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Increased Risk of Intracerebral Hemorrhage Among Patients With Hepatitis C Virus Infection

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Abstract: This research explored whether hepatitis C virus (HCV) infection leads to the development of intracerebral hemorrhage (ICH).

Using Taiwan National Health Insurance claims data, 9023 patients newly diagnosed with HCV infection between 2000 and 2010 were identified, and 36,092 age- and sex-frequency-matched patients without HCV infection were selected randomly as the control group. The risk of ICH for patients with HCV infection and comorbidities of diabetes, hypertension, ischemic heart disease, hyperlipidemia, atrial fibrillation, alcoholic liver disorder, and head injury was evaluated at the end of 2011.

The risk of ICH was higher in the HCV cohort than in the control group, with an adjusted hazard ratio (aHR) of 1.60 (95% confidence interval [CI]: 1.24–2.06), estimated using a multivariate Cox regression model. Age-specific analysis revealed that the risk of ICH in the HCV patients was higher in the younger groups, with aHRs of 1.92 (95% CI: 1.18–3.11) and 2.45 (95% CI: 1.52–3.98) in the ≤55 and 56 to 64 years age groups, respectively. The risk of ICH increased with the severity of HCV infection, from an aHR of 1.66 (95% CI: 1.21–2.30) in mild HCV patients to 2.12 (95% CI: 1.47–3.06) in severe HCV patients. For patients without comorbidities, the risk of ICH was 2.33 (95% CI: 1.36–3.98) higher in the HCV cohort than in the control group.

We found that HCV infection is associated with an increased risk to develop ICH, particularly in the patients with relatively younger ages.

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Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval, HCV = hepatitis C virus, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, ICH = intracerebral hemorrhage, NHIRD = National Health Insurance Research Database.

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INTRODUCTION

Intracerebral hemorrhage (ICH) is one of the main causes of debilitation and death among adults.^{1–3} ICH patients consume more socioeconomic resources and represent a greater health care burden than patients with ischemic stroke. ICH comprises approximately 10% to 20% of all strokes,^{1–3} and some pathological changes in the cerebral arteriolar wall, such as death and proliferation of vascular wall smooth muscle cells, ectasia of arteriolar walls with formation of microaneurysms,² and subsequent rupture of the microaneurysms,^{1–3} are frequently observed in ICH. Some traditional risk factors for ICH, including hypertension,^{1–6} diabetes,^{1,2,4–6} hyperlipidemia,^{5,6} ischemic heart disease (IHD),^{4–6} atrial fibrillation (AF),^{4,5} alcoholic liver disorder (ALD),^{1–3,6} and head injury,^{7,8} may trigger these pathological changes in the cerebral arteriolar walls. However, in approximately 10% to 25% of patients, the risk factors for ICH remain unclear,^{6,9} particularly among younger patients.^{6,10}

The role of chronic inflammation in increasing the formation of arterial ectasia and microaneurysms in coronary arteries has been proven in the literature.^{11,12} Some studies have also connected the development of ICH with chronic vasculitis in cerebral arterioles caused by viral infections such as human immunodeficiency virus (HIV)^{13,14} and varicella-zoster virus (VZV),^{13,15} and autoimmune diseases such as systemic lupus erythematosus (SLE)^{16,17} and rheumatoid arthritis (RA).^{16,18} Nevertheless, how inflammations trigger the cerebral arteriolar ectasia and subsequent generation and rupture of microaneurysms remains unknown.

Transmitted through the use of injection drug, blood transfusions, and unsafe therapeutic injections, the hepatitis C virus (HCV) has infected approximately 130 million people globally and has become a major worldwide health issue.^{19,20} HCV can lead to chronic liver disease, hepatic cirrhosis, and hepatocellular carcinoma, thereby increasing the socioeconomic burden.^{19,20} A few clinical studies have linked chronic HCV infection with the subsequent development of ICH, but the relevance of those studies is limited by their small sample sizes.^{21,22} Because the majority of the Taiwanese population is enrolled in the National Health Insurance (NHI) program of Taiwan, this study used a subset of the NHI claims database for the period of 2000 to 2010 to investigate the association

between HCV infection and the risk of ICH with a 12-year follow-up period.

MATERIALS AND METHODS

Data Source

This study enrolled patients from the 1 million insured in the Longitudinal Health Insurance Database (LHID), which comprises data derived from the National Health Insurance Research Database (NHIRD) for the period of 2000 to 2011.^{23,24} The data in the NHIRD are derived from Taiwan's NHI program, which was implemented in 1995 and covers >98% of the population of Taiwan. The details in the LHID include the medical facilities where patients were enrolled, the types of medical services provided, and demographic information. When the data of outpatient and inpatient enrollments were accessed into the LHID, they required the approval of the insurance authorities. Patient identification numbers, which are linked to data files, are scrambled before the release of files to researchers to ensure patient privacy. This study was approved by the Institutional Review Board of China Medical University (CMU-REC-101-012). Disease diagnoses were identified according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Study Subjects

The HCV cohort comprised patients with HCV (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, and V02.62) newly diagnosed between January 1, 2000 and December 31, 2010 without a previous history of stroke (ICD-9-CM codes 430–438). Patients with a history of HCV and hepatitis B virus (HBV) infections (ICD-9-CM 070.20, 070.22, 070.30, 070.32, and V02.61) during 1996 to 1999, or age <20 years were excluded. The date of the initial diagnosis of HCV infection was defined as the entry date. The control group comprised randomly selected patients without hepatitis infection or a history of stroke, sex- and age-frequency-matched to those in the HCV cohort at a ratio of 4:1. The flow chart of patient selection in HCV and control cohorts was shown in Figure 1.

Outcome and Relevant Variables

Both the HCV and the control cohorts were followed up until the end of 2011 to determine the incidence of ICH (ICD-9-CM code 431). Relevant factors to ICH were sex, age, annual

outpatient visits during the study period, medicine for HCV treatment (Ribavirin and Peginterferon), and comorbidities of diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), IHD (ICD-9-CM codes 410–414), hyperlipidemia (ICD-9-CM codes 272.0–272.4), AF (ICD-9-CM code 427.31), ALD (ICD-9-CM code 571.2), and head injury (ICD-9-CM codes 959.01, 432.1, 852.2, and 852.3). The risk of ICH was evaluated for patients with or without these variables.

Statistical Analysis

The *t* test and χ^2 test were used to compare the distributions of continuous and discrete variables, respectively, between the HCV cohort and the control group. The incidence of ICH was estimated per 1000 person-years, measured from the entry date to the initial ICH diagnosis, death, withdrawal from the insurance program, or the end of 2011. The HCV cohort and the control group were compared using the Cox regression model to determine the hazard ratios (HRs) and 95% confidence intervals (CIs), with stratification for sex, age (≤ 55 , 56–64, and ≥ 65 years), and comorbidity stratum (with and without anyone comorbidity including hyperlipidemia, hypertension, IHC, AF, diabetes, ALD, and head injury). The interaction tests for HCV and age, HCV and sex, and HCV and comorbidity were estimated using Cox proportional hazard regression. Multivariable Cox proportional hazard regression was adjusted for age, sex, annual outpatient visits, medicine for HCV treatment, and comorbidities.

The risk for ICH was further evaluated according to the severity of HCV infection, determined as HCV patients without (mild) and with hospitalization for HCV infection (severe). Incidence rates of ICH were measured for levels of severity, as well as adjusted hazard ratios (aHRs) relative to the control group. Trend test of ICH and the HCV severity was assessed using Cox proportional hazard regression. The effects of medical treatment on the ICH risk among HCV patients were also evaluated. The cumulative proportional incidences of ICH were further plotted for both cohorts by using the Kaplan–Meier model, and the log-rank test was used to determine the difference. A 2-tailed $P < 0.05$ was defined as significant. SAS Version 9.1 (SAS Institute Inc, Cary, NC) was used for all statistical analyses.

RESULTS

Men were slightly more in the both cohorts of HCV and controls (51.9%). Approximately one-fourth of the patients were >65 years old. After comparing with controls, the comorbidity correlated to ICH (such as diabetes, hypertension, hyperlipidemia, IHD, AF, ALD, and head injury) was significantly higher prevalent in the HCV cohort. The annual outpatient visit for HCV cohort was significantly higher than controls (29.8% vs 18.0%) (Table 1).

The risk of ICH was higher for men and elderly patients (Table 2). The comorbidities of hypertension, diabetes, ALD, and head injury were associated with a higher risk of ICH in all patients (Table 2). However, the HCV cohort had a greater risk of ICH than the comparison group (aHR = 1.68, 95% CI: 1.24–2.27 and 2.33, 95% CI: 1.36–3.98, respectively) regardless of comorbidities (Table 3). The overall risk of ICH was 1.83 times higher in the HCV cohort than in the control group (95% CI: 1.41–2.38). The incidence rates for ICH in the HCV and comparison cohorts were 1.60 and 0.94 per 1000 person-years, respectively (Table 2). The incidence of ICH increased with age in both cohorts (Table 3), but the age-specific risk for ICH was

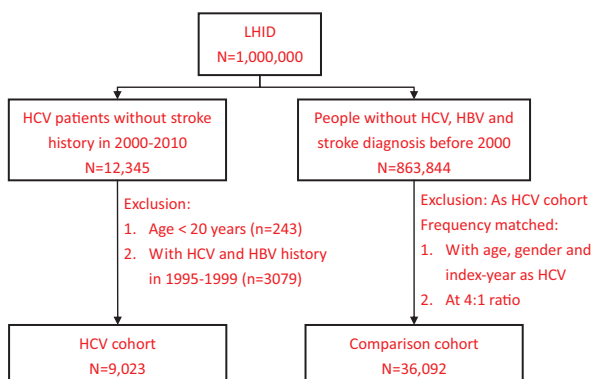


FIGURE 1. Flow chart for study subjects. HBV = hepatitis B virus, HCV = hepatitis C virus, LHID = Longitudinal Health Insurance Database.

TABLE 1. Demographic Factors and Comorbidities in the Hepatitis C Virus Infection and Control Groups

	Control N = 36,092		HCV Infection N = 9023		P
	n	%	n	%	
Age*, y					0.99
≤55	21,831	60.5	5212	57.2	
56–64	6001	16.6	1746	19.4	
≥65	8260	22.9	2065	22.9	
Mean (SD)†	52.3	(15.2)	52.7	(14.9)	
Sex					0.99
Women	17,356	48.1	4339	48.1	
Men	18,736	51.9	4684	51.9	
Comorbidity at baseline*					
Hyperlipidemia	6096	16.9	1934	21.4	<0.0001
Hypertension	9380	26.0	313	34.5	<0.0001
Ischemic heart disease	4073	11.3	1450	16.1	<0.0001
Atrial fibrillation	199	0.55	77	0.85	0.001
Diabetes	3436	9.52	1515	16.8	<0.0001
Alcoholic liver disorder	72	0.20	159	1.76	<0.0001
Head injury	2598	7.20	1071	11.9	<0.0001
Mean annual OPD visit, mean (SD)†	18.0	(16.5)	29.8	(21.2)	<0.0001
Mean follow-up duration, y (SD)†	6.23	(3.18)	5.80	(3.33)	<0.0001
Medicine use for HCV					
Only Peginterferon			6	0.07	
Only Ribavirin			8	0.09	
Both			1055	11.7	

HCV = hepatitis C virus, OPD = outpatient, SD = standard deviation.

* χ^2 test.

† *t* test.

significantly higher in the 56 to 64 years old HCV patients (aHR = 2.45, 95% CI: 1.51–3.98) (Table 3). The Kaplan–Meier plot showed that the cumulative incidence of ICH was higher in the HCV cohort than in the control group (log-rank $P < 0.0001$) (Figure 2).

Comparing the correlation between the severities of HCV infection with the risk of ICH revealed a dose–response association. The risk of developing ICH increased with the severity of HCV infection (Table 4). Compared with the control group, the aHRs for patients with HCV infection increased from 1.66 (95% CI: 1.21–2.30) for those with mild infection to 2.12 (95% CI: 1.47–3.06) for those with severe infection. HCV patients with medical treatment had a relatively lower ICH risk than those without medical treatment, with aHRs of 0.19 (95% CI: 0.03–1.38) and 1.83 (95% CI: 1.41–2.38), respectively (Table 4).

DISCUSSION

Previous studies have shown that patients with viral infections, such as HIV^{13,14} and VZV,^{13,15} and autoimmune diseases, such as SLE^{16,17} and RA,^{16,18} are at a higher risk of ICH. In the present study, HCV patients were compared with patients without this infectious disease in a 12-year follow-up period, and the HCV patients had a 1.60 times higher risk of ICH. A dose–response association with the severity of HCV infection was also observed. Persistent inflammation due to HCV infection might cause pathological changes in cerebral arterioles, which might trigger ICH development, as noted in some viral infections (eg, VZV and HIV infections) and autoimmune disorders (eg, RA and SLE). HCV-related chronic liver disease,

hepatic cirrhosis,^{19,20} and hepatocellular carcinoma might impair the human coagulation functions that might further enhance the risk of ICH noted in the present study.

More than 50% of our study patients were men and >75% were <65 years of age (Table 1). This is consistent with prior studies, noting that middle-aged men or younger are at higher risk of HCV infection.^{20,25,26} Men were more susceptible to the development of ICH than women (Table 2), which has been proven in prior studies.^{1–6,27} The most critical risk factor for ICH is age.^{1–6,27,28} The incidence rates of ICH increased with age in both the HCV and control groups in this study. Nevertheless, the observed age-specific aHRs for the HCV cohort and the control group were higher for relatively younger patients, with the higher aHRs of 1.92 and 2.54 noted in the ≤55 and 56 to 64 years age groups, respectively, decreasing to 1.33 in the ≥65-year age group (Table 3). Because the younger patients had fewer comorbidities associated with ICH, HCV is a more critical risk factor for younger patients than older patients. It is clear from this research that the risk of ICH increased in conjunction with HCV severity. These findings suggest a causal role of HCV in the development of ICH.

Comorbidities for Intracerebral Hemorrhage

Numerous studies have shown that the development of ICH risk is positively associated with older age,^{1–6,27,28} male sex,^{1–6,27} and the comorbidities of hypertension,^{1–6,27,28} diabetes,^{1,2,4–6,27,28} hyperlipidemia,^{5,6,27–29} IHD,^{4–6,27} AF,^{4,5,27,28} ALD,^{1–3,6,28} and head injury.^{7,8} In this study, the risk of ICH increased in participants with the comorbidities of hypertension, diabetes, ALD, and head injury (Table 2).

TABLE 2. Incidence and Hazard Ratios for Intracerebral Hemorrhage, Stratified by Demographic Factors and Comorbidities

	Event	P-Y	IR	Crude HR (95% CI)	Adjusted HR [†] (95% CI)
HCV infection					
No	211	224,959	0.94	1.00	1.00
Yes	84	52,364	1.60	1.71 (1.33–2.20)***	1.83 (1.41–2.38)***
Age, y					
≤55	89	172,382	0.52	1.00	1.00
56–64	80	49,154	1.63	3.16 (2.33–4.27)***	2.44 (1.78–3.36)***
≥65	126	55,796	2.26	4.38 (3.34–5.75)***	2.92 (2.15–3.98)***
Sex					
Women	121	136,157	0.89	1.00	1.00
Men	174	141,176	1.23	1.39 (1.10–1.75)**	1.56 (1.23–1.97)***
Comorbidity					
Hyperlipidemia					
No	242	230,499	1.05	1.00	–
Yes	53	46,834	1.13	1.08 (0.80–1.45)	–
Hypertension					
No	119	205,499	0.58	1.00	1.00
Yes	176	71,834	2.45	4.24 (3.56–5.35)***	2.77 (2.11–3.65)***
IHD					
No	235	245,600	0.96	1.00	1.00
Yes	60	31,733	1.89	1.98 (1.49–2.62)***	0.80 (0.60–1.09)
Atrial fibrillation					
No	292	276,110	1.06	1.00	—
Yes	3	12,223	2.45	2.31 (0.74–7.20)	—
Diabetes					
No	241	250,012	0.96	1.00	1.00
Yes	54	27,320	1.98	2.05 (1.53–2.76)***	1.08 (0.79–1.47)
Alcoholic liver disorder					
No	291	276,523	1.05	1.00	1.00
Yes	4	810	4.94	4.67 (1.74–12.5)**	2.95 (1.09–8.02)*
Head injury					
No	259	258,553	1.00	1.00	1.00
Yes	36	18,779	1.92	1.91 (1.35–2.71)***	1.72 (1.21–2.45)**
Annual outpatient visit					
Medicine use for HCV					
No	294	270,493	1.09	1.00	1.00
Yes	1	6839	0.15	0.14 (0.02–0.96)*	0.11 (0.02–0.76)*

CI = confidence interval, HCV = hepatitis C virus, HR = hazard ratio, IHD = ischemic heart disease, IR = incidence rate per 1000 person-years, P-Y = person-years. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

[†] Adjusted HR: mutually adjusted with age, sex, annual outpatient visits, medicine use, and all comorbidities that had significant differences in crude model.

Strengths and Limitations

This study had the advantages of a large sample size and a longitudinal design with minimal loss to follow-up. The large sample size enabled stratified analysis of data for examining the differences among sex, age, comorbidities, and severity of HCV. The dose–response relationship correlating to severity of HCV reinforces the validity of this research. Insurance claims for health care reimbursements in the Taiwan NHI program are under rigorous surveillance to prevent fraud. The NHI investigation system helps validate the diagnoses listed in insurance claims.

Nevertheless, this study also had limitations. First, information on some risk factors for cardiovascular diseases was not available in the claims data, including physical activity, lifestyle factors, and alterations of patients' immunity associated with HCV infection. Second, the results of laboratory data, for example, liver function tests (eg, alanine aminotransferase,

aspartate aminotransferase, γ -glutamyl transferase, alkaline phosphatase, and bilirubin), serum levels of HCV antigen titers and anti-HCV antibodies, serum C-reactive protein level and erythrocyte sedimentation rate, are unavailable in the NHIRD. Therefore, it was impossible to measure the relationship between various immune conditions in different HCV patients and the risk of ICH. Third, information regarding patients' personal habits and behaviors, such as alcohol consumption and cigarette smoking, are unavailable in the database. However, the relatively low smoking rate (<3.5%) among Taiwanese women³⁰ and the similar prevalence of ICH in men and women imply that cigarette smoking and alcohol consumption were unlikely to be confounders that would bias the correlation between HCV infection and ICH. This study estimated the risk of ICH in patients with HCV infection and revealed a higher prevalence of comorbidities in the patients with HCV infection than in the control group. However, after adjustment for these

TABLE 3. Incidence and Hazard Ratios for Intracerebral Hemorrhage Between the Hepatitis C Virus Infection and Control Groups, Stratified by Demographic Factors and Comorbidities

	Control		HCV Infection		HR (95% CI)	
	Event	IR	Event	IR	Crude	Adjusted
Age, y [†]						
≤55	62	0.44	27	0.82	1.85 (1.18–2.90)**	1.92 (1.18–3.11)**
56–64	51	1.30	29	2.93	2.24 (1.42–3.54)***	2.45 (1.51–3.98)***
≥65	98	2.12	28	2.90	1.37 (0.90–2.09)	1.33 (0.87–2.05)
Sex [‡]						
Women	91	0.83	30	1.15	1.40 (0.92–2.11)	1.53 (0.99–2.35)
Men	120	1.04	54	2.06	1.96 (1.42–2.71)***	2.03 (1.45–2.84)***
Comorbidity stratum ^{§,¶}						
No	63	0.45	19	0.77	1.70 (1.02–2.85)*	2.33 (1.36–3.98)**
Yes	148	1.73	65	2.35	1.36 (1.01–1.82)*	1.68 (1.24–2.27)***

CI = confidence interval, HCV = hepatitis C virus, HR = hazard ratio, IR = incidence rate per 1000 person-years. **P* < 0.05; ***P* < 0.01; ****P* < 0.001. All interaction tests *P* > 0.05 in Cox proportional hazard regression.

[†] Adjusted for sex, annual outpatient visits, medicine use, and all comorbidities that had significant differences in crude model (except hyperlipidemia and atrial fibrillation).

[‡] Adjusted for age, annual outpatient visits, medicine use, and all comorbidities that had significant differences in crude model (except hyperlipidemia and atrial fibrillation).

[§] Adjusted for age, sex, annual outpatient visits, and medicine use.

[¶] Comorbidity included hyperlipidemia, hypertension, ischemic heart disease, atrial fibrillation, diabetes, alcoholic liver disorder, and head injury.

confounding factors, the risk of ICH remained higher in the HCV cohort than in the comparison group. Thus, HCV infection is likely a causal factor in the development of ICH. The exact pathogenic mechanisms involved in this relationship warrant further research.

CONCLUSIONS

This study revealed a significant relationship between the risk of ICH and HCV infection. The results also showed that the

risk of ICH increases with the severity of HCV infection. Further research is required to confirm our results, particularly regarding younger patients and more severe cases of HCV infection. The findings in this study could lead to a useful method of preventing ICH for patients with HCV infection, particularly those of a younger age.

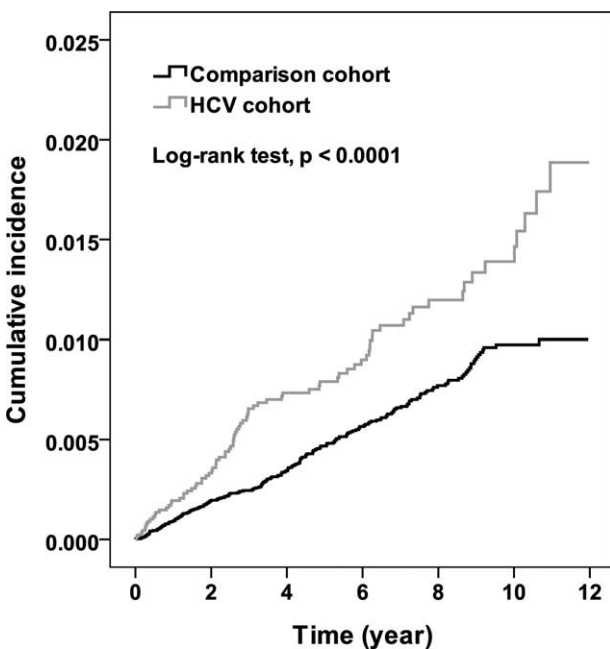


FIGURE 2. Comparison of cumulative incidence rates for intracerebral hemorrhage between the hepatitis C virus infection and control groups, demonstrated with the Kaplan–Meier model.

TABLE 4. Incidence and Hazard Ratios for Intracerebral Hemorrhage, Stratified by Hepatitis C Virus Infection With or Without Hospitalization During the Study Period, or Stratified by Hepatitis C Virus Infection With or Without Medical Treatment During the Study Period

	N	Event	IR	aHR (95% CI)
Model 1 [†]				
Control group	36,092	211	0.94	1.00
Hospitalization due to HCV infection				
No	5656	47	1.37	1.66 (1.21–2.30)**
Yes	3367	37	2.05	2.12 (1.47–3.06)***
<i>P</i> for trend				0.0001
Model 2 [‡]				
Control group	3692	211	0.94	1.00
Medicine use for HCV				
No	7954	83	1.82	1.83 (1.41–2.38)***
Yes	1069	1	0.15	0.19 (0.03–1.38)

aHR = adjusted hazard ration, CI = confidence interval, HCV = hepatitis C virus, IR = incidence rate per 1000 person-years. ***P* < 0.01; ****P* < 0.001.

[†] Adjusted for age, sex, annual outpatient visits, medicine use, and all comorbidities that had significant differences in crude model (except hyperlipidemia and atrial fibrillation).

[‡] Adjusted for age, sex, annual outpatient visits, and all comorbidities that had significant differences in crude model (except hyperlipidemia and atrial fibrillation).

REFERENCES

1. Ferro JM. Update on intracerebral hemorrhage. *J Neurol*. 2006;253:985–999.
2. Sutherland GR, Auer RN. Primary intracerebral hemorrhage. *J Clin Neurosci*. 2006;13:511–517.
3. Qureshi AI, Tuhim S, Broderick JP, et al. Spontaneous intracerebral hemorrhage. *N Engl J Med*. 2001;344:1450–1460.
4. Mayo NE, Nadeau L, Daskalopoulou SS, et al. The evolution of stroke in Quebec: a 15-year perspective. *Neurology*. 2007;68:1122–1127.
5. Telman G, Hlebtovsky A, Sprecher E, et al. Ethnic disparities in first primary intracerebral hemorrhage in northern Israel. *Neuroepidemiology*. 2010;34:208–213.
6. Lai SL, Chen ST, Lee TH, et al. Spontaneous intracerebral hemorrhage in young adults. *Eur J Neurol*. 2005;12:310–316.
7. Perel P, Roberts I, Bouamra O, et al. Intracranial bleeding in patients with traumatic brain injury: a prognostic study. *BMC Emerg Med*. 2009;9:15.
8. Oertel M, Kelly DF, McArthur D, et al. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. *J Neurosurg*. 2002;96:109–116.
9. Karatay M, Mehmetoğlu R, Erdem Y, et al. The relation between surgically treated spontaneous intracerebral hematomas and mortality: retrospective evaluation of 72 cases. *Türk Nöroloji Dergisi*. 2012;18:83–87.
10. Fogelholm R, Nuutila M, Vuorela AL. Primary intracerebral haemorrhage in the Jyväskylä region, central Finland, 1985–89: incidence, case fatality rate, and functional outcome. *J Neurol Neurosurg Psychiatry*. 1992;55:546–552.
11. Li JJ, Nie SP, Qian XW, et al. Chronic inflammatory status in patients with coronary artery ectasia. *Cytokine*. 2009;46:61–64.
12. Nichols L, Lagana S, Parwani A. Coronary artery aneurysm: a review and hypothesis regarding etiology. *Arch Pathol Lab Med*. 2008;132:823–828.
13. Nagel MA, Mahalingam R, Cohrs RJ, et al. Virus vasculopathy and stroke: an under-recognized cause and treatment target. *Infect Disord Drug Targets*. 2010;10:105–111.
14. Dobbs MR, Berger JR. Stroke in HIV infection and AIDS. *Expert Rev Cardiovasc Ther*. 2009;7:1263–1271.
15. Gilden D, Cohrs RJ, Mahalingam R, et al. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol*. 2009;8:731–740.
16. Zöller B, Li X, Sundquist J, et al. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immunemediated diseases: a nationwide follow-up study from Sweden. *BMC Neurol*. 2012;12:41.
17. Emsley HC, Tyrrell PJ. Inflammation and infection in clinical stroke. *J Cereb Blood Flow Metab*. 2002;22:1399–1419.
18. Holmqvist M, Gränsmark E, Mantel Ä, et al. Occurrence and relative risk of stroke in incident and prevalent contemporary rheumatoid arthritis. *Ann Rheum Dis*. 2013;72:541–546.
19. Alter MJ. Epidemiology of hepatitis C virus infection. *World J Gastroenterol*. 2007;13:2436–2441.
20. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis*. 2005;5:558–567.
21. Karibe H, Niizuma H, Ohyama H, et al. Hepatitis C virus (HCV) infection as a risk factor for spontaneous intracerebral hemorrhage: hospital based case-control study. *J Clin Neurosci*. 2001;8:423–425.
22. Aiba T, Watanabe T, Koike T, et al. C-type hepatitis in spontaneous intracerebral hemorrhage. *No To Shinkei*. 1996;48:1116–1119.
23. Tseng CH, Chen JH, Muo CH, et al. Increased risk of ischaemic stroke amongst patients with chronic osteomyelitis: a population-based cohort study in Taiwan. *Eur J Neurol*. 2015;22:633–639.
24. Tseng CH, Huang WS, Muo CH, Chang YJ, Sung FC. Increased risk of intracerebral hemorrhage among patients with chronic osteomyelitis. *J Neurosurg*. 2015. <http://thejns.org/doi/abs/10.3171/2014.11.JNS141269>. [Epub ahead of print].
25. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med*. 2006;144:705–714.
26. Sievert W, Altraif I, Razavi HA, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver Int*. 2011;31:61–80.
27. Zhang J, Wang Y, Wang GN, et al. Clinical factors in patients with ischemic versus hemorrhagic stroke in East China. *World J Emerg Med*. 2011;2:18–23.
28. Abbott RD, Curb JD, Rodriguez BL, et al. Age-related changes in risk factor effects on the incidence of thromboembolic and hemorrhagic stroke. *J Clin Epidemiol*. 2003;56:479–486.
29. Bozulolcay M, Nalbantoglu M, Gozubatik-Celik RG, et al. Hypercholesterolemia as one of the risk factors of intracerebral hemorrhage. *Acta Neurol Belg*. 2013;113:459–462.
30. Health Promotion Administration, Taiwan. *Taiwan Tobacco Control Annual Report 2014*. Taipei: Ministry of Health and Welfare, Taiwan; 2014.