Chung Shan Medical Journal 2016; 27:21-30

Original Article

The association between hypertension and viral hepatitis disease: a pilot study

Chia-Chi Lung[1*], Chun-Chih Lin[2], Shou-Shou Kuo[3]

[1] *Department of Public Health and Institute of Public Health, Chung Shan Medical University/ Department of Family and Community Medicine, Chung Shan Medical University Hospital, No.110, Sec.1, Jianguo N.Rd., Taichung 40201, Taiwan, R.O.C*

[2] *Department of Natural Biotechnology/ Graduate Institute of Natural Healing Sciences, Nanhua University, No. 55, Nanhua Rd., Dalin Township, Chiayi County 622, Taiwan, Republic of China (R.O.C.)*

[3] *Department of Public Health and Institute of Public Health, Chung Shan Medical University*

Hypertension, is an important risk factor for many non-infectious diseases. Very few studies have investigated the association between hypertension and infectious disease. In this study, we performed a prospective cohort analysis to explore the association between hypertension and viral hepatitis disease. The data were from the Taiwan's National Health Insurance Research Database (TNHIRD), which is a source database of the national health care system of Taiwan. The ICD-9-CM diagnostic codes were used to define cases of hypertension from January 1, 2005 to December 31, 2005. Cases of hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) disease were identified from 2007-2009. In regard to viral hepatitis disease, the association of hypertension and HAV or HCV disease was statistically significant by adjusting diabetes mellitus or obesity. The results indicated that HAV or HCV infection was significantly associated with hypertension, but not with HBV. Although the biologic mechanisms underlying the association of hypertension-HCV are unclear, the association discovered in this study may facilitate the management in hypertension and HCV.

Key words: hypertension, viral hepatitis disease, HAV, HBV, HCV

Introduction

Hypertension, an incommunicable disease, is an important risk factor for cardiovascular disease[1], stroke[2,3], Alzheimer disease [4,5], dementia [6,7], cognitive decline [8], left ventricular hypertrophy [9], cervical artery dissection [10], colonic diverticular bleeding [11] and eye abnormality [12]. Besides, hypertension is a possibly important risk factor in association with non-vascular impairment and has also been associated with an increased incidence of breast cancer [13], kidney disease or cancer [14], gout [15], nephropathy [16], and uterine leiomyomata [17]. In the same light, the synergistic effects of hypertension and dengue hemorrhagic fever or ischemic stroke on diabetes mellitus have been documented [18]. Previous findings have shown hypertension to be an important risk factor for many diseases.

On the other hand, viral hepatitis B/ C disease are frequently associated with hepatoma, which is of major public health importance [19,20]. Hepatoma has become the leading cause of death among Taiwanese adults, with 53.60 morbidity (per

* Corresponding Author:
Affiliation:
CCLung: TEL: +886-4-24730022 ext. 12181; FAX: :+886-4-23248179; email: dinoljc@csmu.edu.tw
CCLin: TEL: +886-972019645; FAX:+886-5-2427195; email: benjasado@gmail.com
SS Kuo: TEL: +886-4-912778180; FAX: :+886-4-23248179; email: shoushou_kuo@episil.com

100,000) in men and 21.69 in women reported in 2009 and 36.55 mortality of in men and 14.03 in women in 2011[21]. While many studies have investigated the association between hypertension and non-infectious diseases, few research works have been conducted to assess the relationship between hypertension and infectious disease. Therefore, the purpose of this study is to explore the association between hypertension and viral hepatitis disease.

Material and Methods

Data Sources and Sampling

Our data were from the Taiwan's National Health Insurance Research Database (TNHIRD), which is a source database of the national health care system of Taiwan (http://nhird.nhri.org.tw/en/index.htm). TNHIRD contains detailed clinical records of every patient during each visit. The database also included primary and secondary diagnostic codes as well as prescription orders. The National Health Insurance (NHI) program of Taiwan began in 1995 and finances compulsory universal health care for 99% of the estimated 23 million residents[22]. The data used for the analyses included just those individuals with insurance. The database included demographic data, all health-care encounters, expenditure, enrolment and withdrawal dates. All identifiers of all patients were completely removed before the release of the documentation and the encrypted data used in our study cannot link to any of the specific individual. All researchers who wish to use the NHIRD and its data subsets are required to sign a written agreement declaring that they have no intention of attempting to obtain information that could potentially violate the privacy of patients or care providers (http://nhird.nhri.org.tw/en/Data_Protection.html). This study, using de-identified secondary data, was exempt from full review by the internal Review Board.

The National Health Research Institutes (NHRI) randomly sampled 1,000,000 insured from the registry, and created the Longitudinal Health Insurance Database in 2005 (LHID2005). In this study, we retrieved a randomized sample of 40,000 from LHID2005. Diagnostics guidelines from the "International Classification of Diseases, 9th Revision, Clinical Modification" (ICD-9-CM) were used to identify the diseases of interests.

Definition of Hypertension

The ICD-9-CM diagnostic codes 401and 402 were used to describe or define cases of hypertension from January 1, 2005 to December 31, 2005. Patients were identified from data subsets CD or DD. CD indicated the ambulatory care expenditures by visit, and DD indicated the inpatient expenditures by admission.

Definition of HAV, HBV, HCV disease

In the follow-up period (from January 1, 2007 to December 31, 2009), the incident case of HAV, HBV and HCV disease were identified. Cases of HAV, HBV and HCV disease were identified from the 2007-2009 data using the ICD-9-CM diagnostic codes: 0700 and 0701 (HAV); 0702 and 0703 for HBV; 0704 and 0705 for HCV.

Patients less than 20 years old, HIV infection, HAV, HBV, and HCV disease from January 1, 2005 to December 31, 2006 were excluded from the cohort. A total of 5037 patients with hypertension (48.79% men) satisfied the requirement for this study. For each hypertensive patient, a control subject who matched the patient's sex was chosen.

Confounders

Demographic characteristics such as gender and geographical region can be collected from registry of beneficiaries of the TNHIRD. In this study, two main branches of the NHI have been categorized based on geographic and administrative districts: Northern (Taipei City, Taipei County, Keelung City, Kinmen County, Lianjiang County, Taoyuan County, Hsinchu City, Hsinchu County, Miaoli County), and others (Taichung City, Taichung County, Changhua County, Nantou County, Tainan City, Tainan County, Chiayi City, Chiayi County, Yunlin County, Kaohsiung City, Kaohsiung County, Pingtung County, Penghu County, Yilan County, Hualien County, Taitung County). Hypertension is usually associated with metabolic disorders such as obesity and diabetes, and may

contribute to disease susceptibility. We adjusted the potential confounders such as age, diabetes and obesity.

Statistical analyzes

All statistical analyses were performed using the SAS statistical package v.9.2 (SAS Institute Inc.). We used t test to analyze the differences between age variable and Pearson's $\chi 2$ test to test the association between sex and geographical region among hypertensive and non-hypertensive (control) individuals. In addition, we used multivariate Cox's proportional hazard regression models to evaluate the association between hypertension (independent variable) and HAV, HBV and HCV disease (dependent variable) during the 3-year follow-up period. Sociodemographic characteristics and other potential confounders (diabetes mellitus, obesity) were adjusted. Significant differences were considered significant at a p-value < 0.05.

Results

Characteristics of the population are described in Table 1. Overall, the study cohort included 5037 hypertensive cases and 5037 controls. The average age (61.27 years) of the hypertension group was higher than that of the control group (p<0.0001). There were 36.5% hypertensive and 7.35% non hypertensive cases (control) suffering from diabetes mellitus. The proportion of obesity in hypertensive individuals (46.45%) was higher than in the control group (12.34%).

Table 2 showed the summary statistics of factors associated with HAV, HBV and HCV disease. In case of HAV or HCV disease, hypertension was found to be an interrelated factor. A significant association between HAV or HCV disease and hypertension was found among subjects without diabetes or obesity (p<0.05).

The crude hazard ratios and 95% CI of hypertension associated with HAV, HBV and HCV disease are shown in Table 3. The crude HR (95%CI) of hypertension was 1.83 (1.16-2.88) for HAV, 0.86 (0.6-1.23) for HBV, and 2.13 (1.32-3.42) for HCV. The HR of hypertension and HAV disease for subjects without diabetes was 2.20 (95% CI=1.33-3.60); it was 1.77 (95% CI=1.03-3.05) for

Table 1. ***Sociodemographic characteristics of study population***

Variable	*Hypertension*		*p-value*
	Presence (n=5037)	*Absence (n=5037)*	
Age (mean±SD)	61.27±13.91	40.18±14.21	<0.0001
Gender			
Male (%)	2458 (48.79)	2458 (48.79)	1.00
Geographical Region			
Northern (%)	2387 (47.38)	2635 (52.31)	<0.0001
Diabetes mellitus			
Yes (%)	1839 (36.50)	369 (7.35)	<0.0001
Obesity			
Yes (%)	2340 (46.45)	622 (12.34)	<0.0001

SD: standard deviation

Table 2. ***Summary of statistics for factors associated with HAV, HBV and HCV disease***

Variable	*HAV*			*HBV*			*HCV*		
	Presence (n=82)	*Absence*	*p-value*	*Presence (n=166)*	*Absence*	*p-value*	*Presence (n=78)*	*Absence*	*p-value*
Hypertension			0.007			0.085			0.001
Presence	53	4984		72	4965		53	4984	
(%)	(1.05)	(98.95)		(1.43)	(98.57)		(1.05)	(98.94)	
Absence	29	5008		94	4943		25	5012	
(%)	(0.58)	(99.42)		(1.86)	(98.13)		(0.50)	(99.50)	
Age									
< 65									
Hypertension			0.065			0.642			0.032
Presence	27	2843		58	2812		24	2846	
(%)	(0.94)	(99.06)		(2.02)	(97.98)		(0.84)	(99.16)	
Absence	27	4679		89	4671		21	4685	
(%)	(0.57)	(99.43)		(1.89)	(98.11)		(0.45)	(99.55)	
≧ 65									
Hypertension			0.338			0.092			0.847
Presence	26	2141		14	2153		29	2138	
(%)	(1.20)	(98.80)		(0.60)	(99.40)		(1.34)	(98.66)	
Absence	2	329		5	326		4	327	
(%)	(0.60)	(99.40)		(1.51)	(98.49)		(1.21)	(98.79)	

subjects without obesity. The HR of hypertension and HCV disease was 2.34 (95% CI=1.34-4.09) times higher among subjects without diabetes mellitus, while the HR of hypertension and HCV disease was 3.18 (95% CI=1.70-5.92) times higher among subjects without obesity.

Table 4 shows the association between hypertension and HAV or HCV disease after adjusting for sociodemographic factors (i.e. age) and comorbidities (i.e. diabetes mellitus, obesity). After adjusting for age, diabetes mellitus or obesity, multivariate Cox regression analysis showed that hypertension was significantly associated with HAV disease ($p<0.05$), with HR of 1.86, 2.00 and 1.76, respectively. With regard to HCV disease, to study the associations separately adjusting diabetes mellitus or obesity, the association of hypertension and HCV disease was statistically significant, with HR of 1.91, and 1.84.

Discussion

According to the ICD-9-CM, the definition of hypertension is coded as 401 to 405, excluding the complicating pregnancy, childbirth, or the puerperium (642.0-642.9) and coronary vessels (410.00-414.9). To reduce potential for misdiagnosed hypertension in this study, a narrow

Table 2. ***Summary of statistics for factors associated with HAV, HBV and HCV disease (continued)***

Variable	*HAV*			*HBV*			*HCV*		
	Presence (n=82)	*Absence*	*p-value*	*Presence (n=166)*	*Absence*	*p-value*	*Presence (n=78)*	*Absence*	*p-value*
Diabetes mellitus									
Yes									
Hypertension			0.917			0.150			0.729
Presence	14	1825		26	1813		21	1818	
(%)	(0.76)	(99.24)		(1.41)	(98.59)		(1.14)	(98.86)	
Absence	3	366		9	360		5	364	
(%)	(0.81)	(99.19)		(2.44)	(98.56)		(1.36)	(98.64)	
No									
Hypertension			0.001			0.193			0.004
Presence	39	3159		46	3152		32	3316	
(%)	(1.22)	(98.78)		(1.44)	(98.56)		(1.00)	(99.00)	
Absence	26	4642		85	4583		20	4648	
(%)	(0.56)	(99.44)		(1.82)	(98.18)		(0.43)	(99.57)	
Obesity									
Yes									
Hypertension			0.300			0.000			0.226
Presence	26	2314		37	2303		24	2316	
(%)	(1.11)	(99.89)		(1.58)	(98.42)		(1.03)	(98.97)	
Absence	4	618		26	596		10	612	
(%)	(0.64)	(99.36)		(4.18)	(95.82)		(1.61)	(98.39)	
No									
Hypertension			0.037			0.406			0.000
Presence	27	2670		35	2662		29	2668	
(%)	(1.00)	(99.00)		(1.30)	(98.70)		(1.08)	(98.92)	
Absence	25	4390		68	4347		15	4400	
(%)	(0.57)	(99.43)		(1.54)	(98.46)		(0.34)	(99.66)	

definition of hypertension was adopted; in which those fulfilled with code 403 to 405 were excluded from this study to avoid misclassification resulting from renal disease or secondary hypertension. Alternatively, although the HAV, HBV, or HCV in this study was identified by ICD-9-CM, the validity of disease status was diagnosed by the physician or confirmed by laboratory. Given the high accuracy of data registration in NHIRD, prospective study design (i.e. hypertension reported prior to the diagnosis of HAV, HBV, or HCV), misclassification of hypertension was likely to be non-differential.

Table 3. ***Crude hazard ratios (HR, 95% CI) of factors predictive of HAV, HBV and HCV disease (2007-2009)***

Variable	*HAV*		*HBV*		*HCV*	
	HR	*95% CI*	*HR*	*95% CI*	*HR*	*95% CI*
Hypertension (presence/absence)	1.83	1.16-2.88	0.86	0.60-1.23	2.13	1.32-3.42
Age						
< 65						
Hypertension (presence/absence)	1.64	0.97-2.80	1.15	0.77-1.70	1.90	1.05-3.37
≧ 65						
Hypertension (presence/absence)	2.00	0.47-8.40	0.61	0.17-2.16	1.11	0.40-3.20
Diabetes mellitus						
Yes						
Hypertension (presence/absence)	0.94	0.27-3.26	0.92	0.35-2.41	0.85	0.31-2.24
No						
Hypertension (presence/absence)	2.20	1.33-3.60	0.79	0.50-1.20	2.34	1.34-4.09
Obesity						
Yes						
Hypertension (presence/absence)	1.74	0.60-4.70	0.40	0.22-0.73	0.63	0.30-1.33
No						
Hypertension (presence/absence)	1.77	1.03-3.05	0.95	0.58-1.53	3.18	1.70-5.92

Information bias was minimized by the use of the high accuracy of data registration for consistent clinical documentation. Additionally, selection bias was minimized because the study subjects were from NHIRD database. Despite this, possible disease misclassifications (non-differential) cannot be ruled.

It remains unclear to what extent the increased risk of hypertension in HAV or HCV could be explained by major biological and lifestyle risk factors. Nonetheless, the differences in risk factors responsible for viral hepatitis may be attributed to disease-susceptibility, lifestyle and dietary habits, or immunity. A noncausal relationship may have existed between hypertension and viral hepatitis disease. The cause-effect relationships have not been established due to limited documents. The main risk factors for HCV disease include; blood transfusion, sexual contact, medical or dental treatment, a reused syringe, family members or close contacts who are anti-HCV positive, and injecting drug use[23,24]. In this study, we found that hypertension increased the risk of HCV disease nearly twofold than the control group. After adjusting for age, hypertension was associated with a 1.5-fold increase in the risk for HCV disease, although the difference did not reach statistical significance. The younger subjects (<65 years of age) had a higher risk of developing HCV disease although the mechanism underlying such an increase is not fully understood. We postulated the biological mechanism linking hypertension with HCV disease is through immunodeficiency. Abnormalities of the immune response can be secondary to renal failure. Elevated diastolic blood pressure may increase renal cell damage through oxidative stress and renal expression of oxidant and antioxidant enzymes [25]. Uncontrolled or long term hypertension causes renal damage directly or indirectly, thus increasing the

Table 4. ***Adjusted hazard ratios (HR, 95% CI) of factors predictive of HAV and HCV disease (2007-2009)***

Model	*HR*	*95% CI*
HAV disease		
Model 1	1.86	1.07-3.25
Model 2	2.00	1.25-3.21
Model 3	1.76	1.08-2.86
HCV disease		
Model 1	1.50	0.85-2.66
Model 2	1.91	1.15-3.18
Model 3	1.84	1.10-3.07

Model 1: Adjusted variables included age.
Model 2: Adjusted variables included diabetes mellitus.
Model 3: Adjusted variables included obesity.

individual's susceptibility to immunodeficiency disorder and infective agents. On the other hand, hypertension is closely related to stroke events[26]. Immunomodulation and inflammation are frequently seen in patients with central nervous system injury or stroke. Frequent infections are leading causes of deaths in patients suffering from stroke[27]. In contrast, co-morbidities such as hypertension, diabetes mellitus, and obesity are among the few leading causes of mortality and morbidity globally[28], and have been associated with severe clinical manifestations of HCV disease[29,30]. The relationship between hypertension and viral hepatitis disease is complex. Nonetheless, the transmission pattern of hepatitis A disease for the most part was dependent on dietary habit. In our study, after adjusting the potential risk factors, hypertension remained an independent risk factor of HAV disease; this may be attributed to inappropriate diets and lifestyle of the hypertensive patient subjects with hypertension. However, the major role played by diets in such an association has not been conclusively demonstrated. The relationship between hypertension and HAV disease remains to be clarified. The present study found that hypertension was associated with a higher relative risk of HCV disease. Although the mechanism of action is unknown, this study using large-scale population-based cohort obtains a association between hypertension and HCV disease. Perhaps it can provide some information in public health and be of significant value for the government and health care providers.

Some of the limitations of the study included the absence of the health-related behaviors or status such as smoking, alcohol consumption, diet, BMI, physical activities, blood transfusion and education. Another limitation of the study included insufficient information on the use antihypertensive medications and lifestyle modifications. In other words, both systolic and diastolic hypertension was not taken into account and their associations were not assessed. An important limitation of our study was dependent on binary classification of hypertension and the severity of hypertension (blood pressure measurements, for example) was unavailable. If chronic hepatitis risk is higher for people with higher blood pressure, as evidence suggests, the higher blood pressures among hypertensive subjects could explain the observed hazard ratios compared subjects with lower pressures. In addition, HCV disease being a chronic infection that may stay asymptomatic for longtime (even lifelong). It is likely that some of the HCV disease detected in the follow up period had been acquired prior to 2005 which could be in favor of reverse causation.

This is a large scale population based on prospective cohort study to investigate the

association between hypertension and viral hepatitis disease. The sizable number of follow-up in this study offers a longitudinal view of the study subjects' viral hepatitis disease over time. Statistical analysis indicated that HAV or HCV disease was significantly associated with hypertension, but not with HBV. The mechanism between hypertension and HAV or HCV disease is needed to be clarified in future study. Understand the mechanisms between hypertension and HAV or HCV disease may facilitate clinical management.

List of abbreviations

HAV: hepatitis A virus disease
HBV: hepatitis B virus disease
HCV: hepatitis C virus disease
TNHIRD: Taiwan's National Health Insurance Research Database
NHRI: National Health Research Institutes
LHID2005: Longitudinal Health Insurance Database in 2005

Competing interests

The authors report no conflicts of interest.

Author's contributions

Lung CC and Lin CC formulated the concept and design of the study. Lung CC and Kuo HH performed the data analysis and drafted the manuscript. All authors approved the final manuscript.

Acknowledgments and Disclosures

The authors would like to thank Nfor ON for help with the grammatical review and native-English edit of the paper.

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