

Association of Gallbladder Polyp and Stroke

A Nationwide, Population-Based Study

Chien-Hua Chen, MD, MPH, Cheng-Li Lin, MSc, and Chia-Hung Kao, MD

Abstract: Gallbladder polyp (GP) and stroke share several metabolic disorders as risk factors. We assessed the association between GP and subsequent stroke risk.

From 2000 to 2011, patients with GP aged >20 years were identified from the Longitudinal Health Insurance Database 2000. Of the 15,975 examined patients, 12,780 and 3195 were categorized into the non-GP and GP cohorts, respectively. The relative risks of stroke were estimated using the Cox proportional hazard model after adjusting for age, sex, and comorbidities.

The overall incidence of stroke was higher in the GP cohort than in the non-GP cohort (6.66 vs 5.20/1000 person-yr), with an incidence rate ratio (IRR) of 1.28 (95% confidence interval [CI] = 1.15–1.42). The risk of stroke was 1.32-fold (95% CI = 1.06–1.63) in patients with GP compared with patients without GP after adjusting for age, sex, income level, urbanization level, occupation and comorbidities of gallstone, alcohol-related illness, diabetes, hyperlipidemia, hypertension, obesity, COPD, coronary heart disease, and asthma. Furthermore, the stroke risk was higher among elderly patients (with 1-yr intervals; adjusted HR [aHR] = 1.06, 95% CI = 1.05–1.07), the male sex (aHR = 1.62, 95%

CI = 1.35–1.96), lower income level (aHR = 1.37, 95% CI = 1.02–1.85 for level I; aHR = 1.62, 95% CI = 1.25–2.10 for level II), living in second urbanized areas (aHR = 1.28, 95% CI = 1.00–1.63), alcohol-related illness (aHR = 1.56, 95% CI = 1.07–2.28), diabetes (aHR = 1.78, 95% CI = 1.41–2.24), and hypertension (aHR = 2.74, 95% CI = 2.19–3.42).

GP is associated with stroke; however, GP may be less influential than other risk factors are, such as male sex, lower income level, alcohol-related illness, diabetes, and hypertension, on stroke development. Additional studies are required to clarify whether GP is a risk factor for or an epiphenomenon of stroke development.

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Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, GP = gallbladder polyp, HR = hazard ratios, IRR = incidence rate ratio, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database.

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From the Digestive Disease Center, Show-Chwan Memorial Hospital, Changhua (C-HC); Hungkuang University, Taichung (C-HC); Meiho University of Technology, Pingtung (C-HC); School of Medicine, China Medical University (C-LL); Management Office for Health Data, China Medical University Hospital (C-LL); Graduate Institute of Clinical Medicine Science and School of Medicine, College of Medicine, China Medical University (C-HK); Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan (C-HK).

Correspondence: Chia-Hung Kao, Graduate Institute of Clinical Medicine Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung City 404, Taiwan (e-mail: d10040@mail.cmuh.org.tw).

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INTRODUCTION

Gallbladder polyp (GP) is clinically defined as tumor outgrowth from the gallbladder mucosa; GP is usually detected incidentally in ultrasonographs or in resected gallbladder specimens after cholecystectomy.¹ GPs are easily diagnosable through ultrasonography, with reported sensitivity and specificity higher than 92% and 95%, respectively.² In ultrasonography, a GP is defined as an intraluminal lesion with a smooth border abutting the gallbladder wall. In contrast to the lesion observed in gallstones, a GP is immobile and with no acoustic shadow.³ Furthermore, ultrasonography is increasingly used during physical examinations of symptomatic and asymptomatic patients; therefore, the reported prevalence of GPs is expected to increase. The prevalence of GPs in Taiwan was reported to be approximately 6.9% to 9.5%.^{4,5} Several possible mechanisms underlie GP development. First, a high pool of biliary cholesterol increases the hepatic acyl-CoA:cholesterolacyltransferase 2 (ACAT2) activity and esterifies cholesterol. Subsequently, the cholesterol is engulfed by the macrophages and is deposited in the gallbladder mucosa. Third, cholesterol deposition stimulates papillary hyperplasia of the gallbladder mucosa and impairs the contractility of the gallbladder. Finally, the stasis of venous and lymphatic systems disturbs cholesterol absorption and secretion mechanisms of the gallbladder mucosa to result in the development of cholesterol polyps.^{6–10} Nevertheless, adenomyomatosis and inflammatory polyps are related to chronic inflammation with bile sludges or gallstones. The risk factors for GPs remain inconclusive, although the male sex, glucose intolerance, obesity, and several components of metabolic syndrome are possibly related to GP development.^{11–14} These suggested GP risk factors also increase the risk of cardiovascular diseases and stroke.¹⁵

Stroke is the second leading cause of mortality and the most common cause of acquired disability worldwide.^{16,17} Furthermore, stroke remains the leading cause of acquired disability and the third leading cause of death in Taiwan.¹⁸ The reported annual incidence rate and stroke prevalence in Taiwan is approximately 330 to 527 and 1427 to 1930 per 100,000 persons, respectively;^{19–23} the proportionate mortality of stroke is approximately 7.2%, with 47 stroke-related deaths per minute, making stroke the fifth leading cause of death in 2012.²⁴ Furthermore, stroke imposes a substantial burden of approximately US\$475 million per year on the national health-care system in Taiwan, and the impact is increasing as the population ages. In Taiwan, ischemic stroke accounted for 74% of all strokes, followed by intracerebral hemorrhage, transient ischemic attack, subarachnoid hemorrhage, and cerebral venous thrombosis. Risk factors for stroke widely vary worldwide; however, hypertension, diabetes, and dyslipidemia are generally accepted as risk factors for stroke.^{25–27}

Assessing the stroke risk after GP development through a large-scale, population-based study is necessary for improving stroke prevention strategies. GP and stroke share several components of metabolic disorders as risk factors. Therefore, we conducted a nationwide, population-based cohort study by analyzing data from a nationwide medical database, namely the National Health Insurance Research Database (NHIRD), to assess the association between GPs and the subsequent stroke risk.

METHODS

Data Source

The National Health Insurance (NHI) program was implemented in Taiwan on March 1, 1995, and since 1998, it is covering more than 99% of the Taiwanese population.²⁸ This population-based study was conducted using the registration and claims data sets from 2000 to 2011 obtained from the Longitudinal Health Insurance Database 2000, a subset of the NHIRD managed by Taiwan's National Health Research Institutes. Data on demographic status, outpatient and inpatient services, and dental services, and physicians and institutions that provided these services were retrieved from the claims data. To maintain patient privacy, all personal identification numbers were encrypted before the databases were released to the public. This study was exempted from a full ethical review by the International Review Board (IRB) of the China Medical University and Hospital Research Ethics Committee (IRB permit number: CMU-REC-101-012).

PATIENTS

The GP cohort included insured patients with GP (ICD-9-CM 575.6) aged >20 years and newly diagnosed during 2000 to 2010 with no history of stroke (ICD-9-CM 430-438). The date of GP diagnosis was designated as the index date. Patients without GP aged >20 years and without a history of GP and stroke were frequency-matched to each patient in the GP cohort with respect to sex, age (5-yr intervals), and baseline year.

Ethics Statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to

access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMU-REC-101-012). The IRB also specifically waived the consent requirement.

Outcome and Comorbidity

All patients were followed up until the occurrence of stroke, withdrawal from the NHI, death, or December 31, 2011, whichever occurred first. Stroke-related comorbidities included gallstone (ICD-9-CM 574), alcohol-related illness (ICD-9-CM 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3), diabetes (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401-405), obesity (ICD-9-CM 278), chronic obstructive pulmonary disease (COPD; ICD-9-CM 491, 492, and 496), coronary heart disease (CHD; ICD-9-CM 410-414), and asthma (ICD-9-CM 493).

Statistical Analyses

The distribution of sex, age (<34, 35–49, 50–64, and ≥65 yr), income level based on paid insurance fee rectified by Taiwan NHI Bureau (levels I, II, and III in the order of increasing income), urbanization level (with level 1 as the most urbanized and level 4 as the least urbanized), occupation (white collar, blue collar, and others), and comorbidities were compared in the GP and non-GP cohorts. Categorical and continuous variables were examined using the χ^2 and Student *t* tests, respectively. We estimated the follow-up (per 1000 person-yr) for measuring the incidence of stroke and subsequently calculated the GP to non-GP cohort relative incidence rate ratios (IRR) and 95% confidence intervals (CI) using the Poisson regression. Univariate and multivariate Cox proportional hazards regression models were used for examining the GP-related stroke risk in both cohorts. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The multivariate model was used for adjusting several variables, such as age, sex, and comorbidities; the results differed significantly from those of the univariate Cox proportion hazards regression model. We plotted the Kaplan–Meier curve for estimating the cumulative incidence of the subsequent stroke risk for the GP and non-GP cohorts. The log-rank test was used for examining the significance of the differences between the cohorts. All statistical analyses were performed using the SAS statistical software (Version 9.3 for Windows; SAS Institute Inc, Cary, NC). $P < 0.05$ was considered significant.

RESULTS

Table 1 shows the baseline characteristics and comorbidities of the GP and non-GP cohorts. Patients in both cohorts were predominantly males and were aged ≥49 years. The mean age of patients in the GP and non-GP cohorts was 47.9 (±14.1) and 47.6 (±14.4) years, respectively. Most subjects of both cohorts had income level II (41.6% vs 45.2%), and tended to reside in urbanized areas higher than level 2 (64.2% vs 60.1%), and more than half of their occupations were white-collar jobs.

The prevalence of all comorbidities was higher in the GP cohort than in the non-GP cohort ($P < 0.01$). During the mean follow-up period of 5.64 and 5.75 years for the GP and non-GP cohorts, respectively, the cumulative incidence of stroke was higher in the GP cohort than in the non-GP cohort (log-rank test, $P < 0.001$; Fig. 1).

Table 2 presents a comparison of the stroke IRRs and HRs of between GP and non-GP cohorts stratified by sex, age,

TABLE 1. Demographic Characteristics and Comorbidity in Patients With and Without Gallbladder Polyp

Variable	Gallbladder Polyp		P Value
	No N = 12,780	Yes N = 3195	
Gender	n (%)	n (%)	0.99
Female	5360 (41.9)	1340 (41.9)	
Male	7420 (58.1)	1855 (58.1)	
Stratify age			0.99
≤34	2456 (19.2)	614 (19.2)	
35–49	5008 (39.2)	1252 (39.2)	
50–64	3712 (29.1)	928 (29.1)	
65+	1604 (12.6)	401 (12.6)	
Age, mean (SD)*	47.6 (14.4)	47.9 (14.1)	0.29
Income level			<0.001
I	2793 (21.9)	588 (18.4)	
II	5775 (45.2)	1330 (41.6)	
III	4212 (33.0)	1277 (40.0)	
Urbanization level†			<0.001
1 (highest)	3944 (30.9)	1103 (34.5)	
2	3736 (29.2)	950 (29.7)	
3	2352 (18.4)	545 (17.1)	
4 (lowest)	2748 (21.5)	597 (18.7)	
Occupation			0.002
White collar	7003 (54.8)	1854 (58.0)	
Blue collar	4113 (32.2)	979 (30.6)	
Others‡	1664 (13.0)	362 (11.3)	
Comorbidity			
Gallstone	273 (2.14)	463 (14.5)	<0.001
Alcohol-related illness	441 (3.45)	230 (7.20)	<0.001
Diabetes	842 (6.59)	274 (8.58)	<0.001
Hyperlipidemia	2030 (15.9)	785 (24.6)	<0.001
Hypertension	2796 (21.9)	807 (25.3)	<0.001
Obesity	163 (1.28)	64 (2.00)	0.008
COPD	934 (7.31)	357 (11.2)	<0.001
CHD	1252 (9.80)	443 (13.9)	<0.001
Asthma	628 (4.91)	230 (7.20)	<0.001

χ² test.

* Two sample T test.

† The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

‡ Other occupations included primarily retired, unemployed, or low income populations.

income level, urbanization level, and occupation. The incidence of stroke was higher in the GP cohort than in the non-GP cohort (6.66 vs 5.20/1000 person-yr), with an IRR of 1.28 (95% CI = 1.15–1.42). Furthermore, the incidence of stroke was higher among males than among females in both cohorts; the sex-specific IRR of stroke was higher for both sexes in the GP cohort. The incidence of stroke increased with age in both cohorts. The age-specific IRR of stroke for the GP to non-GP cohorts was significant for all age subgroups, except for the 50 to 64-year subgroup. However, the GP-related stroke risk was the highest in the ≤34-year subgroup. Income level specific IRR of stroke shows that patients with GP, compared with non-GP, exhibited the higher risk in income levels I and II. GP patients living in most urbanized and least urbanized areas had a higher IRR of stroke. The IRR of stroke between the 2 cohorts were greater in GP patients with white-collar and blue-collar jobs.

Table 3 shows the HRs of stroke categorized by age, sex, income level, urbanization level, occupation, and comorbidity

in the univariate and multivariate Cox proportional hazards regression models. The stroke risk increased in patients with one of the following characteristics: age (with every 1-yr interval) (adjusted HR [aHR] = 1.06, 95% CI = 1.05–1.07), male sex (aHR = 1.62, 95% CI = 1.35–1.96), lower income level (aHR = 1.37, 95% CI = 1.02–1.85 for income level I; aHR = 1.62, 95% CI = 1.25–2.10 for income level II), living in second urbanized areas (aHR = 1.28, 95% CI = 1.00–1.63), GP (aHR = 1.32, 95% CI = 1.06–1.63), alcohol-related illness (aHR = 1.56, 95% CI = 1.07–2.28), diabetes (aHR = 1.78, 95% CI = 1.41–2.24), and hypertension (aHR = 2.74, 95% CI = 2.19–3.42).

Table 4 presents Cox proportional hazard regression analysis for the risk of stroke with joint effect of GP and comorbidity. The coexistence of GP and alcohol-related illness (aHR = 2.10, 95% CI = 1.22–3.63), diabetes (aHR = 2.04, 95% CI = 1.35–3.08), and hypertension (aHR = 3.50, 95% CI = 2.55–4.82) enhanced the stroke risk in the GP cohort.

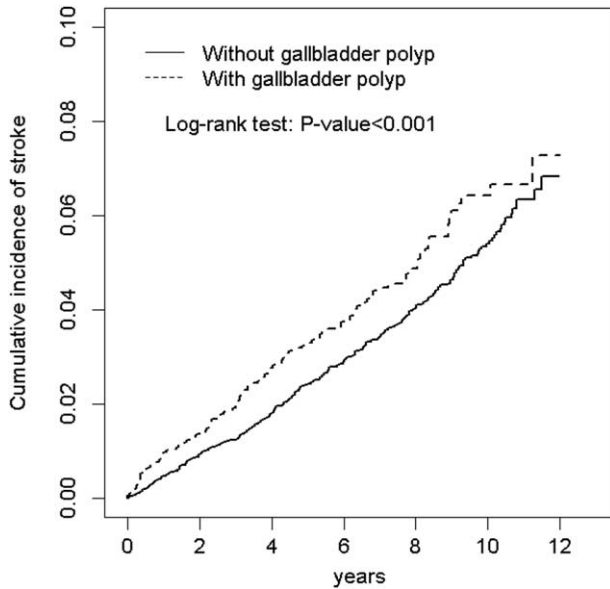


FIGURE 1. Cumulative incidence of stroke for patients with and without gallbladder polyp.

DISCUSSION

According to our review of relevant literature, this is the first population-based study to assess the association between GP and subsequent stroke risk. Most studies on the epidemiology of GP have mainly evaluated its prevalence and risk factors.^{4,5,11-14} The possible association between GP and stroke was uninvestigated, although some risk factors for stroke were associated with GP development. Using a nationwide database and the 12-year follow-up approach for patients selected from a representative cohort of 1 million patients covered by the NHI program strengthened the statistical analyses in our study.

Consistent with relevant literature, in this study, most patients in the GP cohort were man (58.1%), and their mean age was 47.9 years. The reason for this male predominance remains unknown. However, estrogen may act as a protective factor during GP development because of its ability to reduce the ACAT2 activity, which reduces the esterification of biliary cholesterol.²⁹ Furthermore, 39.2% of patients in the GP cohort were aged 35 to 49 years, and 58.4% of all patients were aged <50 years. The reason for the decreasing prevalence of GP in elderly patients is unknown, but gallstones, whose prevalence increases with age, possibly obscures GP detection during ultrasonography.⁵

TABLE 2. Comparison of Incidence and Hazard Ratio of Stroke Stratified by Gender, Age, Income level, Urbanization Level, and Occupation Between Patients With and Without Gallbladder Polyp

Variables	Gallbladder Polyp						IRR* (95% CI)
	No			Yes			
	Event	PY	Rate [#]	Event	PY	Rate [#]	
All	382	73,470	5.20	120	18,013	6.66	1.28 (1.15, 1.42)***
Gender							
Female	135	31,017	4.35	47	7645	6.15	1.41 (1.20, 1.66)***
Male	247	42,453	5.82	73	10,367	7.04	1.21 (1.05, 1.39)**
Stratify age							
≤34	5	14,314	0.35	6	3601	1.67	4.77 (3.72, 6.11)***
35-49	52	30,263	1.72	18	7496	2.40	1.40 (1.17, 1.67)***
50-64	141	20,509	6.88	36	5020	7.17	1.04 (0.85, 1.27)
65+	184	8383	22.0	60	1895	31.7	1.44 (1.13, 1.84)**
Income level							
I	108	15,200	7.11	35	3259	10.7	1.51 (1.21, 1.88)***
II	201	33,457	6.01	60	7448	8.06	1.34 (1.15, 1.57)***
III	73	24,813	2.94	25	7306	3.42	1.16 (0.96, 1.41)
Urbanization level [†]							
1 (highest)	89	22,624	3.93	30	6237	4.81	1.22 (1.01, 1.48)*
2	113	21,177	5.34	34	5403	6.29	1.18 (0.97, 1.44)
3	67	13,843	4.84	19	3059	6.21	1.28 (0.99, 1.66)
4 (lowest)	113	15,826	7.14	37	3315	11.2	1.56 (1.26, 1.95)***
Occupation							
White collar	142	39,901	3.56	47	10,425	4.51	1.27 (1.09, 1.47)**
Blue collar	169	24,043	7.03	55	5493	10.0	1.42 (1.19, 1.70)***
Others [‡]	71	9526	7.45	18	2095	8.59	1.15 (0.85, 1.55)

IRR* = incidence rate ratio, PY = person-yr, Rate[#] = incidence rate, per 1000 person-years.

[†] The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

[‡] Other occupations included primarily retired, unemployed, or low-income populations.

* P < 0.05.

** P < 0.01.

*** P < 0.001.

TABLE 3. Hazard Ratios of Stroke in Association With Age, Sex, Income Level, Urbanization Level, Occupation and Comorbidities in Univariable and Multivariable Cox Regression Models

Variable	Crude HR (95% CI)	Adjusted [†] HR (95% CI)
Age, years	1.08 (1.07, 1.09) ^{***}	1.06 (1.05, 1.07) ^{***}
Sex (male vs female)	1.29 (1.07, 1.54) ^{**}	1.62 (1.35, 1.96) ^{***}
Income level		
I	2.55 (1.97, 3.30) ^{***}	1.37 (1.02, 1.85) [*]
II	2.10 (1.66, 2.64) ^{***}	1.62 (1.25, 2.10) ^{***}
III	1 (Reference)	1 (Reference)
Urbanization level [‡]		
1 (highest)	1 (Reference)	1 (Reference)
2	1.34 (1.06, 1.71) [*]	1.28 (1.00, 1.63) [*]
3	1.23 (0.94, 1.63)	1.17 (0.89, 1.55)
4 (lowest)	1.90 (1.50, 2.42) ^{***}	1.25 (0.96, 1.62)
Occupation		
White collar	1 (Reference)	1 (Reference)
Blue collar	2.02 (1.66, 2.45) ^{***}	1.02 (0.80, 1.28)
Others [§]	2.04 (1.58, 2.62) ^{***}	0.93 (0.71, 1.23)
Baseline comorbidities (yes vs no)		
Gallbladder polyp	1.28 (1.04, 1.57) [*]	1.32 (1.06, 1.63) [*]
Gallstone	1.61 (1.14, 2.27) ^{**}	0.87 (0.61, 1.24)
Alcohol-related illness	1.83 (1.26, 2.64) ^{**}	1.56 (1.07, 2.28) [*]
Diabetes	4.26 (3.43, 5.28) ^{***}	1.78 (1.41, 2.24) ^{***}
Hyperlipidemia	2.02 (1.66, 2.45) ^{***}	0.74 (0.60, 1.00)
Hypertension	6.98 (5.81, 8.39) ^{***}	2.74 (2.19, 3.42) ^{***}
Obesity	1.29 (0.61, 2.73)	1.10 (0.52, 2.33)
COPD	3.07 (2.46, 3.84) ^{***}	0.95 (0.74, 1.22)
CHD	4.05 (3.35, 4.90) ^{***}	1.05 (0.85, 1.31)
Asthma	2.38 (1.78, 3.17) ^{***}	1.02 (0.75, 1.39)

Adjusted HR[†] = multivariable analysis including age sex, income level, urbanization level, occupation, and comorbidities of gallstone, alcohol-related illness, diabetes, hyperlipidemia, hypertension, obesity, COPD, CHD, and asthma, Crude HR = relative hazard ratio.

[‡] The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

[§] Other occupations included primarily retired, unemployed, or low-income populations.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

Our results are consistent with those of previous studies, which have revealed that GP and stroke share several common risk factors.^{11–14,25–27} The present epidemiological study demonstrated that stroke is associated with increasing age, the male sex, lower income level, living in second urbanized areas, GP, alcohol-related illness, diabetes, and hypertension. Compared with the comparison cohort, GP was more common in men and patients with higher income level, living in higher urbanized areas, white collar jobs, gallstone disease, alcohol-related illness, diabetes, hyperlipidemia, hypertension, obesity, COPD, CHD, and asthma. Despite the association between GP and several established risk factors for stroke, our study showed that GP was associated with stroke development after adjustment for age, sex, income level, urbanization level, occupation, and comorbidities of gallstone, alcohol-related illness, diabetes, hyperlipidemia, hypertension, obesity, COPD, coronary heart disease, and asthma. However, future studies must ascertain whether GP is a risk factor for or an epiphenomenon of stroke development.

GP and stroke may be associated due to their common pathophysiological features. First, a study demonstrated that apolipoprotein B (apoB) is present in the gallbladder mucosa, and the receptor binding properties of apoB genotypes are altered

in patients with stroke, thus predisposing them to the development of cholesterol polyps. Furthermore, in patients with cholesterol polyps, the ACAT2 activity is enhanced, which subsequently enhances the incorporation of cholesteryl esters into blood apoB to increase low-density lipoprotein cholesterol (LDL-C) levels and to develop atherosclerosis.^{29–31} Since the diagnosis of GP is mainly based on imaging studies, different types of polyps must have been included in our cohort. However, cholesterol polyps have been supposed to constitute the majority (60%–70%) of polyps.³ Mendez-Sanchez et al even suggested cholesterol polyps are not associated high serum cholesterol level.⁶ Notably, our results were consistent with the literature to demonstrate hyperlipidemia was only found in 24.6% of our GP patients (Table 1). The possible explanation for the association between increased risk of stroke and cholesterol polyps observed in the patients with normal serum cholesterol levels is ACAT2 contributes proatherosclerotic effect by facilitating cholesterol absorption in the liver and intestines to incorporate cholesteryl esters (CEs) into apoB-containing lipoproteins, which mainly accumulate in the intima of arteries, with disproportionately less increased serum cholesterol level.³² Moreover, ACAT2 also contribute the main atherosclerotic effect by decreasing

TABLE 4. Cox Proportional Hazard Regression Analysis for the Risk of Stroke With Joint Effect of Gallbladder Polyp and Comorbidity

Variables		N	Eventn	Adjusted HR [†] (95% CI)
Gallbladder polyp	Alcohol-related illness			
No	No	12,339	366	1 (Reference)
No	Yes	441	16	1.54 (0.93, 2.55)
Yes	No	2965	106	1.29 (1.03, 1.62)*
Yes	Yes	230	14	2.10 (1.22, 3.63)**
Gallbladder polyp	Diabetes			
No	No	11,938	303	1 (Reference)
No	Yes	842	79	1.89 (1.46, 2.46)***
Yes	No	2921	93	1.37 (1.08, 1.74)*
Yes	Yes	274	27	2.04 (1.35, 3.08)**
Gallbladder polyp	Hypertension			
No	No	9984	132	1 (Reference)
No	Yes	2796	250	2.87 (2.25, 3.67)***
Yes	No	2388	43	1.46 (1.03, 2.06)*
Yes	Yes	807	77	3.50 (2.55, 4.82)***

Adjusted HR[†] = adjusted for age, sex, monthly income (NT\$), urbanization level, occupation, and other comorbidities.

* $P \leq 0.05$.

** $P \leq 0.01$.

*** $P \leq 0.001$.

high-density lipoprotein cholesterol, decreasing polyunsaturated cholesteryl esters, and the production of greater low-density lipoprotein cholesterol particles. Second, the expression of the complement receptor type 2 (CR2) increases in patients with GP, and CR2-mediated immune response enhances GP development.³³ Following cholesterol polyps, adenomyomatosis and inflammatory polyps are the common types of GP in descending order of frequency.³ In addition, both adenomyomatosis and inflammatory polyps are closely related to chronic inflammation with or without gallstone disease. The activation of immune responses can increase inflammatory cytokines, thus inducing endothelial dysfunction and atherosclerosis. Finally, the association between alcohol-related illness, diabetes, and hypertension can induce the development of both GP and atherosclerosis. A multinational, case-control study demonstrated that alcohol consumption has a J-shaped relationship with ischemic stroke and is associated with a steadily increasing risk of intracerebral hemorrhagic stroke.²⁵ The association between alcohol consumption and stroke was suggested in an animal study of squirrel monkeys: a regular ingestion of small concentrations of alcohol increased high-density lipoprotein cholesterol (HDL-C) levels, whereas binge drinking resulted in increased LDL-C and apoB levels, without a favorable effect on the HDL-C levels.³⁴ Consequently, alcohol-related illness is apparently associated with binge alcohol consumption, although detailed drinking habits were not available in our study data sets. Diabetes predisposes patients to GP development by impairing gallbladder emptying and suppressing bile secretion. Furthermore, diabetes can induce atherosclerosis by producing cytokines through oxidative stress and by inducing dyslipidemia.³⁵ A previous study demonstrated the association between the variation in apoB gene and essential hypertension.³⁶

The prevalence of crucial risk factors for stroke was higher in the GP cohort than in the non-GP cohort; therefore, GP and stroke may be associated because of the common risk factors. Nevertheless, GP can be reasonably concluded to increase the stroke risk in the GP cohort, because the possible confounding effect of the risk factors for stroke was substantially minimized

in our study. Moreover, GP-induced stroke risk may increase with younger age because of the absence or low prevalence of stroke-associated comorbidities in younger patients. In addition, our findings also revealed that the risk of stroke development increased gradually over the follow-up period (Fig. 1). These findings, in addition to the results of the subgroup analyses, confirm the possible causal association between GP and stroke and suggest that GP is a crucial risk factor for stroke in younger patients. However, our results revealed that GP may be inferior to the conventional risk factors for stroke, such as male sex, lower income level, alcohol-related illness, diabetes, and hypertension, in contributing to stroke development (Table 3).

Strengths and Limitations

The present study has several strengths. This study included a large sample size, and the patients belonged to a stable population sampled from approximately 99% of all Taiwanese residents. Furthermore, we used a longitudinal, and not a cross-sectional, approach for evaluating the association between GP and stroke.

Our study has certain limitations. First, stroke-related lifestyle factors were not completely assessed in this study. However, we adjusted the potential stroke-associated comorbidities, and GP was persistently associated with stroke development. The NHIRD lacked of educational backgrounds, exercise, and diet data; nevertheless, we already used COPD to replace smoking habits, alcohol-related illness to replace alcohol drinking habits, occupations to replace educational backgrounds, and paid insurance fee to replace household income for adjustment in this study. Our results were consistent with the literature to demonstrate low income level was associated with an increased risk of stroke, which might be explained by poor maternal nutrition in fetal stage, socioeconomic deprivation in childhood, or inadequate healthy habits in adulthood.³⁷ Second, we could not confirm the histopathological characteristics of GPs. However, referring patients with GPs without signs of malignancy to surgery is unethical. Moreover,

in relevant literature, GP was diagnosed through ultrasonography alone, whose accuracy for GP diagnosis exceeds 90%. Finally, the temporal association between GP and stroke development could not be ascertained in our study. However, most patients (58.4%) with GP were aged <50 years, and our study revealed that GP strongly contributed to stroke development in younger patients. Furthermore, the cumulative incidence of stroke was higher in the GP cohort than in the non-GP cohort, although the mean follow-up period was shorter in the GP cohort than in the non-GP cohort (5.64 vs 5.75 yr).

CONCLUSION

This nationwide, population-based cohort study revealed that GP independently increases the stroke risk, although GP and stroke share several risk factors. However, additional studies are necessary to clarify whether GP is a risk factor for or an epiphenomenon of stroke development.

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