European Journal of Internal Medicine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Long-term risk of pancreatitis and diabetes after cholecystectomy in patients with cholelithiasis but no pancreatitis history: A 13-year follow-up study

Ming-Shian Tsai [a], Cheng-Li Lin [b,c], Yao-Chun Hsu [d], Hui-Ming Lee [a], Chia-Hung Kao [e,f,g,*]

[a] Department of General Surgery, E-Da Hospital and I-Shou University, Kaohsiung, Taiwan
[b] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[c] College of Medicine, China Medical University, Taichung, Taiwan
[d] Department of Gastroenterology, E-Da Hospital and I-Shou University, Kaohsiung, Taiwan
[e] Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, Taichung, Taiwan
[f] School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan
[g] Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 21 May 2015
Received in revised form 21 June 2015
Accepted 22 June 2015
Available online xxxx

Keywords:
Pancreatitis
Cholelithiasis
Cholecystectomy
Cohort study
National Health Insurance Research Database (NHIRD)

ABSTRACT

Background & aim: Patients with biliary pancreatitis are suggested to undergo cholecystectomy to prevent the recurrence of pancreatitis. However, it remains controversial whether cholecystectomy is associated with reduced risks of pancreatitis and diabetes in patients with cholelithiasis and no history of pancreatitis.
Methods: From Taiwan's National Health Insurance Research Database, we identified the following cohorts and analyzed the long-term risks of pancreatitis and diabetes in each cohort: 1) cholecystectomy cohort: cholelithiasis patients who had no history of pancreatitis and diabetes and underwent cholecystectomy; and 2) comparison cohort: cholelithiasis patients who had no history of pancreatitis and diabetes and did not undergo cholecystectomy.
Results: The cholecystectomy group and the comparison group had similar distributions of age, sex, and comorbidities, except for hyperlipidemia. The proportion of patients in the cholecystectomy group who underwent endoscopic cholangiographic procedures was higher than that in the comparison group. Cholecystectomy was associated with a reduced risk of pancreatitis (adjusted hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.36–0.68). Age-specific analyses showed that pancreatitis risk was decreased in patients younger than 50 and older than 65 years. Both men and women exhibited reduced risks of pancreatitis after cholecystectomy. However, cholecystectomy was not associated with changes in the risk for diabetes.
Conclusion: Cholecystectomy for cholelithiasis is associated with a reduced risk of pancreatitis, but not of diabetes, in patients without previous history of pancreatitis and diabetes.

1. Introduction

Cholelithiasis, or gallstones, is associated with pancreatitis in nearly one-third of patients experiencing pancreatitis [1–3]. Although the incidence of biliary pancreatitis has increased in the previous 2 decades, no reduction was observed in the case-fatality rate in patients with pancreatitis [3,4]. Therefore, preventing the occurrence of biliary pancreatitis and its associated complications is imperative. Because the migration of gallstones has been regarded as a crucial factor causing recurrent pancreatitis, cholecystectomy is generally recommended in healthy patients experiencing biliary pancreatitis [5–7].

Although an association between gallstones and pancreatitis has been recognized for more than 100 years, the effect of cholecystectomy on this risk has not been extensively studied. Moreover, it is controversial whether cholecystectomy can reduce the risks of pancreatitis and probably subsequent diabetes in patients with cholelithiasis who did not previously experience pancreatitis. Studies have shown that patients with gallstones smaller than 5 mm in diameter have a significantly increased risk of developing acute biliary pancreatitis [8,9]. Cholecystectomy appeared to facilitate reducing the risk of pancreatitis only in these patients [8].

However, a study that enrolled patients who were diagnosed with gallstones between 1950 and 1970 reported that cholecystectomy reduced the risk of pancreatitis in patients with cholelithiasis, regardless of whether previous pancreatitis had occurred [10]. However, laparoscopic cholecystectomy (LC) was not universally applied during the study period. Moreover, because the overall incidence of pancreatitis

Abbreviations: HR, hazard ratio; CI, confidence interval; NHIRD, National Health Insurance Research Database; LC, laparoscopic cholecystectomy; NHI, National Health Insurance; LHID2000, the Longitudinal Health Insurance Database 2000; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

* Corresponding author at: Graduate Institute of Clinical Medical Science and, School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der, Road, Taichung 404, Taiwan. Tel.: +886 4 22052121x7412; fax: +886 4 22336174.
E-mail address: d10040@mail.cmuh.org.tw (C.-H. Kao).

http://dx.doi.org/10.1016/j.ejim.2015.06.013
0953-6205/

reported in the study was low [10], performing cholecystectomy to prevent pancreatitis was suggested only if a patient had previously experienced pancreatitis.

In consideration of the great advancement of minimally invasive surgery and the increased incidence of biliary pancreatitis during the past 2 decades, reappraising whether cholecystectomy could reduce the risk of biliary pancreatitis in patients who have not previously experienced pancreatitis is essential. In addition to conducting this reappraisal, we aimed to determine whether cholecystectomy is associated with reduced risk of subsequent diabetes because it is well established that pancreatitis may lead to the onset of diabetes [11]. In this 13-year follow-up study, we compared the risks of pancreatitis and diabetes in patients with gallstone diseases but no history of pancreatitis or diabetes by analyzing a broadly representative population-based cohort from Taiwan's National Health Insurance Research Database (NHIRD).

2. Methods

2.1. Data source

Taiwan launched a single-payer National Health Insurance (NHI) program on March 1, 1995. The NHI program covers more than 99% of the approximately 23.74 million residents of Taiwan (http://www.nhi.gov.tw/english/index.aspx). For research purposes, the Taiwan National Health Research Institutes manages and releases the NHIRD annually. The data used in this study originated from the Longitudinal Health Insurance Database 2000 (LHID2000), which is a subset of the NHIRD that contains all claims data of one million beneficiaries from 1996 to 2011. No significant differences exist in age, sex, or health care costs between the sampled group and all enrollees in the NHI program. The LHID2000 provides encrypted patient identification numbers; records on patients' sex, date of birth, and dates of admission and discharge; ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes of diagnoses and procedures; and details on prescriptions and costs covered by NHI. This study was exempted from full ethical review (IRB permit number: CMU-REC-101-012). Informed consent was not required because the datasets were devoid of identifiable personal information.

2.2. Sampled patients

All patients who had a history of cholelithiasis (ICD-9-CM code 574) between 2000 and 2010 were included in the study population. Patients with cholecystectomy (ICD-9-CM procedure codes 51.22 and 51.23) were assigned to the cholecystectomy cohort. Patients who had a history of pancreatitis (ICD-9-CM codes 577.0 and 577.1) or diabetes (ICD-9-CM code 250), those who were younger than 20 years, and those for whom complete information was lacking were excluded. The date of the cholecystectomy was used as the index date. The comparison cohort was randomly selected from the remaining patients who had cholelithiasis but did not undergo cholecystectomy. For each patient in the cholecystectomy cohort, 2 comparison patients without a history of diabetes or pancreatitis were identified and frequency-matched according to age (within 5-year spans), sex, and the year of the index date.

2.3. Outcome and comorbidities

All patients were followed up until they received a new diagnosis of pancreatitis or diabetes during the follow-up period. Each patient was monitored from the index date until he or she was diagnosed with pancreatitis or diabetes or until he or she was censored because of loss to follow-up, death, withdrawal from insurance, or the end of December 31, 2011. Patients with claims records showing a history of hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), hepatitis B (ICD-9-CM codes 070.2, 070.3, and V02.61), hepatitis C (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, V02.62, and 070.7), cirrhosis of the liver (ICD-9-CM codes 571.5 and 571.6), or alcohol-related illness (ICD-9-CM codes 291, 303, 305, 571.0, 571.1, 571.3, 790.3, and V11.3, including alcoholic psychoses, alcohol dependence syndrome, alcohol abuse, alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis and alcoholic liver damage) identified at the baseline were considered to have comorbidities. We also considered inspection performed using choledochoscopy.

2.4. Statistical analysis

The demographic characteristics and comorbidities of patients with cholelithiasis who underwent cholecystectomy and those who did not undergo cholecystectomy, including age (20–49 years, 50–64 years, and ≥65 years), sex, and comorbidities, were compared using a chi-square test. We used a Student's *t* test for continuous variables. Age-, sex-, and comorbidity-specific incidence densities (1000 person-years) of pancreatitis and diabetes were estimated. Univariable and multivariable Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for pancreatitis and diabetes in patients with cholelithiasis who underwent cholecystectomy compared with those in the comparison cohort. The multivariable models were simultaneously adjusted for age; sex; comorbid hypertension, hyperlipidemia, hepatitis B, hepatitis C, cirrhosis of the liver, and alcoholic liver disease; and inspection through choledochoscopy. The cumulative incidence of pancreatitis and diabetes in both cohorts was assessed using the Kaplan–Meier method, and the differences between the curves were evaluated using a log-rank test. All statistical analyses were performed using SAS statistical software (Version 9.3 for Windows; SAS Institute, Inc., Cary, NC, USA). A 2-tailed p value < .05 was considered statistically significant.

3. Results

The cholecystectomy cohort comprised 4467 persons and the comparison cohort comprised 8823 persons (Table 1). In the present study, 42.5% of the patients were younger than 49 years and 57.2% were female. The mean ages for the cholecystectomy and comparison cohorts were 54.3 (SD = 16.0) and 54.5 (SD = 16.0) years, respectively.

Table 1
Comparison of demographics and comorbidity among cholelithiasis patients with and without cholecystectomy.

	Cholecystectomy				
	No (N = 8823)		Yes (N = 4467)		
	n	%	n	%	p-Value
Age, year					0.76
≤49	3689	41.8	1898	42.5	
50–65	2662	30.2	1331	29.8	
≥65	2472	28.0	1238	27.7	
Mean (SD)[a]	54.5	16.0	54.3	16.0	0.56
Sex					0.57
Female	5001	56.7	2555	57.2	
Male	3822	43.3	1912	42.8	
Comorbidity and procedures					
Hypertension	3219	36.5	1689	37.8	0.13
Hyperlipidemia	2222	25.2	1048	23.5	0.03
Hepatitis B	687	7.79	319	7.14	0.18
Hepatitis C	399	4.52	179	4.01	0.17
Cirrhosis	277	3.14	149	3.34	0.54
Alcohol-related illness	485	5.50	202	4.52	0.02
Inspection					
Choledochoscopy	428	4.85	542	12.1	<0.001

Chi-square test; SD: standard deviation.
[a] Two sample *t*-test.

Please cite this article as: Tsai M-S, et al, Long-term risk of pancreatitis and diabetes after cholecystectomy in patients with cholelithiasis but no pancreatitis history: A 13-year follow-up study, Eur J Intern Med (2015), http://dx.doi.org/10.1016/j.ejim.2015.06.013