


Erectile Dysfunction in Men With Gallbladder Stone Disease: A Nationwide Population-Based Study

American Journal of Men's Health
March-April 2019: 1–10
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1557988319839589
journals.sagepub.com/home/jmh


Chien-Hua Chen, MD^{1,2,3}, Cheng-Li Lin, MSc^{4,5},
and Chia-Hung Kao, MD^{6,7,8} 

Abstract

We assessed the risk of erectile dysfunction after the diagnosis of gallbladder stone disease. We identified 9,362 men aged ≥ 20 years diagnosed with gallbladder stone disease between 2000 and 2011 from Taiwan's National Health Insurance Research Database as the study cohort, and we randomly selected 9,362 men from the nongallbladder stone disease population by 1:1 frequency-matching with the case cohort based on age, the index date for the diagnosis of gallbladder stone disease, and comorbidities as the control cohort. All subjects were followed until December 31, 2011, for measuring the erectile dysfunction incidence. The risk of organic erectile dysfunction was higher in the gallbladder stone disease cohort than the nongallbladder stone disease cohort (4.01 vs. 2.69 per 1,000 person-years, adjusted hazard ratio = 1.41, 97.5% confidence interval [1.12, 1.78]), but the risk of psychogenic erectile dysfunction was comparable between the gallbladder stone disease cohort and the nongallbladder stone disease cohort (0.40 vs. 0.28 per 1,000 person-years, adjusted hazard ratio = 1.37, 97.5% confidence interval [0.67, 2.79]). Moreover, gallbladder stone disease men with cholecystectomy exhibited a lower risk of developing organic erectile dysfunction than gallbladder stone disease men without cholecystectomy (adjusted hazard ratio = 0.58, 97.5% confidence interval [0.41, 0.80]). The risk of organic erectile dysfunction contributed by gallbladder stone disease was only significantly higher in men aged ≥ 65 years (adjusted hazard ratio = 2.21, 97.5% confidence interval [1.34, 3.63]) and in men with comorbidities (adjusted hazard ratio = 1.42, 97.5% confidence interval [1.09, 1.85]). The risk of psychogenic erectile dysfunction contributed by gallbladder stone disease was nonsignificant in each age group and in men with or without comorbidities. Gallbladder stone disease is associated with an increased risk of organic erectile dysfunction, but it has no association with psychogenic erectile dysfunction. History of cholecystectomy for gallbladder stone disease may ameliorate the risk of organic erectile dysfunction; it requires more studies to ascertain the protective mechanism and to clarify whether the existence of gallbladder stone disease is an epiphenomenon or independent risk factor of erectile dysfunction.

Keywords

gallbladder stone disease, organic erectile dysfunction, psychogenic erectile dysfunction, cholecystectomy

Received November 16, 2018; revised February 24, 2019; accepted March 3, 2019

Erectile dysfunction is defined as the incapability of achieving or maintaining sufficient penile erection to experience satisfactory vaginal intercourse (Shamloul & Ghanem, 2013). The prevalence of erectile dysfunction increases with age, and it mainly affects men aged >40 years. Erectile dysfunction is estimated to affect 322 million men worldwide by 2025, and erectile dysfunction is considered a major public health concern for the increasing aging male population (McMahon, 2014). Erectile dysfunction is mainly caused by organic and psychogenic factors. Rigid erections in the morning, night, or at any sexual thought

indicate psychogenic erectile dysfunction. Furthermore, psychogenic erectile dysfunction frequently presents with a sudden onset, intermittent course, or short duration. By contrast, organic erectile dysfunction frequently presents with a gradual onset, progressive course, or long duration (Shamloul & Ghanem, 2013). The development of erectile dysfunction has been associated with diabetes, hypertension, hyperlipidemia, depression, and metabolic syndrome (Shamloul & Ghanem, 2013). Moreover, erectile dysfunction is considered a marker of cardiovascular disorders (Raheem, Su, Wilson, & Hsieh, 2017).



Gallbladder stone disease is the most common gastrointestinal disorder requiring hospitalization, and approximately 800,000 cholecystectomies are annually performed in the United States of America (Lamberts, 2018). Most patients with gallbladder stone disease are asymptomatic; however, gallbladder stone disease can cause biliary pain, cholecystitis, cholangitis, pancreatitis, gallbladder cancer, and even gallstone ileus (Gurusamy & Davidson, 2014). The reported prevalence of gallbladder stone disease in Western countries is approximately 10%, whereas the overall prevalence of gallbladder stone disease in our population-based study conducted in Taiwan was approximately 5% (Chen et al., 2006; Stinton & Shaffer, 2012). The risk factors associated with gallbladder stone disease include the female sex, aging, obesity, hyperlipidemia, diabetes, and alcohol consumption (Shabanzadeh, Sørensen, & Jørgensen, 2016). Considering the increasing prevalence of metabolic syndrome worldwide, the prevalence of gallbladder stone disease is expected to increase, particularly in developing countries (Lamberts, 2018).

It has been well recognized that gallbladder stone disease is closely associated with cardiovascular disease due to shared risk factors in common, such as metabolic disorders, and shared pathogenesis, such as cholesterol deposition for the gallstone formation and atherosclerotic plaque formation (Singh et al., 2018; Targher & Byrne, 2015; Twickler, Cramer, & van Erpecum, 2005; Upala, Sanguankee, & Jaruvongvanich, 2017). Similarly, erectile dysfunction has been regarded as a marker for the severity of cardiovascular disease since they share common pathophysiological mechanisms of atherosclerosis and endothelial dysfunction for the penile artery and the coronary artery (Nehra et al., 2012; Raheem et al., 2017). Moreover, psychological stress is associated with gallbladder stone disease due to liability to bile stasis and impaired gallbladder emptying (Dragos, Tanasescu, Comsa, Minca, & Olteanu, 2015). Similarly, psychological stress is associated with the development of organic and psychogenic erectile dysfunction (Shamloul & Ghanem, 2013; Yafi et al., 2016).

Therefore, gallbladder stone disease and erectile dysfunction share many risk factors, either constitutional

disorders or psychological factors. However, no study has discussed the association between gallbladder stone disease and erectile dysfunction. In this study, we hypothesized that a history of gallbladder stone disease is associated with an increased risk of erectile dysfunction. We conducted a nationwide population-based cohort study by analyzing data from the National Health Insurance Research Database of Taiwan for assessing the association between gallbladder stone disease and the subsequent development of organic and psychogenic erectile dysfunction.

Methods

Data Source

Data were obtained from the Longitudinal Health Insurance Database 2000, which is a database of Taiwan's National Health Insurance program. Taiwan's National Health Insurance program, established in 1995, is a mandatory universal health insurance program and covers approximately 99% of the 23 million Taiwanese residents (National Health Insurance Research Database, 2015). Longitudinal Health Insurance Database 2000 has been adequately described in previous studies (Hsu et al., 2016; Wang, Chang, Lin, Lin, & Kao, 2015). In addition, the personal identification of each beneficiary was encrypted to avoid the potential for ethical violations. In the Longitudinal Health Insurance Database 2000, diseases were identified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Patients

We included men aged ≥ 20 years diagnosed with gallbladder stone disease (ICD-9-CM 574.0, 574.1, 574.2, 574.6, 574.7, 574.8, and 574.9) between 2000 and 2011 in the gallbladder stone disease cohort, and the date of gallbladder stone disease diagnosis was defined as the index date. Men with a history of organic or psychogenic erectile dysfunction (ICD-9-CM 607.84 and

¹Digestive Disease Center, Chang-Bing Show-Chwan Memorial Hospital, Lukang Town, Taiwan, ROC

²Digestive Disease Center, Show-Chwan Memorial Hospital, Changhua, Taiwan, ROC

³Department of Food Science and Technology, Hungkuang University, Taichung, Taiwan, ROC

⁴Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan, ROC

⁵College of Medicine, China Medical University, Taichung, Taiwan, ROC

⁶Graduate Institute of Biomedical Sciences and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan, ROC

⁷Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan, ROC

⁸Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan, ROC

Corresponding Author:

Chia-Hung Kao, MD, Professor, Graduate Institute of Biomedical Sciences and School of Medicine, China Medical University, Taichung. No. 2, Yuh-Der Road, Taichung 404, Taiwan, ROC.

Emails: d10040@mail.cmuh.org.tw; dr.kaochiahung@gmail.com

302.72, respectively) before the index date, aged <20 years, or with an incomplete demographic information were excluded. The control cohort was selected from the men without a history of cholelithiasis (ICD-9-CM 574) or erectile dysfunction, including psychogenic and organic erectile dysfunction, as documented in the Longitudinal Health Insurance Database 2000. The index date was assigned based on the date for the diagnosis of gallbladder stone disease in the case cohort, and one male beneficiary without gallbladder stone disease was frequency-matched with each male patient in the gallbladder stone disease cohort according to age (in 5-year intervals), index date, and comorbidities including coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, hypertension, diabetes, hyperlipidemia, depression, anxiety, asthma, and alcohol-related illness. We identified the first diagnosis of organic and psychogenic erectile dysfunction as the study endpoint. All enrolled subjects were followed from the index date until the study endpoint; withdrawal from the National Health Insurance; or December 31, 2011—which ever occurred first.

Comorbidities

We considered several established risk factors for organic and psychogenic erectile dysfunction, including coronary artery disease (ICD-9-CM 410–414), chronic obstructive pulmonary disease (ICD-9-CM 490–496), chronic kidney disease (ICD-9-CM 580–589), hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), depression (ICD-9-CM 296.2, 296.3, 300.4, and 311), anxiety (ICD-9-CM 300), asthma (ICD-9-CM 493), and alcohol-related illness (ICD-9-CM 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3). Moreover, comorbidity was treated as a time varying covariate.

Patient and Public Involvement

The dataset used in this study is managed by the Taiwan Ministry of Health and Welfare, which approved our application to access these data. Any researcher interested in accessing this dataset should submit an application form to the Ministry of Health and Welfare for requesting access (Email: stcarolwu@mohw.gov.tw). The contact information for Taiwan Ministry of Health and Welfare is No. 488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (ROC) and Phone: +886-2-8590-6848. The National Health Insurance Research Database has encrypted patient personal information to protect privacy, and the researchers were provided with anonymous identification numbers associated with relevant claims information, including

sex, date of birth, medical services received, and prescriptions. Patient consent is not required to access the National Health Insurance Research Database. The Institutional Review Board of China Medical University (CMUH104-REC2-115-CR3) has specifically waived the consent requirement and has approved this study.

Statistical Analysis

We used the chi-square test to determine the differences in categorical demographic variables and comorbidities between the gallbladder stone disease and nongallbladder stone disease cohorts. Furthermore, we used the Student's *t* test to examine the mean age and follow-up time (years) of the two cohorts. We estimated the cumulative incidence of organic and psychogenic erectile dysfunction curves during the follow-up period using the Kaplan–Meier method, and differences between the two cohorts were examined using the log-rank test. The incidence density rates (per 1000 person-years) were calculated for both cohorts. The gallbladder stone disease to nongallbladder stone disease cohort hazard ratio and 95% confidence interval were estimated using the univariate and multivariate Cox proportional hazards regression model. The *p* value was set at .025 using the Bonferroni correction method. The following risk factors for organic and psychogenic erectile dysfunction were included as covariates in the multivariate models: age, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, hypertension, diabetes, hyperlipidemia, depression, anxiety, asthma, and alcohol-related illness. For further data analysis, we assessed the effects of cholecystectomy on the risk of developing organic and psychogenic erectile dysfunction in men with gallbladder stone disease and compared their risk with that of the nongallbladder stone disease cohort. SAS 9.4 software (SAS Institute, Cary, NC, USA) was used for data management and statistical analysis. A two-sided *p* value of <.05 was considered significant.

Results

The baseline characteristics and comorbidities of all enrolled subjects are presented in Table 1. Compared with the nongallbladder stone disease cohorts, the distribution of age was younger in the gallbladder stone disease, with 37.7% of men in the gallbladder stone disease cohort aged ≤49 years. The mean age of the gallbladder stone disease and nongallbladder stone disease cohorts were 56.4 (standard deviation = 15.9) and 56.8 years (standard deviation = 15.8), respectively. Coronary artery disease, hypertension, and hyperlipidemia were more prevalent in the nongallbladder stone disease cohort than in the gallbladder stone disease cohort (all *p* < .05).

Table 1. Demographic Characteristics and Comorbidities in Cohorts With and Without Gallbladder Stone Disease.

Variable	Gallbladder stone disease		p value
	No N = 9,362	Yes N = 9,362	
Age, years			.02
≤49	3,319 (35.5)	3,527 (37.7)	
50–64	2,732 (29.2)	2,724 (29.1)	
65+	3,311 (35.4)	3,111 (33.2)	
Mean ± standard deviation ^a	56.8 (15.8)	56.4 (15.9)	.04
Comorbidity			
Coronary artery disease	2,375 (25.4)	2,227 (23.8)	.01
Chronic obstructive pulmonary disease	1,696 (18.1)	1,616 (17.3)	.13
Chronic kidney disease	1,071 (11.4)	1,050 (11.2)	.63
Hypertension	4,161 (44.5)	3,904 (41.7)	.001
Diabetes	1,281 (13.7)	1,239 (13.2)	.37
Hyperlipidemia	2,544 (27.2)	2,416 (25.8)	.03
Depression	409 (4.37)	440 (4.70)	.28
Anxiety	568 (6.07)	591 (6.31)	.49
Asthma	751 (8.02)	746 (7.97)	.89
Alcohol-related illness	616 (6.58)	709 (7.57)	.01

Note. Chi-square test.

^at test.

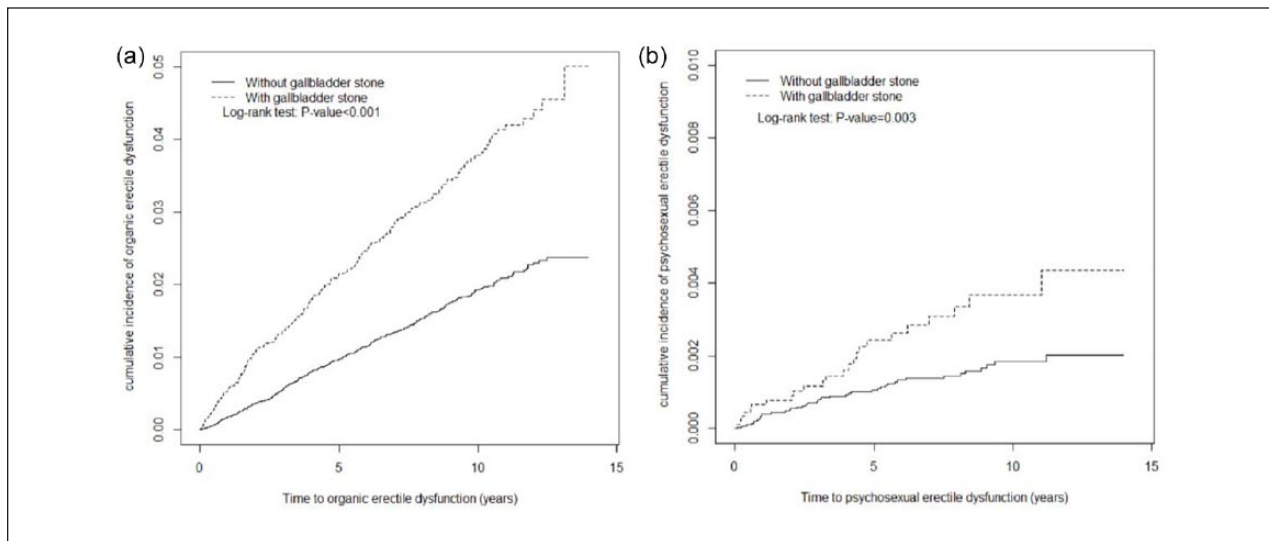


Figure 1. Cumulative incidence comparison of organic erectile dysfunction (a) and psychosexual erectile dysfunction (b) for men with (dashed line) or without (solid line) gallbladder stone disease.

However, alcohol-related illness was more prevalent in the gallbladder stone disease cohort ($p < .05$). The mean follow-up duration was 6.44 (standard deviation = 3.86) and 6.39 years (standard deviation = 3.82) for the gallbladder stone disease and nongallbladder stone disease cohorts, respectively. Among the gallbladder stone cohort, the mean follow-up duration was 6.58 (standard

deviation = 3.87) and 6.37 years (standard deviation = 3.83) for the cholecystectomy and noncholecystectomy cohorts, respectively.

Figure 1(a) presents a higher cumulative incidence of organic erectile dysfunction in the gallbladder stone disease cohort than in the nongallbladder stone disease cohort (log-rank test, $p < .001$). The risk of organic erectile dysfunction

Table 2. Incidence of Organic and Psychogenic Erectile Dysfunction Stratified by Age and Comorbidity and Cox Model Measured Hazards Ratio for Men With Gallbladder Stone Disease and Without Gallbladder Stone Disease.

Variables	Gallbladder stone disease				Crude hazard ratio (95% confidence interval)	Adjusted hazard ratio ^b (97.5% confidence interval)
	No		Yes			
	Event	Rate ^a	Event	Rate ^a		
All	178	2.98	266	4.41	1.41 [1.16, 1.70]*	1.41 [1.13, 1.75]**
Organic erectile dysfunction	161	2.69	242	4.01	1.41 [1.15, 1.72]*	1.41 [1.12, 1.78]**
Stratified by age						
≤49	50	2.16	79	3.22	1.34 [0.94, 1.91]	1.34 [0.89, 2.02]
50–64	81	4.45	100	5.57	1.19 [0.92, 1.83]	1.19 [0.85, 1.67]
65+	30	1.62	63	3.54	2.21 [1.43, 3.41]*	2.21 [1.34, 3.63]**
Comorbidity ^c						
No	41	1.77	59	2.55	1.35 [0.90, 2.02]	1.35 [0.85, 2.14]
Yes	120	3.28	183	4.92	1.42 [1.13, 1.79]*	1.42 [1.09, 1.85]**
Psychogenic erectile dysfunction	17	0.28	24	0.40	1.37 [0.73, 2.55]	1.37 [0.67, 2.79]
Stratified by age						
≤49	6	0.26	8	0.33	1.20 [0.41, 3.48]	1.20 [0.35, 4.06]
50–64	7	0.38	11	0.61	1.59 [0.62, 4.12]	1.59 [0.54, 4.73]
65+	4	0.22	5	0.28	1.26 [0.34, 4.72]	1.26 [0.28, 5.71]
Comorbidity ^c						
No	5	0.22	11	0.48	1.96 [0.68, 5.66]	1.96 [0.58, 6.59]
Yes	12	0.33	13	0.35	1.06 [0.48, 2.33]	1.06 [0.43, 2.60]

Note. hazard ratio = relative hazard ratio.

^aRate = incidence rate, per 1,000 person-years. ^bAdjusted hazard ratio = multivariable analysis including age, and comorbidities of coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, hypertension, diabetes, hyperlipidemia, depression, anxiety, asthma and alcohol-related illness. ^cMen with any one of the comorbidities (including coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, hypertension, diabetes, hyperlipidemia, depression, anxiety, asthma, and alcohol-related illness) were classified as the comorbidity group.

* $p < .05$. ** $p < .025$.

increased with the increasing follow-up duration after a diagnosis of gallbladder stone disease. However, Figure 1(b) presents a comparable cumulative incidence of psychogenic erectile dysfunction between the gallbladder stone disease cohort and the nongallbladder stone disease cohort (log-rank test, $p = .28$).

The incidence of organic and psychogenic erectile dysfunction stratified by age and comorbidity and Cox model measured hazards ratio for men with gallbladder stone disease and without gallbladder stone disease are presented in Table 2. Overall, we observed 444 cases of organic and psychogenic erectile dysfunction with 266 and 178 in the gallbladder stone disease and nongallbladder stone disease cohorts, respectively. The incidence density of all-cause erectile dysfunction was 4.41 per 1,000 person-years and 2.98 per 1,000 person-years for the gallbladder stone disease and nongallbladder stone disease cohorts, respectively (crude hazard ratio = 1.41, 95% confidence interval [1.16, 1.70]), with an adjusted hazard ratio of 1.41 (97.5% confidence interval [1.13, 1.75]). The overall incidence of organic erectile dysfunction was 1.41-fold higher in the gallbladder stone disease cohort than in the nongallbladder stone disease cohort

(4.01 vs. 2.69 per 1,000 person-years), with an adjusted hazard ratio of 1.41 (97.5% confidence interval [1.12, 1.78]). The risk of organic erectile dysfunction contributed by gallbladder stone disease was only significantly higher in men aged ≥ 65 years (adjusted hazard ratio = 2.21, 97.5% confidence interval [1.34, 3.63]) and in men with comorbidities (adjusted hazard ratio = 1.42, 97.5% confidence interval [1.09, 1.85]). The overall incidence of psychogenic erectile dysfunction was comparable between the gallbladder stone disease cohort and the nongallbladder stone disease cohort (0.40 vs. 0.28 per 1,000 person-years), with an adjusted hazard ratio of 1.37 (97.5% confidence interval [0.67, 2.79]). The risk of psychogenic erectile dysfunction contributed by gallbladder stone disease was nonsignificant in each age group and in men with or without comorbidities.

The Cox model with hazard ratios and 97.5% confidence intervals of organic and psychogenic erectile dysfunction associated with gallbladder stone disease and covariates are presented in Table 3. Gallbladder stone disease (adjusted hazard ratio = 1.41, 97.5% confidence interval [1.12, 1.78]) was associated with the development of organic erectile dysfunction. However, gallbladder was

Table 3. Cox Model With Hazard Ratios and 97.5% Confidence Intervals of Organic and Psychogenic Erectile Dysfunction Associated With Gallbladder Stone Disease and Covariates.

Variable	Organic erectile dysfunction		Psychosexual erectile dysfunction	
	Adjusted hazard ratio ^a	(97.5% confidence interval)	Adjusted hazard ratio ^a	(97.5% confidence interval)
Gallbladder stone disease	1.41	[1.12, 1.78]**	1.37	[0.67, 2.79]
Age, years	0.99	[0.98, 1.00]	0.99	[0.96, 1.02]
Baseline comorbidities (yes vs. no)				
Coronary artery disease	1.17	[0.89, 1.55]	1.38	[0.55, 3.48]
Chronic obstructive pulmonary disease	1.09	[0.81, 1.47]	1.35	[0.51, 3.52]
Chronic kidney disease	1.43	[1.07, 1.92]**	1.17	[0.41, 3.35]
Hypertension	1.27	[0.96, 1.69]	0.70	[0.28, 1.73]
Diabetes	1.16	[0.87, 1.55]	1.21	[0.45, 3.29]
Hyperlipidemia	1.32	[1.03, 1.69]	0.97	[0.42, 2.23]
Depression	1.52	[1.06, 2.18]**	0.66	[0.12, 3.57]
Anxiety	1.90	[1.41, 2.57]**	1.33	[0.43, 4.12]
Asthma	0.84	[0.57, 1.24]	1.43	[0.47, 4.32]
Alcohol-related illness	1.04	[0.73, 1.49]	1.00	[0.48, 2.10]

Note. ^aAdjusted hazard ratio = multivariable analysis including age and comorbidities of coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, hypertension, diabetes, hyperlipidemia, depression, anxiety, asthma, and alcohol-related illness.

** $p < .025$.

Table 4. Cox Proportional Hazard Regression Analysis for the Risk of Organic Erectile Dysfunction—Joint Effect of Gallbladder Stone Disease With Comorbidity.

Variables		Event	Rate ^a	Adjusted HR ^b (97.5% confidence interval)	
Gallbladder stone disease	Chronic kidney disease	No	134	2.49	
		No	27	4.52	1 [Reference]
		Yes	201	3.71	1.46 [0.90, 2.37]
		Yes	41	6.65	1.42 [1.10, 1.82]**
Gallbladder stone	Depression	No	149	2.57	2.05 [1.35, 3.10]**
		No	12	6.44	1 [Reference]
		Yes	229	3.95	1.60 [0.81, 3.19]
		Yes	13	5.46	1.47 [1.16, 1.86]**
Gallbladder stone	Anxiety	No	142	2.48	1 [Reference]
		No	19	7.18	2.08 [1.18, 3.66]**
		Yes	222	3.88	1.52 [1.19, 1.93]**
		Yes	20	6.45	1.84 [1.06, 3.20]

Note. PY = person-years.

^aRate = incidence rate per 1,000 person-years. ^bAdjusted HR = hazard ratio adjusted for age and other comorbidities.

** $p < .025$.

not associated with development of psychogenic erectile dysfunction (adjusted hazard ratio = 1.37, 97.5% confidence interval [0.67, 2.79]).

The joint effect of gallbladder stone disease with comorbidity for the risk of developing organic erectile dysfunction is presented in Table 4. Compared with men without gallbladder stone disease and without chronic

kidney disease, men with gallbladder stone disease alone (adjusted hazard ratio = 1.42, 97.5% confidence interval [1.10, 1.82]) or combined with chronic kidney disease (adjusted hazard ratio = 2.05, 97.5% confidence interval [1.35, 3.10]) exhibited a high risk of organic erectile dysfunction. Compared with men without gallbladder stone disease and without depression, men with gallbladder

Table 5. Incidences and Hazard Ratios of Organic and Psychogenic Erectile Dysfunction in Gallbladder Stone Disease Stratified by Cholecystectomy.

Variable	N	Event	PY	Rate ^a	Crude HR (97.5% CI)	Adjusted HR ^b (97.5% CI)	Crude HR (97.5% CI)	Adjusted HR ^b (97.5% CI)
Organic erectile dysfunction								
Nongallbladder stone disease	9,362	161	59,806	2.69	I [Reference]	I [Reference]		
Gallbladder stone disease								
Without cholecystectomy	5,758	179	36,510	4.90	1.82 [1.43, 2.32]***	1.68 [1.32, 2.15]**	I [Reference]	I [Reference]
With cholecystectomy	3,604	63	23,774	2.65	0.99 [0.71, 1.38]	0.98 [0.70, 1.37]	0.54 [0.39, 0.75]**	0.58 [0.41, 0.80]**
Psychogenic erectile dysfunction								
Nongallbladder stone disease	9,362	17	59,806	0.28	I [Reference]	I [Reference]		
Gallbladder stone disease								
Without cholecystectomy	5,758	18	36,510	0.49	1.73 [0.81, 3.70]	1.66 [0.77, 3.57]	I [Reference]	I [Reference]
With cholecystectomy	3,604	6	23,774	0.25	0.90 [0.31, 2.60]	0.90 [(0.31, 2.60]	0.52 [0.18, 1.49]	0.53 [0.18, 1.55]

Note. hazard ratio = relative hazard ratio.

^aRate = incidence rate, per 1,000 person-years. ^bAdjusted hazard ratio = multivariable analysis including age, and comorbidities of coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, hypertension, diabetes, hyperlipidemia, depression, anxiety, asthma, and alcohol-related illness.

****p* < .025.

stone disease alone exhibited a 1.47-fold high risk of organic erectile dysfunction (97.5% confidence interval [1.16, 1.86]). Compared with men without gallbladder stone disease and without anxiety, men with gallbladder stone disease alone exhibited a 1.52-fold high risk of organic erectile dysfunction (97.5% confidence interval [1.19, 1.93]).

The incidences and hazard ratios of organic and psychogenic erectile dysfunction in gallbladder stone disease stratified by cholecystectomy are presented in Table 5. The mean time from the diagnosis of gallbladder stone disease to cholecystectomy was 5.31 years (standard deviation = 3.76). Compared to men in the nongallbladder stone disease cohort, gallbladder stone disease without cholecystectomy had a much higher risk of developing organic erectile dysfunction (adjusted hazard ratio = 1.68, 97.5% CI [1.32, 2.15]). Whereas gallbladder stone disease with cholecystectomy exhibited a significantly lower risk of developing organic erectile dysfunction than gallbladder stone disease without cholecystectomy (adjusted hazard ratio = 0.58, 97.5% CI [0.41, 0.80]). Moreover, the risk of organic erectile dysfunction was comparable between the nongallbladder stone cohort and the gallbladder stone cohort with cholecystectomy (adjusted hazard ratio = 0.98, 97.5% CI [0.70, 1.37]). However, cholecystectomy has no association with the development of psychogenic erectile dysfunction.

Discussion

In 2010, only 10.7% of people were aged >65 years in Taiwan (Li, Cheng, Liang, Wu, & Lotus Shyu, 2013). Furthermore, we observed that 33.2% of men with gallbladder stone disease were aged >65 years, and our results supported that gallbladder stone disease is associated with aging. The higher prevalence of gallbladder stone disease in the older men population may be a consequence of

increased intestinal absorption of cholesterol, enhanced biliary secretion of cholesterol, decreased synthesis and secretion of bile salts, and impaired gallbladder emptying in the aging process (Cao & Eslick, 2018; Shabanzadeh et al., 2016; Upala et al., 2017). Our findings showed that hypertension, hyperlipidemia, and diabetes were the most common comorbidities in order of frequency for men with gallbladder stone disease (Table 1). The association between hypertension and gallbladder stone disease remains unknown; however, an increased sympathetic tone with impaired gastrointestinal motility is suggested to be a risk factor common for gallbladder stone disease in hypertensive patients (Yu et al., 2017). High-density lipoprotein cholesterol is a protective factor for gallbladder stone disease development, whereas hypertriglyceridemia often results in supersaturated bile and impaired gallbladder emptying to enhance gallbladder stone disease development (Dhamnetiya, Goel, Dhiman, & Pathania, 2018; Singh et al., 2018). Moreover, diabetes can contribute gallbladder stone disease development because insulin resistance increases cholesterol secretion into bile, and hyperglycemia can impair gallbladder emptying (Shafqet & Sharzei, 2017).

Except depression, anxiety, and alcohol-related illness, the prevalence of other comorbidities was lower in men with gallbladder stone disease than in those without gallbladder stone disease (Table 1). However, our findings consistently revealed gallbladder stone disease was associated with an increased risk of organic erectile dysfunction after adjusting for age and comorbidities, including coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, hypertension, diabetes, hyperlipidemia, depression, anxiety, asthma, and alcohol-related illness. Moreover, comorbidity has been treated as a time varying covariate in our study to minimize the possibility that men with gallbladder disease without comorbidities may be prone to develop erectile dysfunction due

to the development of the comorbidities later in life. Moreover, our results suggest that the risk of organic erectile dysfunction increased with an increase in the follow-up duration, rather than in the immediate days, after a diagnosis of gallbladder stone disease. All these findings consistently indicate that gallstone disease is closely associated with the development of organic erectile dysfunction. It should be noted that the risk of organic erectile dysfunction contributed by gallbladder stone disease was particularly significant in men aged ≥ 65 years and in men with comorbidities; therefore, our findings may provide a reference for the screening or treatment of organic erectile dysfunction in men with gallbladder stone disease. However, gallbladder stone disease is not associated with the development of psychogenic erectile dysfunction in our study. The main causes of psychogenic erectile dysfunction are complex and include fear of performance failure during intercourse and multiple developmental, cognitive, affective, and interpersonal factors, which may explain the cause for lacking well recognized risk factors for the development of psychogenic erectile dysfunction in our study (Shamloul & Ghanem, 2013).

Cholecystectomy clinically is only indicated for biliary complications, but we have demonstrated that gallbladder stone disease increased the risk of organic erectile dysfunction and the risk after cholecystectomy would diminish to a level comparable to that of the nongallbladder stone disease cohort. Beyond a biliary tract disease, gallbladder stone disease may be a marker of organic erectile dysfunction. The protective mechanism of cholecystectomy against the development of organic erectile dysfunction cannot be ascertained in this observational study, and more studies are required to determine whether gallbladder stone disease is a risk factor or an epiphenomenon of organic erectile dysfunction.

The association of gallbladder stone disease with erectile dysfunction may be due to the following common pathophysiological mechanisms. Firstly, the saturation of cholesterol into bile for enhancing the development of gallbladder stone disease is similar to the pathogenesis of atherosclerotic plaque deposition in the penile arteries of organic erectile dysfunction (Singh et al., 2018; Targher & Byrne, 2015; Upala et al., 2017). Secondly, patients with gallbladder stone disease have low plasma levels of insulin-like growth factor-1, which impairs postprandial gallbladder emptying. Similarly, the antiatherosclerotic effect of insulin-like growth factor-1 diminishes in patients with gallbladder stone disease with low plasma insulin-like growth factor-1 levels (Fan, Chen, & Dai, 2017; Shabanzadeh, 2018). Thirdly, gallbladder stone disease is characterized by an increased degree of inflammation and oxidative stress (Grattagliano, Ciampi, & Portincasa, 2017). Similarly, increased oxidative stress increases the susceptibility to atherosclerosis in penile

arteries of men with organic erectile dysfunction (Maiorino, Bellastella, & Esposito, 2015). Finally, a bidirectional association has been established between gallbladder stone disease and psychosocial stress (Yafi et al., 2016). Patients with gallbladder stone disease tend to be more obsessive, and autonomic nervous dysfunction with impaired gallbladder emptying was more prevalent in these patients. A bidirectional association has also been recognized between erectile dysfunction and psychosocial stress (Langer et al., 2017; Shamloul & Ghanem, 2013). Men with erectile dysfunction exhibit a higher risk of psychosocial stress than those without erectile dysfunction, and smooth muscle dysfunction beyond endothelial dysfunction supposedly develops before the onset of systemic vascular diseases (Lane-Cordova, Kershaw, Liu, Herrington, & Lloyd-Jones, 2017). Our findings strongly support the association between psychosocial stress and organic erectile dysfunction.

Our study has several merits. Firstly, our study is the first population-based study to examine the association between gallbladder stone disease and the subsequent development of erectile dysfunction. Secondly, our statistical analyses included data from a national database with a 12-year observation period for the representative cohort of 1,000,000 citizens covered by the National Health Insurance program. Thirdly, the enrolled men were sampled from a population of approximately 99% of Taiwanese residents to provide the generalizability of the findings in Taiwan. However, more international studies are required to ascertain this possible global generalizability. In addition, our longitudinal cohort study facilitated the evaluation of the temporal association between gallbladder stone disease and erectile dysfunction.

Our study has several limitations. Firstly, we could have neglected potential confounding factors because the National Health Insurance Research Database did not provide detailed information on erectile dysfunction-related lifestyle and socioeconomic status. The National Health Insurance Research Database lacked data on educational background, exercise and work loadings, and beneficiary height and weight. However, we replaced alcohol drinking habits with alcohol-related illness and replaced smoking habits with the diagnosis of chronic obstructive pulmonary disease for adjustment. Furthermore, gallbladder stone disease was consistently associated with organic erectile dysfunction development after controlling for age, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, hypertension, diabetes, hyperlipidemia, depression, anxiety, asthma, and alcohol-related illness. Secondly, we did not include men not enrolled in the National Health Insurance program, but the program currently has covered more than 99% of Taiwan's population. Thirdly, the surveillance bias may exist in our study due to

the misclassification of asymptomatic gallbladder stone disease into nongallbladder stone disease and men with gallbladder stone disease might have more medical accessibility to yield the diagnosis of erectile dysfunction. The diagnosis made of gallbladder stone disease mainly relied on imaging studies, such as ultrasound, computed tomography, or magnetic resonance imaging, rather than on the development of symptoms in Taiwan. However, by comparing the incidence of erectile dysfunction between the gallbladder stone disease men with cholecystectomy and without cholecystectomy, our findings supported the ameliorating effect of cholecystectomy against the development of organic erectile dysfunction among the gallbladder stone disease cohort even though the follow-up duration was longer in the cholecystectomy subjects. Therefore, the association between organic erectile dysfunction and the existence of gallbladder stone disease is validated in this sensitivity analysis. Finally, men not seeking medical consultation for erectile dysfunction could not be enrolled in our study; therefore, the risk of erectile dysfunction might be underestimated. The code of erectile dysfunction was made by the urologists, who have treated the patients and enrolled erectile dysfunction as the main diagnosis in their claims. Moreover, the accuracy of a medical diagnosis, according to ICD-9-CM, was regularly audited by related specialists and physicians based on the standard clinical criteria. The National Health Insurance program is operated by a single institute, the Bureau of National Health Insurance, without competitors. Health-care providers would receive severe disciplinary actions if they were found inappropriately designating inaccurate ICD-9-CM codes. Regarding the accuracy of the claims codes in our dataset, the literature has shown a substantial concordance between the claims of common chronic diseases, medication, and medical resource utilization, either based on the patient self-reports or review of the medical records (Cheng et al., 2014; Wu, Lai, Gau, Wang, & Tsai, 2014).

In conclusion, the findings of our population-based cohort study indicate that gallbladder stone disease is associated with an increased risk of organic erectile dysfunction, but it has no association with psychogenic erectile dysfunction. Cholecystectomy for gallbladder stone disease may ameliorate the risk of organic erectile dysfunction, but it requires more studies to ascertain the protective mechanism and to clarify whether the existence of gallbladder stone disease is an epiphenomenon of or independent risk factor of erectile dysfunction.

Author Contributions

The authors' individual contributions are mentioned as follows. Conception and design: Chien-Hua Chen and Chia-Hung Kao. Administrative support: Chia-Hung Kao. Data collection and organization: All authors. Data analysis and interpretation: All

authors. Manuscript writing: All authors. Final approval of the manuscript: All authors.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from the Ministry of Health and Welfare, Taiwan (MOHW107-TDU-B-212-123004), China Medical University Hospital (CMU106-ASIA-12, DMR-107-192); Academia Sinica Stroke Biosignature Project (BM10701010021); MOST Clinical Trial Consortium for Stroke (MOST 107-2321-B-039 -004-); Tseng-Lien Lin Foundation, Taichung, Taiwan; and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

ORCID iD

Chia-Hung Kao  <https://orcid.org/0000-0002-6368-3676>

References

- Cao, A. M., & Eslick, G. D. (2018). Epidemiology and pathogenesis of gallstones. In M. R. Cox, G. D. Eslick & R. Padbury (Eds.), *The management of gallstone disease* (pp. 53–66). Cham, Switzerland: Springer.
- Chen, C.-H., Huang, M.-H., Yang, J.-C., Nien, C.-K., Etheredge, G. D., Yang, C.-C., ... Yueh, S.-K. (2006). Prevalence and risk factors of gallstone disease in an adult population of Taiwan: An epidemiological survey. *Journal of Gastroenterology and Hepatology*, *21*(11), 1737–1743.
- Cheng, C.-L., Lee, C.-H., Chen, P.-S., Li, Y.-H., Lin, S.-J., & Yang, Y.-H. K. (2014). Validation of acute myocardial infarction cases in the National Health Insurance Research Database in Taiwan. *Journal of Epidemiology*, *24*(6), 500–507.
- National Health Insurance Research Database. (2015). *Taiwan*. Retrieved from <http://nhird.nhri.org.tw/en/index.html>
- Dhamnetiya, D., Goel, M. K., Dhiman, B., & Pathania, O. P. (2018). Gallstone disease and quantitative analysis of independent biochemical parameters: Study in a tertiary care hospital of India. *Journal of Laboratory Physicians*, *10*(4), 448–452.
- Dragos, D., Tanasescu, M. D., Comsa, M. O., Minca, A., & Olteanu, D. (2015). Psychological features associated with gallstone disease. *Romanian Medical Journal*, *62*(1), 49–58.
- Fan, L. L., Chen, B. H., & Dai, Z. J. (2017). The relation between gallstone disease and cardiovascular disease. *Scientific Reports*, *7*, 15104.
- Grattagliano, I., Ciampi, S. A., & Portincasa, P. (2017). Gallbladder disease: Relevance of oxidative stress. In J.

- Gracia-Sancho & J. Salvadó (Eds.), *Gastrointestinal tissue: Oxidative stress and dietary antioxidants* (pp. 187–194). Cambridge, MA: Academic Press.
- Gurusamy, K. S., & Davidson, B. R. (2014). Gallstones. *BMJ*, *348*, g2669.
- Hsu, C.-W., Lin, C.-S., Chen, S.-J., Lin, S.-H., Lin, C.-L., & Kao, C.-H. (2016). Risk of type 2 diabetes mellitus in patients with acute critical illness: A population-based cohort study. *Intensive Care Medicine*, *42*(1), 38–45.
- Lamberts, M. P. (2018). Indications of cholecystectomy in gallstone disease. *Current Opinion in Gastroenterology*, *34*(2), 97–102.
- Lane-Cordova, A. D., Kershaw, K., Liu, K., Herrington, D., & Lloyd-Jones, D. M. (2017). Association between cardiovascular health and endothelial function with future erectile dysfunction: The multi-ethnic study of atherosclerosis. *American Journal of Hypertension*, *30*(8), 815–821.
- Langer, R., Langer, B., Mahajan, R., Sharma, E., Gupta, R. K., & Kumari, R. (2017). Exploring psychosocial issues in patients of erectile dysfunction: A study in tertiary care setting. *International Journal of Medical Science and Public Health*, *6*(6), 1050–1055.
- Li, H.-J., Cheng, H.-S., Liang, J., Wu, C.-C., & Lotus Shyu, Y.-I. (2013). Functional recovery of older people with hip fracture: Does malnutrition make a difference? *Journal of Advanced Nursing*, *69*(8), 1691–1703.
- Maiorino, M. I., Bellastella, G., & Esposito, K. (2015). Lifestyle modifications and erectile dysfunction: What can be expected? *Asian Journal of Andrology*, *17*(1), 5–10.
- McMahon, C. G. (2014). Erectile dysfunction. *Internal Medicine Journal*, *44*, 18–26.
- Nehra, A., Jackson, G., Miner, M., Billups, K. L., Burnett, A. L., Buvat, J., ... Wu, F. C. W. (2012). The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clinic Proceedings*, *87*, 766–778.
- Raheem, O. A., Su, J. J., Wilson, J. R., & Hsieh, T.-C. (2017). The association of erectile dysfunction and cardiovascular disease: A systematic critical review. *American Journal of Men's Health*, *11*(3), 552–563.
- Shabanzadeh, D. M. (2018). Incidence of gallstone disease and complications. *Current Opinion in Gastroenterology*, *34*(2), 81–89.
- Shabanzadeh, D. M., Sørensen, L. T., & Jørgensen, T. (2016). Determinants for gallstone formation—A new data cohort study and a systematic review with meta-analysis. *Scandinavian Journal of Gastroenterology*, *51*(10), 1239–1248.
- Shafqet, M., & Sharzei, K. (2017). Diabetes and the pancreaticobiliary diseases. *Current Treatment Options in Gastroenterology*, *15*(4), 508–519.
- Shamloul, R., & Ghanem, H. (2013). Erectile dysfunction. *The Lancet*, *381*, 153–165.
- Singh, R. R., Adhikari, S. C., Bastakoti, R., Regmi, S., Baskota, R., & Giri, K. (2018). Determining relation between gallstone and lipid profile. *Birat Journal of Health Sciences*, *3*(2), 418–422.
- Stinton, L. M., & Shaffer, E. A. (2012). Epidemiology of gallbladder disease: Cholelithiasis and cancer. *Gut and Liver*, *6*, 172–187.
- Targher, G., & Byrne, C. D. (2015). Gallstone disease and increased risk of ischemic heart disease. Causal association or epiphenomenon? *Arteriosclerosis, Thrombosis, and Vascular Biology*, *35*, 2073–2075.
- Twickler, M. T. B., Cramer, M.-J. M., & van Erpecum, K. J. (2005). Insulin-like growth factor-1: A common metabolic pathway in the origin of both gallstones and coronary artery disease. *The American Journal of Gastroenterology*, *100*, 2363–2364.
- Upala, S., Sanguankeo, A., & Jaruvongvanich, V. (2017). Gallstone disease and the risk of cardiovascular disease: A systematic review and meta-analysis of observational studies. *Scandinavian Journal of Surgery*, *106*(1), 21–27.
- Wang, C.-C., Chang, C.-T., Lin, C.-L., Lin, I.-C., & Kao, C.-H. (2015). Hepatitis C virus infection associated with an increased risk of deep vein thrombosis: A population-based cohort study. *Medicine (Baltimore)*, *94*(38), e1585.
- Wu, C.-S., Lai, M.-S., Gau, S. S.-F., Wang, S.-C., & Tsai, H.-J. (2014). Concordance between patient self-reports and claims data on clinical diagnoses, medication use, and health system utilization in Taiwan. *PLoS One*, *9*(12), e112257.
- Yafi, F. A., Jenkins, L., Albersen, M., Corona, G., Isidori, A. M., Goldfarb, S., ... Hellstrom, W. J. G. (2016). Erectile dysfunction. *Nature Reviews Disease Primers*, *2*, 16003.
- Yu, K.-J., Zhang, J.-R., Li, Y., Huang, X., Liu, T., Li, C., & Wang, R.-T. (2017). Gallstone disease is associated with arterial stiffness progression. *Hypertension Research*, *40*(1), 31–34.