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Original Article

Increased Risk of Cholecystitis Following Periodontitis and Dental Scaling

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Purpose: The aim of this study was to investigate the risk of cholecystitis following periodontitis and dental scaling.
Methods: We conducted a nationwide population-based retrospective cohort study using the Longitudinal Health Insurance Database 2000 (LHID 2000, from 2000 to 2013), a subset of the National Health Insurance Research Datasets (NHIRD). In total, 25,315 patients with cholecystitis were included in the study group and 101,260 age- and sex-matched individuals were included in the control group. For both groups, severity of periodontitis and incidence of dental scaling 3 years or less before the index date were determined. Subgroup analyses were conducted using different parameters.
Results: We observed a significantly increased risk of cholecystitis with exposure to severe periodontitis (aOR=1.217, 95% CI 1.022–1.448). Significant interactions were noted for age and periodontitis severity with cholecystitis (interaction P=0.0322). Individuals aged 50 to 70 years with severe periodontitis had a 43.6% increased risk of developing cholecystitis (aOR=1.436; 95% CI 1.098–1.877) compared with individuals without periodontitis. Moreover, there was an association between 1-5 dental scaling events 3 years or less before the index date and risk of cholecystitis.
Conclusion: Our findings indicated that an increased risk of cholecystitis is associated with severe periodontitis and dental scaling events within 3 years of its occurrence.

Keywords: cholecystitis; dental scaling; gallstone; periodontitis

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1. Introduction

Cholecystitis is defined as inflammation of the gallbladder and is a common complication of gallstones [1,2]. Other complications of gallstone disease include biliary pancreatitis and acute cholangitis. The national prevalence of gallstones in Asian countries varies between 3.1% and 15.6% [3]. The prevalence of gallstones in Taiwan is between 4.3% (community-based study) and 10.7% (hospital-based study) [1,3]. Cholecystectomy is the gold standard for the treatment of acute cholecystitis and gallstone disease [4]. Periodontitis is one of the most prevalent oral diseases in Taiwan. Severe periodontitis can cause destruction of the periodontal ligament, alveolar bone reduction, and subsequent tooth loss [5]. To date, more than 700 species of oral bacteria have been identified from gingival plaque [6]. Although there is no evidence that a single bacterial species causes periodontitis, application of P. gingivalis to the gingival pocket has been found to accelerate periodontal symptoms in mice [7]. Treatment of periodontal disease mostly involves a mechanical dental procedure (i.e., dental scaling) with or without antibiotic administration.

The pathogenesis of periodontal diseases is modulated by the immune response. Such diseases are considered risk factors for systemic diseases such as obesity, diabetes, rheumatoid arthritis, and osteoporosis, as well as pregnancy complications [8,9]. Associations between periodontitis and digestive diseases, such as Crohn's disease, liver abscess, and pancreatic cancer, have been reported [10–12]. From our laboratory observations, mice with P. gingivalis smeared on their gingivae develop cholecystitis and gallstones more frequently (personal communication). However, the association between periodontitis and cholecystitis in humans has rarely been studied. We hypothesized that individuals with periodontitis exhibit an increased risk of developing cholecystitis and associated complications. By using the unique advantages of the Taiwan National Health Insurance Research Database (NHIRD), including a large population and a long-term follow-up period, we conducted this population-based retrospective cohort study to investigate the association between periodontitis and cholecystitis.

2. Materials and methods

2.1. Data source

The National Health Insurance (NHI) program in Taiwan was launched in 1995 and covers more than 99% of its 23 million inhabitants. The NHIRD contains complete ambulatory and inpatient care claims data from NHI program enrollees. Data for this study were sourced from the Longitudinal Health Insurance Database 2000 (LHID 2000), a subset of the NHIRD. Briefly, the LHID 2000 contains 1 million beneficiaries who were randomly sampled from the Registry for Beneficiaries of the NHIRD in 2000. In this study, registration, claims data, and treatment archives of the LHID 2000 from 2000 to 2013 were extracted for analysis. The data were encrypted by scrambling of identification codes. This study was approved by the Institutional Review Board of Chung Shan Medical University Hospital in Taiwan (CS15134).

2.2. Definition of cholecystitis and matched controls

Cholecystitis patients were identified based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 574.x, 575.0, and 575.10. These patients underwent computerized tomography, abdominal ultrasonography, or retrograde cholangio-pancreatography within 1 month of diagnosis. A 1:4 ratio of randomly sampled controls was selected for the non-cholecystitis cohort based on the index dates. They were matched by age and sex. Moreover, they had a risk of cholecystitis and could become cases at the index date.

2.3. Definition of periodontitis exposure and dental scaling

Severity of periodontitis was assessed by modifying Huang et al.'s method: no periodontitis, mild periodontitis (ICD9-CM codes 523.0, 523.1, 523.2, 523.3, 523.4, 523.5, 523.8, or 523.9 and concurrent antibiotic therapy or scaling more than twice per year), moderate periodontitis (periodontitis diagnosis and treatment with subgingival curettage), and severe periodontitis (periodontitis diagnosis and treatment with periodontal flap operation, gingivectomy, or odontectomy) (Table 1) [13].

Table 1. Criteria for assessing periodontitis severity

Severity	Treatment	Claim code
Mild periodontitis	Only antibiotic therapy or scaling more than twice per year by certified dentist	
Moderate periodontitis	Subgingival curettage—full mouth	91006C
	Subgingival curettage—1/2 arch	91007C
	Subgingival curettage—< 3 teeth	91008C
Severe periodontitis	Periodontal flap operation—localized	91009B
	Periodontal flap operation—1/3 arch	91010B
	Gingivectomy—< 3 teeth	91011C
	Gingivectomy—1/3 arch	91012C
	Odontectomy—simple case	92015C
	Odontectomy—complicated case	92016C

Levels of severity of periodontitis were identified 3 years or less before the index date or 6 months after the index date. We selected the most severe level of periodontitis when subjects had more than one episode of periodontitis during the study period. To confirm the severity of periodontitis and the incidence of dental scaling 3 years or less before the index date, we excluded repeat cases of periodontitis or cholecystitis before 2003. Moreover, cholecystitis cases diagnosed in 2013 were excluded due to lack of information regarding level of periodontitis severity. We assessed whether each patient received dental scaling every 6 months, 3 years or less before the index date. We could not observe the actual number of dental scaling procedures 3 years or less before the index date, however, as dental scaling is limited to 1 time reimbursement per 6 months in the NHI program. The number of dental scaling procedures was measured according to the number of times the procedure was performed every 6 months over a 3-year period (Figure 1).

2.4. Outcome measurements

We also identified demographic characteristics, level of urbanization of place of residence, low-income households, and co-morbidities in the case and control groups. The demographic characteristics included sex and age. We calculated age (in years) of each subject at the index date and divided the subjects into 4 age groups: ≤30, 30-50, 50-70 and >70 years old. We modified a previous method to classify subjects based on level of urbanization: urban, suburban, and rural [14]. Low-income household records were found in the Registry for Beneficiaries. Certificates of low-income households were examined and approved by the county government. Regarding co-morbidities, we selected diabetes (ICD-9-CM: 250), hyperlipidemia (ICD-9-CM: 272), allergies (ICD-9-CM: 477, 493, 708, 691, 693.0, 693.1, 995.0, 995.1, and 995.3), viral hepatitis (ICD-9-CM: 070.2, 070.3, V02.61, 070.41, 070.44, 070.51, 070.54, V02.62, and 070.7), chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 491,492, and 496), alcohol-related conditions (ICD-

Figure 1. An example of the determination of the number of dental scaling events 3 years or less before the index date. In this case, dental scaling was performed 4 times (every 6 months) during the 3-year period before the index date. Therefore, the total number of dental scaling events was 4.

9-CM: 571.0, 571.1, 571.2, 571.3, and 303), and gout (ICD-9-CM: 070.41, 070.44, 070.51, 070.54, 070.7, and V02.62).

2.5. Study procedures

All statistical analyses were conducted using the SAS statistical package (Version 9.3; SAS Institute, Inc., Cary, NC, USA). The chi-square test was used to compare differences in characteristics between the groups. A *P* value <0.05 was considered statistically significant. The conditional logistic regression model was employed to estimate the odds ratios (ORs) of cholecystitis. The 95% confidence interval (CI) was used to estimate precision. Univariate and multivariate models were constructed to predict crude ORs and adjusted ORs, respectively. To explore the interactions of specific characteristics, periodontitis severity, and dental scaling with risk of cholecystitis, we performed stratified analyses using logistic regression models based on severity of periodontitis, sex, age, urbanization, and whether or not in a low-income household.

3. Results

In total, 25,315 cholecystitis cases and 101,260 age- and sex-matched controls were selected for this study based on the inclusion and exclusion criteria (Figure 2). The cholecystitis group exhibited a greater risk of periodontitis, with dental scaling more likely 6 months or less before the index date

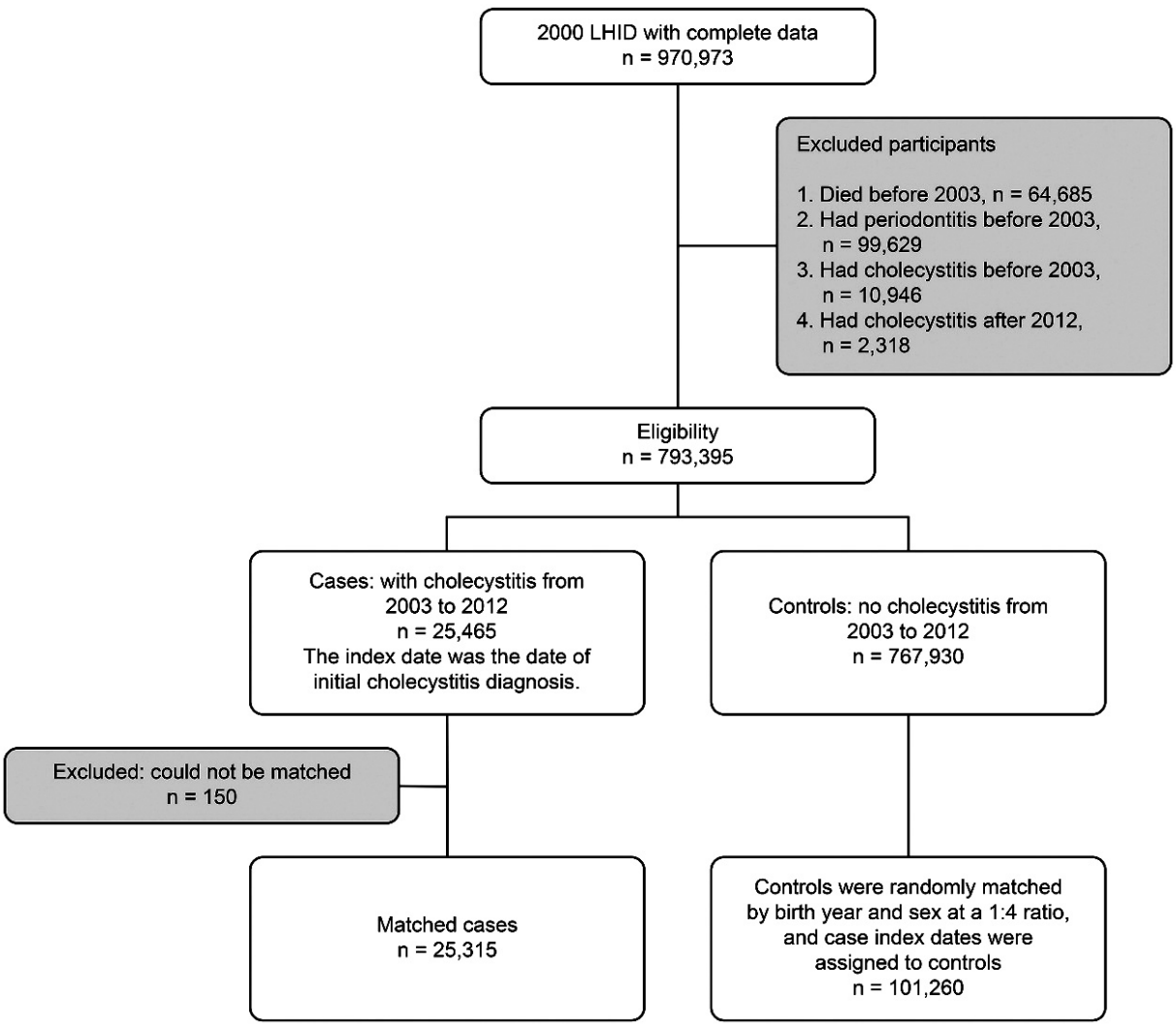

Figure 2. Flow chart of the study subject selection process.

Table 2. Distribution of characteristics in the cholecystitis and age- and sex-matched control groups

Characteristic	Cholecystitis n=25,315	Controls n=101,260	*P* value
Sex			1.000
Male	13,741 (54.28%)	54,964 (54.28%)	
Female	11,574 (45.72%)	46,296 (45.72%)	
Age (years)			1.000
≤ 30	2,136 (8.44%)	8,544 (8.44%)	
30-50	8,246 (32.57%)	32,984 (32.57%)	
50-70	9,304 (36.75%)	37,216 (36.75%)	
> 70	5,629 (22.24%)	22,516 (22.24%)	
Urbanization			< 0.001
Urban	15,649 (61.82%)	60,320 (59.57%)	
Suburban	7,172 (28.33%)	30,257 (29.88%)	
Rural	2,494 (9.85%)	10,683 (10.55%)	
Low income	270 (1.07%)	815 (0.8%)	< 0.001
Co-morbidity			
Diabetes	4,702 (18.57%)	11,975 (11.83%)	< 0.001
Hyperlipidemia	4,877 (19.27%)	13,078 (12.92%)	< 0.001
Allergies	5,600 (22.12%)	16,355 (16.15%)	< 0.001
Viral hepatitis	1,966 (7.77%)	2,503 (2.47%)	< 0.001
COPD	2,495 (9.86%)	6,416 (6.34%)	< 0.001
Alcohol-related conditions	587 (2.32%)	432 (0.43%)	< 0.001
Gout	2,147 (8.48%)	5,955 (5.88%)	< 0.001
Periodontitis	6,690(26.43%)	23,331(23.04%)	< 0.001
No	18,625 (73.57%)	77,929 (76.96%)	
Yes, mild	5,852 (23.12%)	20,430 (20.18%)	
Yes, moderate	655 (2.59%)	2,349 (2.32%)	
Yes, severe	183 (0.72%)	552 (0.55%)	0.33
Number of dental scaling events within 3 years	12,612(49.82%)	44,329(43.78)	< 0.001
0	12,703 (50.18%)	56,931 (56.22%)	
1	6,119 (24.17%)	22,434 (22.15%)	
2	3,366 (13.3%)	11,875 (11.73%)	
3	1,897 (7.49%)	5,960 (5.89%)	
4	838 (3.31%)	2,753 (2.72%)	

5	323 (1.28%)	1,031 (1.02%)	
6	69 (0.27%)	276 (0.27%)	
Dental scaling 6 months or less before the index date	4,330(17.1%)	14,526(14.35%)	<.001

COPD: chronic obstructive pulmonary disease.

and more frequent dental scaling 3 years or less before the index date (Table 2). In addition, subjects in the cholecystitis group were more likely to reside in urban areas (61.82%), be in a low-income household (1.07%), and to have diabetes (18.57%), hyperlipidemia (19.27%), allergies (22.12%), viral hepatitis (7.77%), COPD (9.86%), alcohol-related conditions (2.32%), and gout (8.48%) than those in the control group.

A significantly increased risk of cholecystitis was noted in subjects residing in urban areas; in low-income households (aOR=1.248, 95% CI 1.080–1.441); and with diabetes (aOR=1.534, 95% CI 1.471–1.601), hyperlipidemia (aOR=1.360, 95% CI 1.305–1.418), allergies (aOR=1.322, 95% CI 1.275–1.370), viral hepatitis (aOR=3.028, 95% CI 2.843–3.226), COPD (aOR=1.456, 95% CI 1.379–1.537), alcohol-related conditions (aOR=4.608, 95% CI 4.039–5.257), and gout (aOR=1.262, 95% CI 1.195–1.334) (Table 3). In addition, we observed significantly increased risks of cholecystitis with exposure to severe periodontitis (aOR=1.217, 95% CI 1.022–1.448) and for 1 (aOR=1.179, 95% CI 1.135–1.224), 2 (aOR=1.193, 95% CI 1.135–1.254), 3 (aOR=1.342, 95% CI 1.257–1.433), 4 (aOR=1.235, 95% CI 1.126–1.354), and 5 (aOR=1.282, 95% CI 1.115–1.472) dental scaling events 3 years or less before the index date. However, no significant association (aOR=1.027, 95% CI 0.778–1.354) was observed between cholecystitis risk and 6 dental scaling events 3 years or less before the index date.

Significant interactions were noted for age and periodontitis severity with cholecystitis (interaction *P*=0.0322) (Table 4). The effect of severe periodontitis was significantly higher (aOR=1.436, 95% CI 1.098–1.877) in individuals aged 50 to 70 years. The interaction effects of urbanization level and periodontitis severity on cholecystitis were marginally significant (interaction p=0.0708). In addition, the interaction between severe periodontitis and cholecystitis was statistically significant among subjects living in rural areas (aOR=2.347, 95% CI 1.211– 4.551).

Figures 3(A)–(E) present the relative risk of cholecystitis based on exposure to dental scaling through subgroup analyses of the severity of periodontitis, age, sex, urbanization, and income. We only observed a significant interaction between dental scaling and age, with the effect of dental scaling on cholecystitis increasing in the younger age groups (≤30 and 30–50 years old).

4. Discussion

Acute cholecystitis is defined as an acute inflammatory disease of the gallbladder that is often attributable to the impaction of gallstones in the bladder neck (Hartmann's pouch) or the cystic duct. Other causes include infection by microorganisms, protozoa or parasites; ischemia; motility disorders; direct chemical injury; collagen diseases; and allergic reactions. Acalculous cholecystitis accounts for 5%–10% of all cases [15]. A previous study has reported a bacteremia prevalence of 7.65% in acute cholecystitis [16]. Liver and brain abscesses caused by oral bacteria, such as *Aggregatibacter paraphrophilus* and *Fusobacterium necrophorum*, have been reported [11,17]. *S. intermedius* bacteremia and liver abscess following dental cleaning have also been described [18]. Yeh et al. recently suggested that periodontitis is a risk factor for pyogenic liver abscess among patients aged 20-40 years [19]. Bacteremia and acute acalculous cholecystitis after dental scaling and orthodontic treatment have also been reported [20]. We therefore hypothesized that oral commensal bacteria and periodontal pathogens induce inflammation of the gallbladder or liver tissue damage via blood circulation after dental scaling for the treatment of periodontitis.

Table 3. Conditional logistic regression to estimate the odds ratios of cholecystitis

Characteristic	Univariate model		Multivariate Model	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Urbanization				
Urban	Reference		Reference	
Suburban	0.912(0.884–0.941)	<.001	0.923(0.894–0.954)	<.001
Rural	0.896(0.855–0.94)	<.001	0.896(0.853–0.941)	<.001
Low income (Reference: no)	1.33(1.158–1.527)	<.001	1.248(1.080–1.441)	0.003
Co-morbidity (Reference: no)				
Diabetes	1.798(1.729–1.870)	<.001	1.534(1.471–1.601)	<.001
Hyperlipidemia	1.674(1.611–1.738)	<.001	1.360(1.305–1.418)	<.001
Allergies	1.481(1.431–1.533)	<.001	1.322(1.275–1.370)	<.001
Viral hepatitis	3.358(3.158–3.571)	<.001	3.028(2.843–3.226)	<.001
COPD	1.709(1.623–1.799)	<.001	1.456(1.379–1.537)	<.001
Alcohol-related conditions	5.639(4.968–6.400)	<.001	4.608(4.039–5.257)	<.001
Gout	1.507(1.430–1.589)	<.001	1.262(1.195–1.334)	<.001
Periodontitis				
No	Reference		Reference	
Yes, mild	1.222(1.180–1.265)	<.001	1.035(0.994–1.078)	0.093
Yes, moderate	1.197(1.094–1.308)	<.001	1.010(0.919–1.111)	0.830
Yes, severe	1.419(1.199–1.680)	<.001	1.217(1.022–1.448)	0.027
Number of dental scaling events within 3 years				
0	Reference			
1	1.237(1.195–1.281)	<.001	1.179(1.135–1.224)	<.001
2	1.289(1.234–1.346)	<.001	1.193(1.135–1.254)	<.001
3	1.450(1.371–1.533)	<.001	1.342(1.257–1.433)	<.001
4	1.392(1.284–1.508)	<.001	1.235(1.126–1.354)	<.001
5	1.431(1.260–1.624)	<.001	1.282(1.115–1.472)	0.001
6	1.151(0.883–1.501)	0.300	1.027(0.778–1.354)	0.852
Dental scaling 6 months or less before the index date	1.236(1.191–1.283)	<.001	1.033(0.986–1.083)	0.166

OR: odds ratio; aOR: adjusted odds ratio, adjusted for other covariates, including urbanization, low income, co-morbidities, periodontitis, frequency of dental scaling events during the 3-year period before the index date, dental scaling event 6 months or less before the index date; CI: confidence interval; COPD: chronic obstructive pulmonary disease.

Table 4. Sub-group analyses using unconditional logistic regression to estimate the odds ratios of cholecystitis based on periodontitis

	aOR (95% CI)				
	Periodontitis severity				
	No	Yes, Mild	Yes, Moderate	Yes, Severe	Interaction *P*
Sex					0.2369
Male	Reference	0.952(0.898–1.009)	0.955(0.833–1.095)	1.332(1.026–1.730)	
Female	Reference	1.059(1.006–1.116)	0.980(0.862–1.114)	1.090(0.866–1.371)	
Age					0.0322
≦30	Reference	1.092(0.964–1.238)	0.883(0.411–1.897)	1.021(0.641–1.628)	
30-50	Reference	0.997(0.934–1.065)	0.950(0.808–1.116)	1.104(0.827–1.473)	
50-70	Reference	1.051(0.987–1.119)	0.970(0.848–1.109)	1.436(1.098–1.877)	
>70	Reference	0.960(0.875–1.054)	1.073(0.845–1.363)	0.823(0.445–1.520)	
Urbanization					0.0708
Urban	Reference	1.044(0.995–1.095)	0.971(0.869–1.085)	1.136(0.924–1.397)	
Suburban	Reference	0.948(0.879–1.022)	1.023(0.848–1.235)	1.138(0.792–1.633)	
Rural	Reference	0.997(0.868–1.145)	0.811(0.521–1.262)	2.347(1.211–4.551)	
Low income					0.5725
No	Reference	1.012(0.974–1.052)	0.969(0.882–1.064)	1.191(1.002–1.416)	
Yes	Reference	0.832(0.524–1.321)	1.292(0.353–4.733)	0.633(0.050–8.065)	

aOR: adjusted odds ratio, adjusted for other covariates, including urbanization, low income, co-morbidities, periodontitis, frequency of dental scaling events during the 3-year period before the index date, dental scaling event 6 months or less before the index date; CI: confidence interval.

Most microorganisms in gingival plaque are commensal bacteria and opportunistic pathogens associated with the development and progression of periodontitis. The red complex, which includes *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* (formerly *Bacteroides forsythus*), is considered the most important group of pathogens in adult periodontal disease [21,22]. Dental scaling is the gold standard for preventing and treating periodontitis [9]. However, gingival bleeding is a common outcome of this procedure, especially in severe cases. [23,24]. Periodontopathic microorganisms, such as *P. gingivalis*, *Prevotella intermedia*, and *T. forysthus*, have been discovered in blood cultures after dental scaling and root planing [24]. In addition, oral surgical procedures, including dental extraction, third-molar surgery, dental scaling, endodontic treatment, and bilateral tonsillectomy, can lead to varying degrees of bacteremia [25].

Periodontitis interacts with several liver diseases, such as non-alcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma, and liver transplantation [26]. A diverse spectrum of bacteria has been isolated from bile and blood including *Moraxella osloensis*, *Kluyvera ascorbate*, *Lactobacillus salivarius*, and *Streptococcus bovis* [27–30]. One systematic study of cholecystitic and cholangitic patients with biliary sepsis identified a high percentage (88.3%) of Gram-negative bacteria, including *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Proteus vulgaris*, *Morganella morgagnii*, and *Enterococcus spp.* In addition, anaerobic infections

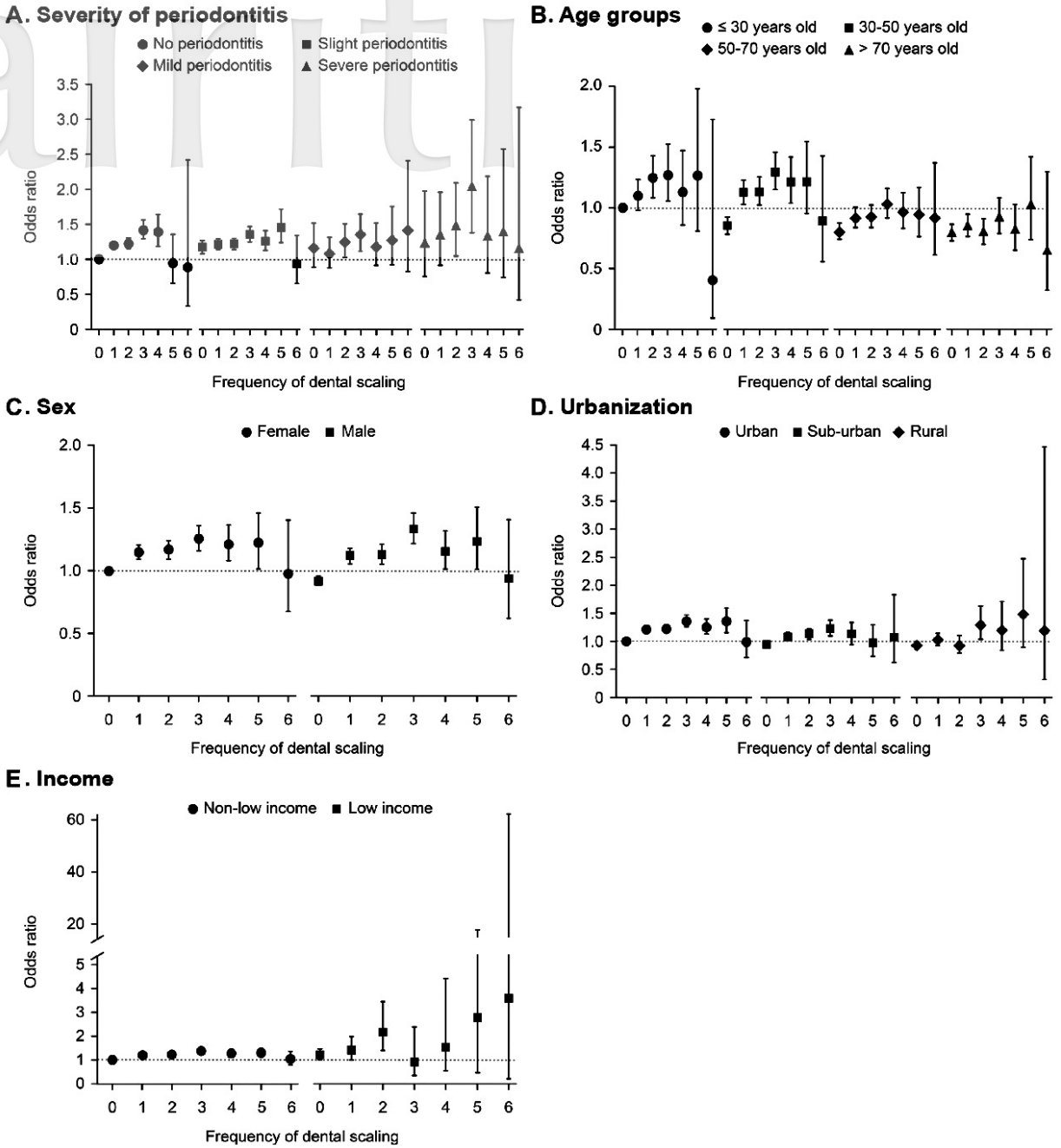

Figure 3. Effects of the frequency of dental scaling 3 years or less before the index date of cholecystitis. Subgroups: (A) severity of periodontitis (Interaction *P*=0.1969), (B) age (Interaction *P*=0.0003), (C) sex (Interaction *P*=0.2377), (D) urbanization (Interaction *P*=0.6328), and (E) income (Interaction *P*=0.4590).

have been noted (6.9%) [31]. We now know that most periodontal bacteria are anaerobes [32]. Moreover, correlations between gallstone formation and bacterial infection have been reported. Gallstone formation is a multifactorial process that involves both physiological and pathological factors. It is a well-established risk factor for cholecystitis. In a previous study, scanning electronic microscopy was used to examine the surface of pigment stones. Pigment gallstone formation has been reported to be associated with bacteria in bile [33], especially when supplied with β-glucuronidase and bacterial

glycocalyx. In another study, bacterial DNA was detected using universal primer pairs to partially amplify the 16S ribosomal RNA gene with 90% of cholesterol stones positive for bacterial DNA [34]. Molecular tools, such as polymerase chain reaction-denaturing gradient gel electrophoresis, have been used to detect bacterial sequences in cholesterol gallstones and 19 species of bacteria have been identified [35]. Therefore, bile infection by bacteria may contribute to the pathogenesis of bile stone formation, leading to the occurrence of cholecystitis. The long-term presence of gallstones is also a well-known risk factor for the development of gallbladder cancer [36].

In this study, we demonstrated an association between periodontitis and cholecystitis. Individuals aged 50 to 70 years with severe periodontitis had a 43.6% increased risk of developing calculous or acalculous cholecystitis (aOR=1.436; 95% CI 1.098–1.877) compared with individuals without periodontitis. Our results suggested that dental scaling is associated with the risk of cholecystitis. Although there was no statistical significance for 6 dental scaling events within 3 years, the sample size was small. In addition, there was a significantly increased risk of cholecystitis among urban residents and those in low-income households. These findings are not completely consistent with previous reports [37,38]. The question of whether dental scaling or socioeconomic status increases the risk of cholecystitis requires further investigation.

The current study provides important implications for the care and prevention of periodontal disease. Good oral hygiene and regular dental scaling not only reduce the occurrence of periodontal disease, but also the risk of calculous or acalculous cholecystitis. In addition, an extensive study on the potential use of prophylactic antibiotics after dental procedures to prevent cholecystitis is urgently needed. The strengths of this study include: the NHIRD covers more than 99% of Taiwan's population with minimal selection bias, large sample size, and multi-institutional follow-up. However, some limitations of the study merit attention. First, the severity of bleeding during dental scaling could not be evaluated and bleeding may affect the duration of bacteremia. Physical examination findings and the severity of disease are not provided in the NHIRD. Second, information regarding ethnicity, nutrition, physical activity, the use of medications, cigarette smoking, alcohol consumption, and diet could not be obtained from the NHIRD. These unmeasured confounders may also affect the risks of cholecystitis and gallstone formation. Third, the study population was comprised of Taiwanese individuals. Extrapolating the results to other populations requires caution. Fourth, like other electronic health databases, coding errors or "upcoding" problems may exist in the NHIRD.

In conclusion, our results indicated that increased risk of cholecystitis is associated with severe periodontitis and dental scaling events within 3 years of occurrence. Further prospective studies are needed to clarify the relationship between these diseases for the development of preventive strategies.

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Author contributions

MSJ and SMC devised and supervised the study. CHC, JYC, JYH, and JCCW acquired the data, performed statistical analyses, and interpreted the data. JYH and YC analyzed and interpreted the data. CHC drafted the manuscript. MSJ and SMC revised the initial draft of the manuscript. All authors have approved the final submitted version.

Conflict of interest

The authors have no conflicts of interest to declare.

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