recurrence was not easily determined. Third, HCV infection was found to be a risk factor for the development of Type 2 diabetes.[34] It is possible that HCV infection induces the onset of diabetes and then the occurrence of cerebrovascular disease. Unfortunately, the incidence of diabetes of our study participants was

Table 3. Multivariate-Adjusted HRs and 95% CIs of Baseline Risk Factors Associated With Cerebrovascular Death

Baseline Risk Factors	Age- and Sex-Adjusted HR (95% CI)	Multivariate-Adjusted HR* (95% CI)
Anti-HCV seropositive versus seronegative	2.10 (1.45–3.05)	2.18 (1.50–3.16)
Male versus female	1.48 (1.15–1.91)	1.03 (0.73–1.47)
Age at recruitment, 10-year increment	2.91 (2.48–3.42)	2.64 (2.23–3.11)
Cigarettes smoking versus never		
Ex-smoker	1.04 (0.53–2.06)	1.07 (0.54–2.12)
Current smoker	2.02 (1.43–2.86)	2.18 (1.54–3.08)
Alcohol consumption versus no	1.26 (0.88–1.81)	(Not included, $P>0.05$)
Body mass index per 1-kg/m^2 increment	1.07 (1.04–1.11)	1.06 (1.02–1.10)
Serum triglycerides level per 1-mmol/L increment	1.39 (1.08–1.79)	1.16 (0.89–1.51)
Serum total cholesterol level per 1-mmol/L increment	1.18 (0.92–1.51)	(Not included, $P>0.05$)
History of diabetes versus no	3.05 (1.99–4.65)	2.64 (1.71–4.08)
History of heart diseases versus no	1.53 (0.79–2.98)	(Not included, $P>0.05$)
History of hypertension versus no	2.09 (1.51–2.91)	1.75 (1.24–2.47)

*Adjusted the variables which remained significant after adjustment for age and sex.

not followed and it was impossible to evaluate whether diabetes played an intermediate role. In this study, history of hypertension was based on self-report, which might thus be underestimated. Because there has never been a report on the association between hypertension and HCV infection, it is believed that the misclassification of self-reported hypertension status was nondifferential between anti-HCV seropositives and seronegatives. Therefore, the residual confounding effect of hypertension is considered limited. Finally, a HCV-infected patient with severe cerebrovascular disease was found to experience both progressive functional recovery and no recurrent stroke events during antiviral therapy.[35] There were very few people had interferon treatment in our study population; thus, it was hard to evaluate whether HCV eradication had impacts on cerebrovascular mortality.

Our study has implications for clinical practice and future researches. Patients infected with HCV need to be consulted by their clinicians about their increased risk for cerebrovascular mortality in addition to hepatic complications. Patients should be encouraged to modify their health behaviors to reduce potential risk for cerebrovascular disease. Chronic HCV infection was related to neurocognitive impairment, which cannot be attributed to coexistent depression or hepatic encephalopathy.[36] The recent detection of HCV genetic sequences in brain tissue raised the possibility of HCV infection of the central nervous system.[37] However, further studies are required to confirm pathological mechanisms. If future additional studies confirm the role of HCV infection and the development of cerebrovascular disease, it may be possible to prevent cerebrovascular disease by using specific antiviral strategies.

In conclusion, HCV infection is associated with an increased risk of cerebrovascular mortality, particularly for those with elevated serum HCV RNA levels.

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Table 4. Multivariate-Adjusted HRs of Cerebrovascular Death for Serum HCV RNA Levels

Molecular Test of HCV RNA	No. (%)	Cerebrovascular Disease Deaths	Multivariate-Adjusted Hazard Ratio (95% CI)†
Anti-HCV seronegatives	22358 (100)	223	1.00 (referent)
Serum HCV RNA level, IU/mL*			
Undetectable	369 (32)	6	1.40 (0.62–3.16)
Detectable with low levels	587 (51)	16	2.36 (1.42–3.93)
Detectable with high levels	198 (17)	6	2.82 (1.25–6.37)
			$P<0.001$ for trend

*Serum HCV RNA levels were tested for 1154 anti-HCV-seropositive participants and the HCV RNA level categorized as undetectable (<25 IU/mL), low (25–1.6×10^5 IU/mL), and high ($>1.6\times10^5$ IU/mL); the cutoff point for low/high levels (1.6×10^5 IU/mL) using the third quartile of all detectable levels.

†All analyses used anti-HCV-seronegative participants as the referent group and included age (10-year increment), sex, cigarette smoking, body mass index (per 1-kg/m^2 increment), serum triglycerides levels (per 1-mmol/L increment), history of diabetes, and hypertension in the multivariate models.

Disclosures

None.

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