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AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

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ORIGINAL ARTICLE

Retrospective Study

Helicobacter pylori infection is associated with the risk and phenotypes of cholelithiasis: A multi-center study and meta-analysis

Shuo-Yi Yao, Xin-Meng Li, Ting Cai, Ying Li, Lun-Xi Liang, Xiao-Ming Liu, Yu-Feng Lei, Yong Zhu, Fen Wang

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Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) is a prevalent pathogen associated with various diseases. Cholelithiasis is also a common condition. *H. pylori* infection has been identified in the biliary system, suggesting its potential involvement in biliary diseases. However, the specific role of *H. pylori* in the development of cholelithiasis remains inconclusive.

AIM

To investigate the potential association between *H. pylori* infection and the development of cholelithiasis.

METHODS

We performed a retrospective study in more than 70000 subjects in health exami-

nation center from 3 institutions in the middle, northern and eastern China, from October 2018 to December 2021, to explore the potential association between *H. pylori* and cholelithiasis through univariate and multivariate analysis. Meanwhile, the influence of *H. pylori* on biliary-related parameters was investigated. A comprehensive analysis of previous studies concerned about *H. pylori* and cholelithiasis was also executed.

RESULTS

In our multi-center study, *H. pylori* was positively associated with cholelithiasis [odds ratio (OR) = 1.103, 95% confidence interval (CI): 1.001-1.216, $P = 0.049$]. Furthermore, *H. pylori* patients had less total and direct bilirubin than uninfected patients, while the total cholesterol and low-density lipoprotein cholesterol were more in *H. pylori*-positive participants ($P < 0.05$). In the published articles, the cohort studies indicated *H. pylori* was a risk factor of cholelithiasis (hazard ratio =1.3280, 95%CI: 1.1810-1.4933, $P < 0.0001$). The pooled results of case-control and cross-sectional studies showed positive association between *H. pylori* and cholelithiasis in Asia (OR = 1.5993, 95%CI: 1.0353-2.4706, $P = 0.034$) but not in Europe (OR = 1.2770, 95%CI: 0.8446-1.9308, $P = 0.246$). Besides, *H. pylori* was related to a higher choledocholithiasis/cholecystolithiasis ratio (OR = 3.3215, 95%CI: 1.1034-9.9986, $P = 0.033$).

CONCLUSION

H. pylori is positively correlated with cholelithiasis, choledocholithiasis phenotype particularly, especially in Asia, which may be relevant to bilirubin/cholesterol metabolism. Cohort studies confirm an increased risk of cholelithiasis in *H. pylori* patients.

Key Words: *Helicobacter pylori*; Cholelithiasis; Bilirubin; Cholesterol; Multi-center

Core Tip: *Helicobacter pylori* (*H. pylori*) infection in the biliary system has been identified but its relationship with cholelithiasis is not clear. This study is to analyze the possible correlation between *H. pylori* and cholelithiasis, and found that *H. pylori* infection was associated with an increased risk of cholelithiasis, particularly the choledocholithiasis phenotype. The metabolism of bilirubin and cholesterol could be a possible explanation for the link between *H. pylori* and cholelithiasis. Patients with *H. pylori* should be screened for cholelithiasis, and *H. pylori* eradication may help prevent cholelithiasis. In the management of cholelithiasis, the potential influence of *H. pylori* infection should also be considered.

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INTRODUCTION

Cholelithiasis is a high-prevalence disease. The global prevalence of gallstones in 21st century is 6.1% with the highest prevalence in South America (11.2%) followed by North America (8.1%), Africa (6.6%), Europe (6.4%), and Asia (5.1%)[1]. Meanwhile, gallstone disease has incidence of 0.47 per 100 person-years[1]. In the United States, the prevalence of gallstone disease was 13.9% from 2017 to March 2020 which is almost twice as in 1988-1994[2]. Gallstone disease is associated with factors including female gender, older age, body mass index, and other variables[1,2]. Additionally, the role of bacteria in cholelithiasis has been extensively researched[3]. Bacteria can hydrolyze bilirubin glucuronide into free bilirubin and glucuronic acid to form calcium bilirubinate through β-glucuronidase[4]. A majority of Chinese patients with calcium bilirubinate stone were found to be infected by β-glucuronidase-active bacteria[5]. Beyond bilirubin conjugates, bacteria also hydrolyze biliary lipids to form calcium salt sediment and brown pigment stones[6]. Furthermore, Stewart *et al*[7] identified bacteria could also serve as the nucleus for stone formation in pigment stones. Moreover, bacteria-associated cholelithiasis may also be related to factors such as phospholipase, mucin, and prostaglandin, *etc*.[8].

Helicobacter pylori (*H. pylori*) infection is the risk factor for gastritis, peptic ulcer, gastric cancer and so on[9,10]. The prevalence of *H. pylori* between 2015 and 2019 in China mainland was 40.0%[11], which is still a heavy burden. *H. pylori* infection in the biliary system has been reported, suggesting a potential relationship with biliary diseases. Various studies found evidence of *H. pylori* infection in bile, gallbladder, and gallstones using different methods[12-14]. However, conclusions regarding the relationship between *H. pylori* and cholelithiasis remain controversial. Some reports indicate that *H. pylori*-infected patients have a higher risk of cholelithiasis[15], while other studies have found no significant association between *H. pylori* and cholelithiasis[16]. The treatment of *H. pylori* could have potential influence on the biliary system. Clarithromycin, a kind of antibiotics commonly used in *H. pylori* eradication, was found to strengthen the contraction of gallbladder in gallstone patients[17]. Besides antibiotics, some natural substance with less side effects, such as *Hericium erinaceus*[18,19], could both inhibit *H. pylori* and benefit biliary system.

Clarifying the association between *H. pylori* infection and cholelithiasis is essential for a deeper understanding of the role of *H. pylori* in the hepatobiliary system. This knowledge could benefit the clinical practice of both *H. pylori* infection and cholelithiasis, holding significant public health implications. Therefore, we conducted a multi-center study encompassing three hospitals from central, northern and eastern China. Additionally, we analyzed evidence from published articles elucidate the potential relationship between *H. pylori* and cholelithiasis.

MATERIALS AND METHODS

New original data

Study subjects: The study included participants underwent health examinations at three centers in the middle, northern and eastern China, from October 2018 to December 2021. The study followed the "Strengthening the Reporting of Observational Studies in Epidemiology" statements[20]. All the included patients received both 14C urease breath test (14C-UBT) and ultrasound examination. At the same time, they also took blood test for related parameters including bilirubin, bile acid, cholesterol and triglyceride levels. The following information was obtained from the health examination results and previous medical records of the participants: (1) Age and gender; (2) The results of 14C-UBT and ultrasound examination; (3) Other relevant medical history, such as major health problems, medication history, and surgical history; and (4) Parameters related to biliary system mentioned above.

According to their examination results and previous medical records, participants would be excluded if one of the following criteria was met: (1) Antibiotic, bismuth, and other antibacterial medicine use history within one month, or proton pump inhibitors use history within half a month; (2) Cholecystectomy history and no stones in the residual biliary system; and (3) *H. pylori* eradication treatment history. This study was conducted in accordance with the principles of the Declaration of Helsinki, and was approved by the clinical research ethics committee of every center (Ethics Committee Approval No. 23277, No. Z-2024-028, and No. G-2024-11). The requirement to obtain informed written consent was waived because the study is retrospective and did not involve the privacy and commercial interests of patients, and measures were taken to anonymize biological samples, and formulated a strict data security management system and technical protection system for the storage, use, and sharing of biological samples and data to ensure data and personal information security.

The diagnosis of cholelithiasis was established through ultrasound examination (Siemens Acuson™ Sequoia 512 Doppler ultrasound, Siemens, German). Based on the ultrasound findings, the study participants were categorized into two groups: The cholelithiasis group (comprising individuals with confirmed cholelithiasis) and the control group (consisting of subjects without evidence of cholelithiasis). The participants received 14C-UBT after fasting for solid and liquid food overnight or for a minimum of 3 hours. The criterion for *H. pylori* positive is a result of 14C-UBT greater than or equal to 100 disintegrations per minute. Professional specialists conducted the test process and interpreted the results.

Statistical analysis: Statistical analysis was conducted using SPSS 26 (IBM Corp., Armonk, NY, United States). Categorical data were expressed as percentages and analyzed using the χ^2 test or Fisher's exact probability method. Measurement data were expressed as mean ± SD and analyzed by *t*-test. Logistic regression was performed to explore factors related to cholelithiasis. The parameters, which have significant difference between cholelithiasis group and control group, and those are known to be related to cholelithiasis, would be included in the multivariable analysis. A P value < 0.05 was considered statistically significant.

Systematic review and meta-analysis

This meta-analysis adheres to the guidelines outlined in meta-analysis of observational studies in epidemiology[21] (Supplementary Table 1) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[22]. The literature screening and data extraction in the systematic review and meta-analysis was conducted by 2 investigators independently.

Search strategy: We conducted a comprehensive literature search in PubMed, Embase, Web of Science, and Cochrane Library databases up to May 10, 2024. The following search strategy was employed: "((Helicobacter pylori) OR (H. pylori) OR (HP) OR (Helicobacter) OR (Helicobacter species) OR (Helicobacter spp.) OR (Helicobacter genus) OR (Helicobacter pylori infection) OR (Helicobacter infection) OR (pylori) OR (enterohepatic Helicobacter spp.) OR campylobacter OR (campylobacter infection) OR campylobacteriosis OR (Campylobacter pylori* OR Campylobacter pylori subsp. Pylori) OR (campylobacter spp)) AND (cholelithiasis or cholecystolithiasis or hepatolithiasis OR choledocholithiasis OR gallstone* OR gall* stone* OR (gallbladder AND stone*) OR (gallbladder AND cholelith*) OR (gallbladder AND lithiasis) OR bilestone* OR (bile AND stone*) OR (bile AND lithiasis) OR (bile AND cholelith*) OR (biliary AND calculus) OR (biliary AND stone*) OR (biliary AND cholelith*) OR (biliary AND lithiasis))". All search results were exported to EndNote 20 (Thomson ResearchSoft, United States) for further screening. Additionally, a manual search was performed to identify any relevant studies not captured by the initial search.

Study screening criteria: The inclusion criteria were: (1) Participants (P): Patients with examination results for cholelithiasis and *H. pylori*; (2) Intervention/exposure (I): *H. pylori* infection; (3) Comparison (C): Participants free of *H. pylori*; (4) Outcomes (O): The prevalence/incidence of cholelithiasis; and (5) Studies (S): Case-control studies, cohort studies, or cross-sectional studies. The exclusion criteria were as follows: Papers not written in English; articles that were not original research; studies conducted on animals or cells; research not pertaining to *H. pylori* or cholelithiasis; and studies for which the necessary data could not be obtained.

Data extraction and quality assessment: The following information was extracted from included studies: Publication year, first author, region, types of cholelithiasis, sample sizes, sample sources and detection methods of *H. pylori*, and *H. pylori* status of each group. The Methodological Index for Non-randomized Studies[23] was employed to assess the quality of the included studies. The maximum attainable score is 24 for comparative studies and 16 for non-comparative studies. A higher score is indicative of superior methodological quality.

Data analysis: Data analysis was performed using the Meta package of R (version 4.3.2)[24]. A P value < 0.05 was considered statistically significant. Heterogeneity was assessed using I^2[25]. If I^2 < 50% the common effect model (also referred to as the fixed effect model[26]) would be used, otherwise we will reduce the heterogeneity by subgroup analysis. If the heterogeneity is still high, the random effect model would be employed. I^2 values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively[27]. Sensitivity analysis was conducted using the leave-one-out method. Publication bias was evaluated using a funnel plot, with a symmetric plot indicating no significant bias[28]. If the Peters' test[29] showed a P value < 0.05, there is significant publication bias.

To determine the relationship between *H. pylori* infection and cholelithiasis, we calculated the summarized odds ratios (OR) of case-control/cross-sectional studies, and hazard ratios of cohort studies with a 95% confidence interval (CI). Subgroup analysis was also performed based on the regions of where the studies were conducted. Furthermore, we analyzed the association between *H. pylori* and various cholelithiasis phenotypes.

RESULTS

New original data

Characteristics of study subjects: There were 77734 participants included in this research after applying the inclusion and exclusion criteria (Figure 1). The number of subjects from the Third Xiangya Hospital, the First Affiliated Hospital of Nanchang University, and Shanxi Coal Central Hospital was 54631, 19241, and 3862, respectively. There were 48159 men and 29575 women. Subjects were divided into 2 groups as mentioned above. The cholelithiasis group included 3838 (4.9%) patients, while the control group included 73896 participants (Table 1).

Association between *H. pylori* and cholelithiasis: According to our data, 23.1% of all the participants were infected by *H. pylori*. *H. pylori* infection rate was significantly higher in cholelithiasis group compared to the control group (25.4% *vs* 23.0%, P = 0.001). Furthermore, cholelithiasis patients exhibited higher female rate, age, total bile acid, total cholesterol, triglyceride, and low-density lipoprotein (LDL)-cholesterol, while high-density lipoprotein (HDL)-cholesterol was higher in control group (P < 0.05) (Table 1). Besides the factors with significant difference between cholelithiasis and control group mentioned above, we also include bilirubin level, a known risk factor of cholelithiasis[30], in the multivariable logistic regression which showed *H. pylori* may be related to cholelithiasis (OR =1.103, 95%CI: 1.001-1.216, P = 0.049). Besides, other factors including age > 60 years, total bile acid, HDL-cholesterol, total bilirubin, direct bilirubin, total cholesterol, triglyceride, and female gender, were also associated with cholelithiasis (Table 2). This study included 74 patients with hepatolithiasis and 3724 cholecystolithiasis patients for phenotype analysis. Patients with both hepatolithiasis and cholecystolithiasis were excluded from this part of the study. The *H. pylori* infection rates didn't differ significantly between hepatolithiasis and cholecystolithiasis patients (Table 3).

***H. pylori* and biliary-system parameters:** To further investigate the possible mechanism of *H. pylori*-related cholelithiasis, we measured parameters associated with the biliary system in *H. pylori*-positive and *H. pylori*-negative participants (Table 3). Patients with hepatopancreatobiliary and metabolic diseases (diabetes, hyperthyroidism, hypothyroidism and others) were excluded from this analysis. A total of 18996 participants (4034 in the *H. pylori*-positive group and 14962 in the *H. pylori*-negative group) were included in this section. Total bilirubin as well as direct bilirubin was significantly lower in the *H. pylori*-positive group. More total cholesterol and LDL-cholesterol were found in the *H. pylori*-infected patients. This meant the metabolism of bilirubin and cholesterol is related to *H. pylori* status, which may contribute to the formation of cholelithiasis.

Systematic review and meta-analysis

Profiles of included studies: A total of 1729 papers were retrieved. After applying the inclusion and exclusion criteria, 47 papers were ultimately included in the analysis. Risk analysis was performed on 44 articles, which collectively included 40624 cholelithiasis cases and 673534 non-cholelithiasis subjects. Phenotype analysis was conducted on 9 articles, encompassing 633 cholelithiasis cases. The literature screening process is illustrated in Figure 2. The characteristics of the included articles are detailed in Table 4 and Supplementary Tables 2 and 3. Biliary-related samples were the most frequently chosen samples, providing direct evidence of *H. pylori* infection in the biliary system (Figure 3A). Polymerase chain reaction/sequencing was the most commonly employed method for detecting *H. pylori* (Figure 3B). The average Methodological Index for Non-randomized Studies score for comparative studies was 16.39 ± 2.10 and for non-comparative studies, it was 11.00 ± 1.00 (Supplementary Tables 2 and 3).

***H. pylori* and cholelithiasis risk:** The analysis included three cohort studies, revealing that *H. pylori* was a risk factor for cholelithiasis (hazard ratio = 1.3280, 95%CI: 1.1810-1.4933, P < 0.0001) (Figure 4A). Among the 41 case-control and cross-sectional studies, a positive association was found between cholelithiasis and *H. pylori* (OR = 1.5042, 95%CI: 1.0698-2.1148, P = 0.019) (Figure 4B). The funnel plot demonstrated symmetry (Supplementary Figure 1), and the Peters' test indicated

Table 1 The characteristics of participants

	Cholelithiasis group	Control group	*P* value
H. pylori+ (*n*)	974	16970	0.001
H. pylori- (*n*)	2864	56926	
Male (*n*)	2287	45872	0.002
Female (*n*)	1551	28024	
Age (years), mean ± SD	51.01 ± 11.95	43.61 ± 12.06	< 0.001
Total bilirubin (μmol/L), mean ± SD	13.1 ± 5.7	13.2 ± 5.5	0.627
Direct bilirubin (μmol/L), mean ± SD	3.8 ± 1.9	3.8 ± 2.4	0.665
Total bile acid (μmol/L), mean ± SD	4.7 ± 7.0	4.0 ± 5.3	< 0.001
Total cholesterol (mmol/L), mean ± SD	5.06 ± 0.99	5.00 ± 0.97	0.001
Triglyceride (mmol/L), mean ± SD	1.98 ± 1.81	1.85 ± 1.84	< 0.001
HDL-cholesterol (mmol/L), mean ± SD	1.28 ± 0.27	1.32 ± 0.30	< 0.001
LDL-cholesterol (mmol/L), mean ± SD	2.89 ± 0.85	2.85 ± 0.82	0.002

H. pylori: *Helicobacter pylori*; *H. pylori*+: *Helicobacter pylori*-positive; *H. pylori*-: *Helicobacter pylori*-negative; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Table 2 The results of multivariable logistic regression on factors associated with cholelithiasis

	OR (95%CI)	*P* value
H. pylori infection	1.103 (1.001-1.216)	0.049
Age > 60 years	2.031 (1.821-2.266)	< 0.001
Total bile acid (μmol/L)	1.017 (1.011-1.023)	< 0.001
HDL-cholesterol (mmol/L)	0.361 (0.296-0.441)	< 0.001
Total bilirubin (μmol/L)	1.027 (1.012-1.043)	0.001
Direct bilirubin (μmol/L)	0.938 (0.897-0.982)	0.006
Total cholesterol (mmol/L)	1.095 (1.038-1.154)	0.001
Triglyceride (mmol/L)	0.969 (0.942-0.997)	0.032
Female gender	1.493 (1.355-1.644)	< 0.001

H. pylori: *Helicobacter pylori*; HDL: High-density lipoprotein; OR: Odds ratio; CI: Confidence interval.

no publication bias (P = 0.259). The sensitivity analysis identified no distinct variation (Supplementary Figure 2). Since the heterogeneity is relatively high, subgroup analyses were performed based on continents. Studies conducted in Asia showed a positive association between cholelithiasis and *H. pylori* (OR = 1.5993, 95%CI: 1.0353-2.4706, P = 0.034), while in Europe, the relationship was not statistically significant (P = 0.246) (Figure 5).

***H. pylori* and the phenotypes of cholelithiasis:** The effect of *H. pylori* on the phenotypes of cholelithiasis was further analyzed. Regarding the position of stones, *H. pylori*-positive patients were more common in the choledocholithiasis group compared to those in the cholecystolithiasis group (OR = 3.3215, 95%CI: 1.1034-9.9986, P = 0.033) (Figure 6A). The chemical components of stones were also investigated. *H. pylori* infection was not found to be related to the chemical components of stones (P = 0.344) (Figure 6B).

DISCUSSION

In addition to gastroduodenal diseases, numerous extra-gastric diseases have been associated with *H. pylori*[31]. There is emerging evidence suggesting *H. pylori* involvement in cholelithiasis[3] but no definitive conclusions have been established. This study aims to provide a comprehensive analysis of the relationship between *H. pylori* and cholelithiasis

Table 3 The results of phenotype analysis and parameters comparison

	H. pylori+	*H. pylori*-	*P* value
Phenotype			
Hepatolithiasis (*n*)	21	53	0.546
Cholecystolithiasis (*n*)	942	2782	
Parameters			
Total bilirubin (μmol/L)	12.5 ± 5.2	13.2± 5.2	< 0.001
Direct bilirubin (μmol/L)	3.6 ± 1.6	3.9 ± 1.6	< 0.001
Total bile acid (μmol/L)	3.8± 5.1	3.6 ± 4.3	0.055
Total cholesterol (mmol/L)	4.84 ± 0.90	4.77 ± 0.86	< 0.001
Triglyceride (mmol/L)	1.26 ± 0.94	1.27 ± 1.00	0.489
HDL-cholesterol (mmol/L)	1.41 ± 0.29	1.41 ± 0.29	0.994
LDL-cholesterol (mmol/L)	2.83 ± 0.76	2.76 ± 0.73	< 0.001

H. pylori: *Helicobacter pylori*; *H. pylori*+: *Helicobacter pylori*-positive; *H. pylori*-: *Helicobacter pylori*-negative; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

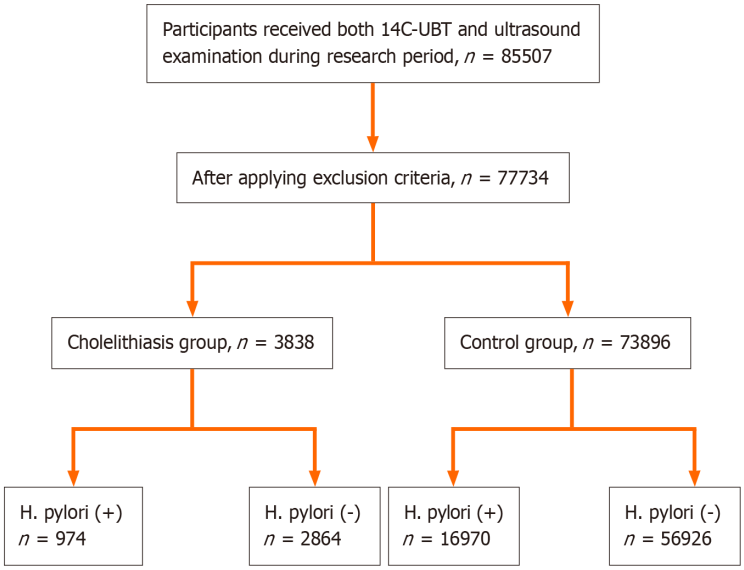

Figure 1 The flow chart of the study subjects screening process. *H. pylori*: *Helicobacter pylori*; 14C-UBT: 14C urease breath test; *H. pylori* (+): *Helicobacter pylori*-positive; *H. pylori* (-): *Helicobacter pylori*-negative (detailed data shown in Table 1).

with both new original data and published articles. This study's finding demonstrate that *H. pylori* infection is correlated with an increased risk of cholelithiasis. Besides, there was a correlation between *H. pylori* and the choledocholithiasis phenotype. But the chemical constituent of stones is not related to *H. pylori*.

In our study, the metabolism of bilirubin and cholesterol could be the possible explanation for *H. pylori*-related cholelithiasis. *H. pylori* may promote cholelithiasis through the enhancement of endogenous β-glucuronidase[32]. This supports our results of lower total bilirubin and direct bilirubin in *H. pylori*-infected patients. More direct bilirubin may be hydrolyzed into free bilirubin to form sediment. According to this theory, direct bilirubin may be negatively related to cholelithiasis, while the relationship between free bilirubin and cholelithiasis should be positive. In our analyses, although the bilirubin level didn't differ between cholelithiasis patients and controls, the multivariable logistic regression found both total bilirubin and direct bilirubin was associated with cholelithiasis, and the results were consistent with the previously proposed theory. In our data, the total cholesterol was higher in *H. pylori*-positive participants, especially LDL-cholesterol. Cytotoxin-associated gene A (*CagA*), a virulence factor of *H. pylori*, could inhibit the uptake of LDL by interacting with the LDL receptor, leading to increased LDL in plasma[33]. The dysregulation of cholesterol metabolism could lead to cholesterol crystal formation, which could develop into gallstones[34]. Increased total cholesterol and LDL is positively correlated with cholesterol stones and cholesterol concentrations in gallstones[35]. In this study, we found total cholesterol and LDL-cholesterol were higher in cholelithiasis patients. The multivariable logistic regression showed

Table 4 The characteristics of included studies

Ref.	Region	Cholelithiasis type	Sample source for *H. pylori*	Method for *H. pylori*	No. of cholelithiasis	No. of non-cholelithiasis
Loosen et al[54], 2024	Germany	Cholelithiasis	Medical records	Medical records	2394	34669
Sermet[55], 2024	Turkey	Cholelithiasis	Gastric biopsy	Histology	8753	5565
Azimirad *et al*[12], 2023	Iran	Common bile duct stones	Bile	16S rDNA sequencing	9	6
Cen *et al*[15], 2023	China	Gallstones	Breath	13C/14C-UBT	60	1132
Hashimoto *et al*[56], 2022	Japan	Gallstones	Serum	Antibody test	14	47
Higashizono *et al* [57], 2022	Japan	Gallstones	Medical records	Medical records	23843	588087
Jahantab *et al*[58], 2021	Iran	Cholelithiasis	Bile	Antigen test	132	/
Kucuk and Küçük [13], 2021	Turkey	Gallstones	Gallbladder	Giemsa	131	82
Zhang *et al*[16], 2020	China	Gallstones	Breath	13C/14C-UBT	935	935
Ari *et al*[59], 2019	Turkey	Gallstones	Gallbladder	Giemsa	27	33
Cherif *et al*[60], 2019	Morocco	Bile duct stones	Gallbladder	IHC	48	41
Kerawala *et al*[61], 2019	Pakistan	Gallstones	Serum	Antibody test	45	45
Fatemi *et al*[62], 2018	Iran	Gallstones	Serum	ELISA	52	25
Xu *et al*[63], 2018	China	Gallstones	Serum	ELISA	995	16976
Seyyedmajidi[64], 2017	Iran	Common bile duct stones	Bile	PCR	150	/
Choi *et al*[65], 2016	Korea	Gallstones	Gastric biopsy	CLO test	39	607
Dar *et al*[66], 2016	India	Hepatobiliary lithiasis	Bile	PCR	50	25
Patnayak *et al*[67], 2016	India	Gallstones	Gallbladder	IHC	40	5
Tajeddin *et al*[68], 2016	Iran	Gallstones	Bile	PCR	74	28
Guraya *et al*[69], 2015	Saudi Arabia	Gallstones	Serum	ELISA	95	30
Zhang *et al*[70], 2015	China	Gallstones	Breath	13C-UBT	882	9134
Murphy *et al*[71], 2014	Finland	Gallstones	Serum	Serology	10	214
Takahashi *et al*[50], 2014	Japan	Gallstones	Serum	ELISA	694	14857
Zhou *et al*[36], 2013	China	Gallstones	Gallbladder	PCR	267	59
Boonyanugomol *et al* [72], 2012	Thailand	Cholelithiasis	Bile	PCR	53	103
Jahani Sherafat *et al* [73], 2012	Iran	Gallstones	Bile	PCR	74	28
Yakoob *et al*[74], 2011	Pakistan	Cholelithiasis	Gallbladder/bile	IHC/PCR	89	49
Bostanoğlu *et al*[75], 2010	Turkey	Calculous cholecystitis	Gallbladder/bile/stone	PCR	47	3
Lee *et al*[14], 2010	Korea	Gallstones	Gallstone	PCR	22	/
Popović *et al*[76], 2010	Serbia	Cholelithiasis	Blood	Serology	3	204
Griniatsos *et al*[77], 2009	Greece	Cholesterol gallstones	Gallbladder	Histology	89	42
Yucebilgili *et al*[78],	Turkey	Cholelithiasis	Gallbladder	PCR	41	27

2009						
Misra *et al*[79], 2007	India	Gallstones	Gallbladder	Histology	116	45
Abayli *et al*[80], 2005	Turkey	Mixed cholesterol gallstones	Gallbladder	HE	77	20
Kobayashi *et al*[81], 2005	Japan	Cholelithiasis	Bile	PCR	30	27
Farshad *et al*[82], 2004	Iran	Gallstones	Gallstone/bile	PCR	33	40
Chen *et al*[83], 2003	New Zealand	Gallstones	Gallbladder	PCR	70	52
Silva *et al*[84], 2003	Brazil	Cholelithiasis	Gallbladder	PCR	46	18
Bulajic *et al*[43], 2002	Yugoslavia	Gallstones	Bile	PCR	63	26
Bulajic *et al*[85], 2002	Yugoslavia	Biliary lithiasis	Bile	PCR	65	7
Fukuda *et al*[86], 2002	Japan	Cholecystolithiasis	Gallbladder/bile	PCR	15	23
Harada *et al*[87], 2001	Japan	Cholelithiasis	Bile/biliary epithelium	PCR	53	16
Myung *et al*[88], 2000	Korea	Hepatolithiasis	Serum	ELISA	30	13
Roe *et al*[89], 1999	Korea	Intrahepatic duct stones	Bile	PCR	11	21
Figura *et al*[90], 1998	Italy	Gallstones	Serum	ELISA	112	112
Kochhar *et al*[91], 1993	India	Common bile duct stone	Gastric biopsy	Giemsa	3	15
Kellosalo *et al*[92], 1991	Finland	Gallstones	Gastric biopsy	WS	47	41

H. pylori: *Helicobacter pylori*; WS: Warthin-Starry silver stain; ELISA: Enzyme-Linked Immunosorbent Assay; PCR: Polymerase chain reaction; HE: Hematoxylin and eosin staining; 13C/14C-UBT: 13C or 14C urease breath test; IHC: Immunohistochemistry; CLO: *Campylobacter*-like organism.

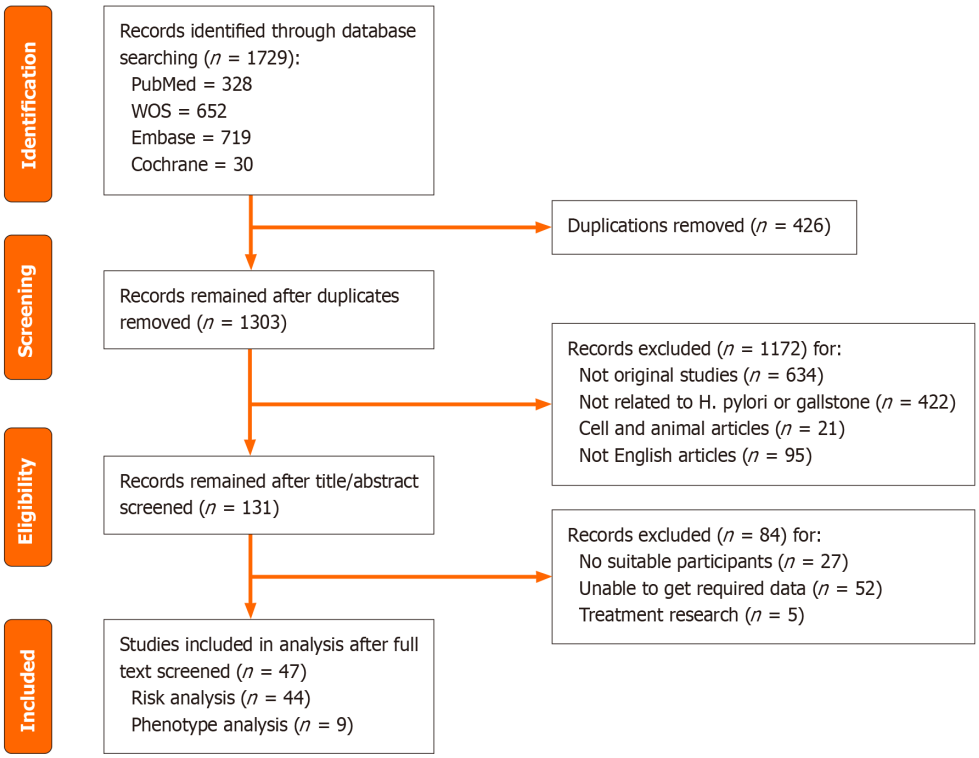

Figure 2 The flow chart of the literature screening process. Detailed included articles shown in Table 4. *H. pylori*: *Helicobacter pylori*; WOS: Wed of Science.

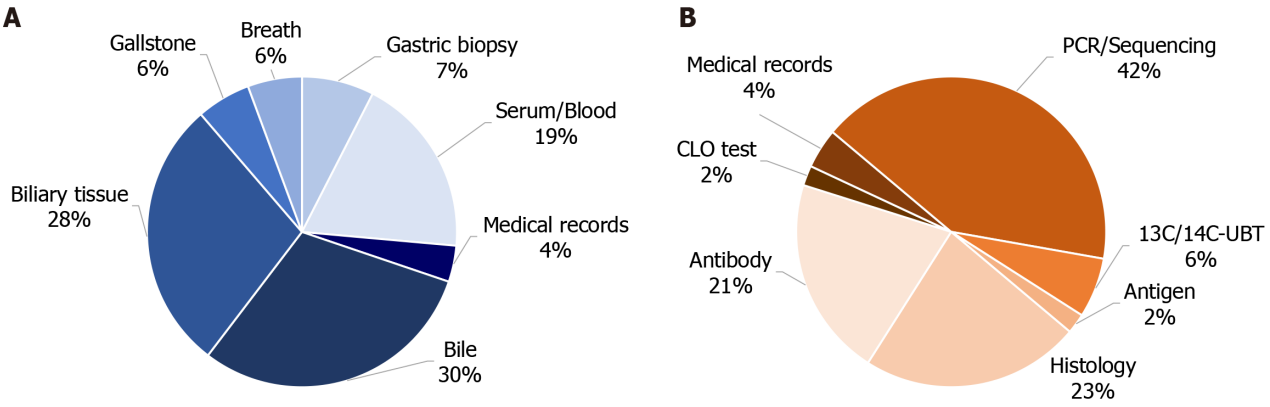

Figure 3 The distribution of sample sources and detection methods for *Helicobacter pylori* of included studies. A: Sample sources for *Helicobacter pylori*; B: Detection methods for *Helicobacter pylori*. Detailed data shown in Table 4. 13C/14C-UBT: 13C or 14C urease breath test; CLO: *Campylobacter* -like organism; PCR: Polymerase chain reaction.

total cholesterol was a factor associated with cholelithiasis but LDL-cholesterol was not. The reason for this could be the interaction between *H. pylori* and LDL-cholesterol, and total cholesterol could partly reflect the level of LDL-cholesterol.

Several other potential mechanisms may contribute to *H. pylori*-related cholelithiasis. The *H. pylori*-infected gallbladder mucosa has been shown to express elevated inducible NO synthase and reactive oxygen species[36]. Free radical reactions can play a role in the formation of gallstones[37]. Additionally the urease enzyme produced by *H. pylori* could induce calcium precipitation through alterations in pH[38]. Phospholipids levels were found to be lower in *H. pylori*-positive patients compared to the *H. pylori*-negative patients[39]. This finding is consistent with increased phospholipase activity in infected bile, which may contribute to gallstones formation by causing the precipitation of calcium palmitate[8]. Considering the potential mechanisms, *H. pylori* may be associated with both cholesterol stones and pigment stones, supporting our results that indicate no relation between *H. pylori* and the chemical composition of gallstones.

In order to get more comprehensive results, we performed a meta-analysis on other similar studies to compare our research to other investigations. The results of the meta-analysis are consistent with our multi-center study but there is heterogeneity. So, we conducted subgroup analysis based on regions to make the heterogeneity decrease. This study found a higher prevalence of *H. pylori* in the cholelithiasis group in Asia but not in Europe. Variances among *H. pylori* strains from different regions could contribute to the differing results. The Western type of *CagA* genes of *H. pylori* were similar in Japan, China, Iran, and the United States but differed from those in Thailand[40]. Additionally, the prevalence of cholelithiasis varies by regions, with higher prevalence in Europe than in Asia[1]. The relatively high prevalence of cholelithiasis in Europe may overshadow the role of *H. pylori*. Furthermore, the prevalence of *H. pylori* is lower in Europe compared to Asia[41]. The lack of study samples in certain regions could also influence the results.

In the meta-analysis, higher *H. pylori* infection rate was found in choledocholithiasis patients when compared with cholecystolithiasis patients, while in our new original data, there was no significant difference in the *H. pylori* status between cholecystolithiasis group and hepatolithiasis group. This may be due to the fact that *H. pylori* is easy to infect the common bile duct but difficult to reach the intrahepatic bile duct, supporting the theory that *H. pylori* in the stomach invades the biliary tract *via* the common bile duct[42]. A correlation between the presence of *H. pylori* in the bile and its presence in the stomach has been stated by Bulajic *et al*[43] and the Western type *CagA* sequences in hepatobiliary disease patients were similar to those in gastric cancer and gastritis patients[40], supporting the hypothesis that *H. pylori* in the biliary system originates from the gastrointestinal tract. However, some analyses have yielded contradictory results. The *ureI*-polymerase chain reaction results of *H. pylori* in certain gallstones differed from those of *H. pylori* in the stomach[44]. The vacuolating cytotoxin A and *CagA* analysis results from gastroduodenal patients were not similar to those from hepatobiliary patients[45]. Similarly, the research of Kafeel *et al*[46] concluded the presence of *H. pylori* in gallbladders was independent of its presence in the stomach. These results support the existence of differences between gastroduodenal and hepatobiliary *H. pylori* strains.

This study offers several advantages. It represents a large-scale multi-center investigation involving over 70000 participants. Our results about the relation between *H. pylori* and the risk of cholelithiasis are consistent with previous research[47-50]. Besides, we also provide some new information on this topic including the possible mechanism of *H. pylori*-related cholelithiasis, and the association between *H. pylori* and the phenotypes of cholelithiasis.

The present study could help the management of both *H. pylori* infection and cholelithiasis. Another study found that *H. pylori* eradication may help prevent gallstones[50], which supports our findings. On the one hand, *H. pylori*-positive patients should be screened for cholelithiasis especially those presenting right upper abdominal pain. On the other hand, patients with cholelithiasis should also consider the possibility of *H. pylori* infection. *H. pylori* is considered one of the common causes of post-cholecystectomy syndrome[51]. Research has identified unresolved pain symptoms after cholecystectomy in some patients and they can be alleviated by *H. pylori* triple therapy[52,53]. This could be attributed to the elimination of *H. pylori*-induced inflammation.

Despite the contributions of this study, certain limitations persist. Foremost, in our new data, there is only position information of stones, neglecting other phenotypes. We didn't include more factors related to cholelithiasis like body mass index in this study because of the lack of required data. Besides, in the meta-analysis, the heterogeneity is relatively

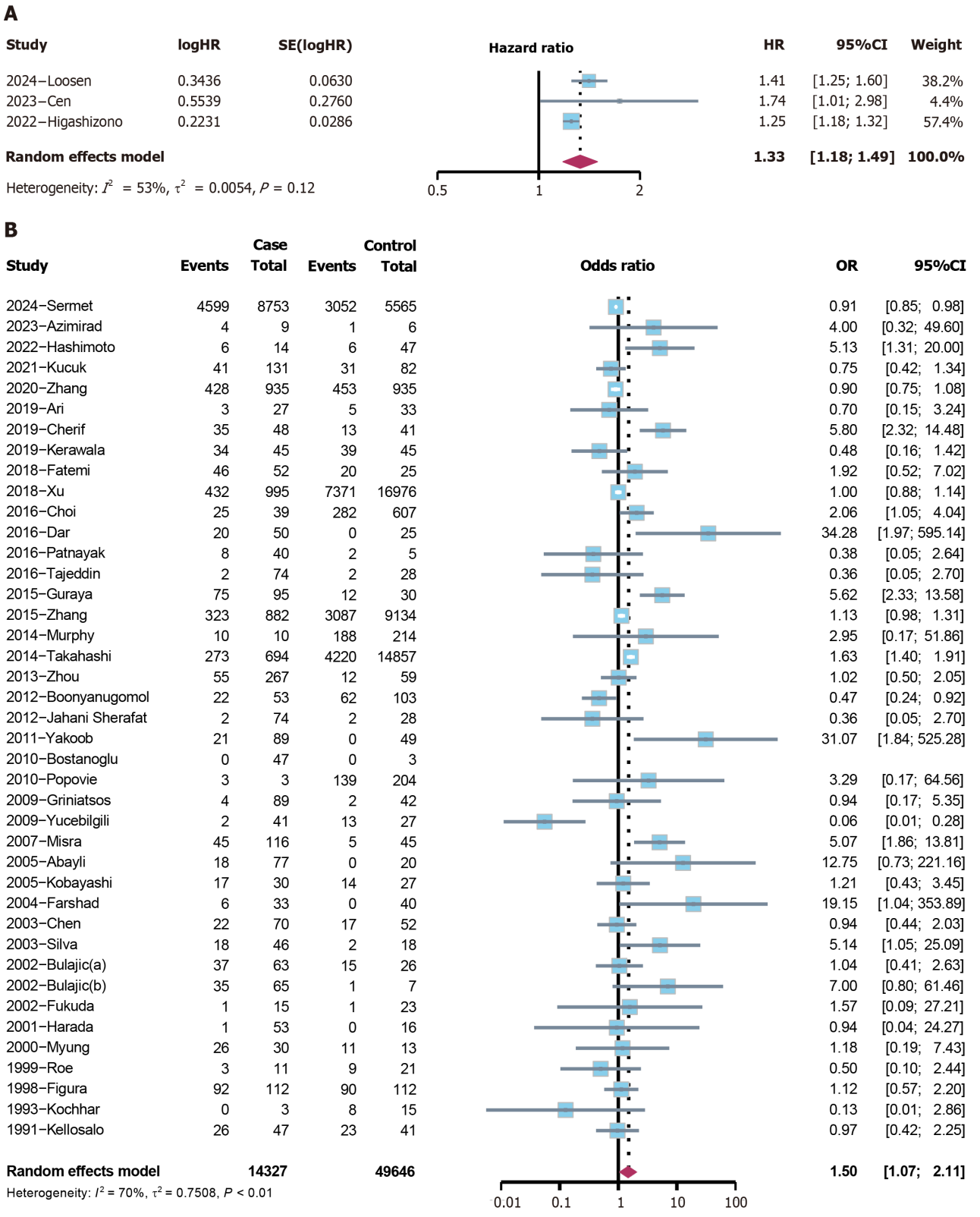

Figure 4 The forest plot of the 44 included studies for the risk analysis of cholelithiasis. A: Cohort studies; B: Case-control and cross-sectional studies. HR: Hazard ratio; CI: Confidence interval; OR: Odds ratio.

high. This may be caused by the differences in regions. We performed subgroup analyses according to study regions to reduce the heterogeneity and make region-specific conclusions but the heterogeneity is still over 50%. There are other possible sources of heterogeneity. For example, the detection methods and sample sources varied in the included studies. The serum test for *H. pylori* antibodies will identify both current and previous infection, while other methods, like UBT, *Campylobacter*-like organism test *etc.*, detect only currently infected patients. Most of the included studies in the meta-analysis were focused on current infection. Since methods, like the serum tests for *H. pylori*, can't distinguish current infection from previous infection, we are not able to make subgroup analysis according to current/previous infection by

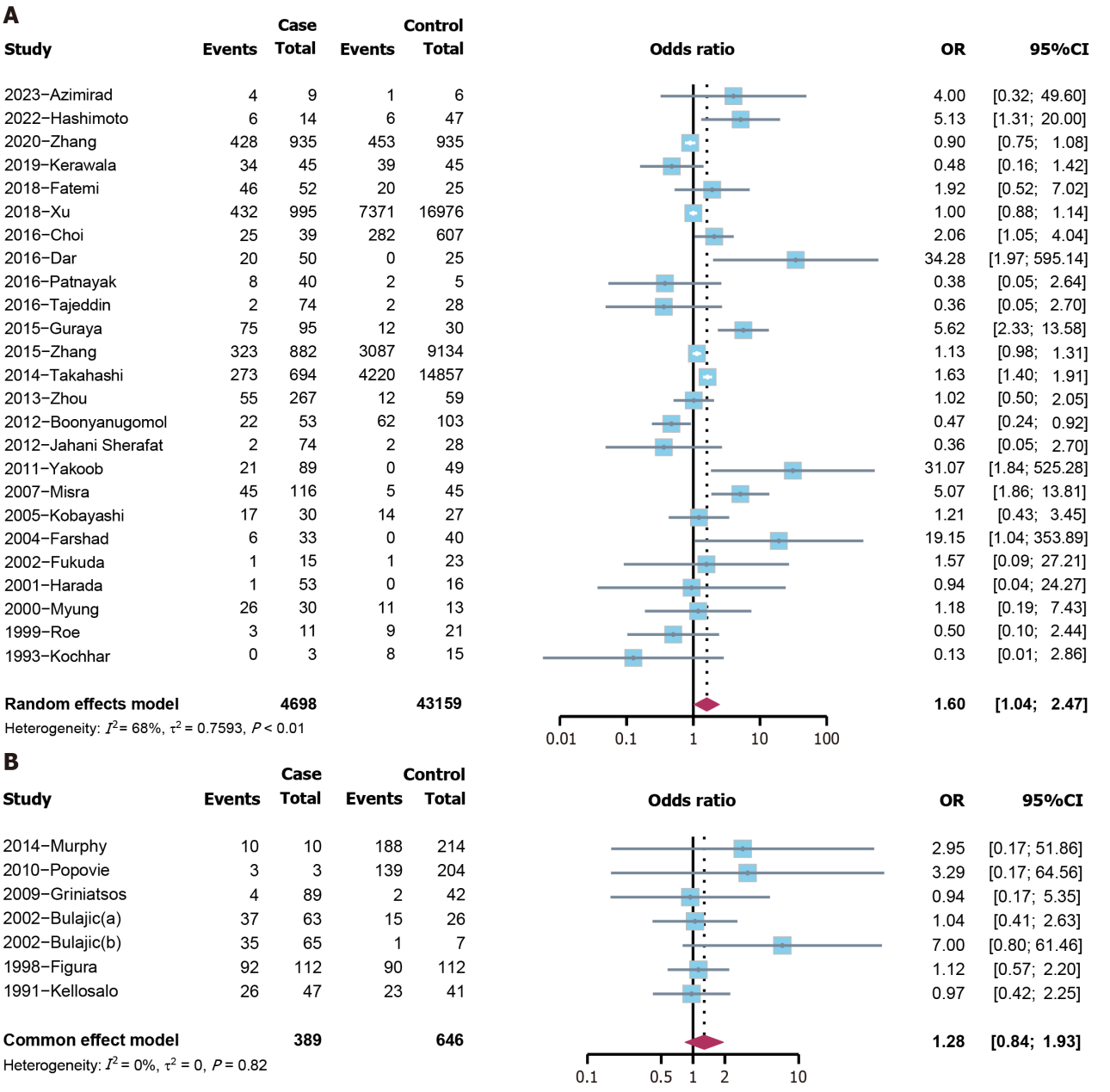

Figure 5 The results of subgroup risk analyses of cholelithiasis. A: The subgroup analysis of studies in Asia; B: The subgroup analysis of studies in Europe. CI: Confidence interval; OR: Odds ratio.

categorizing the detection methods. The inconsistency of inclusion and exclusion criteria among the included articles may also contribute, such as the age of participants. Some articles investigated specifically in adults, while there are also studies included teenagers and children. However, age-specific subgroup analysis couldn't be carried out because of the inaccessibility of detailed raw data of certain studies which included both adults and children. Due to insufficient data, the researched phenotype of cholelithiasis in the meta-analysis was restricted to chemical components and the position of stones. To elucidate the precise role of *H. pylori* in cholelithiasis, further investigations exploring the underlying mechanisms of *H. pylori*-associated cholelithiasis are warranted.

CONCLUSION

In conclusion, our new original data in China revealed *H. pylori* was related to higher prevalence of cholelithiasis. The meta-analysis supported the results of *H. pylori* as a risk factor for cholelithiasis. In the subgroup analyses, *H. pylori* was correlated with an increased risk of cholelithiasis in Asia. Besides, *H. pylori* was specifically related to choledocholithiasis but it was not associated with the chemical components of stones. The underlying mechanism of *H. pylori*-related cholelithiasis could potentially involve the relationship between *H. pylori* and the metabolism of bilirubin and cholesterol, warranting further investigation. Additionally, the routes of *H. pylori* infection to the biliary system require more

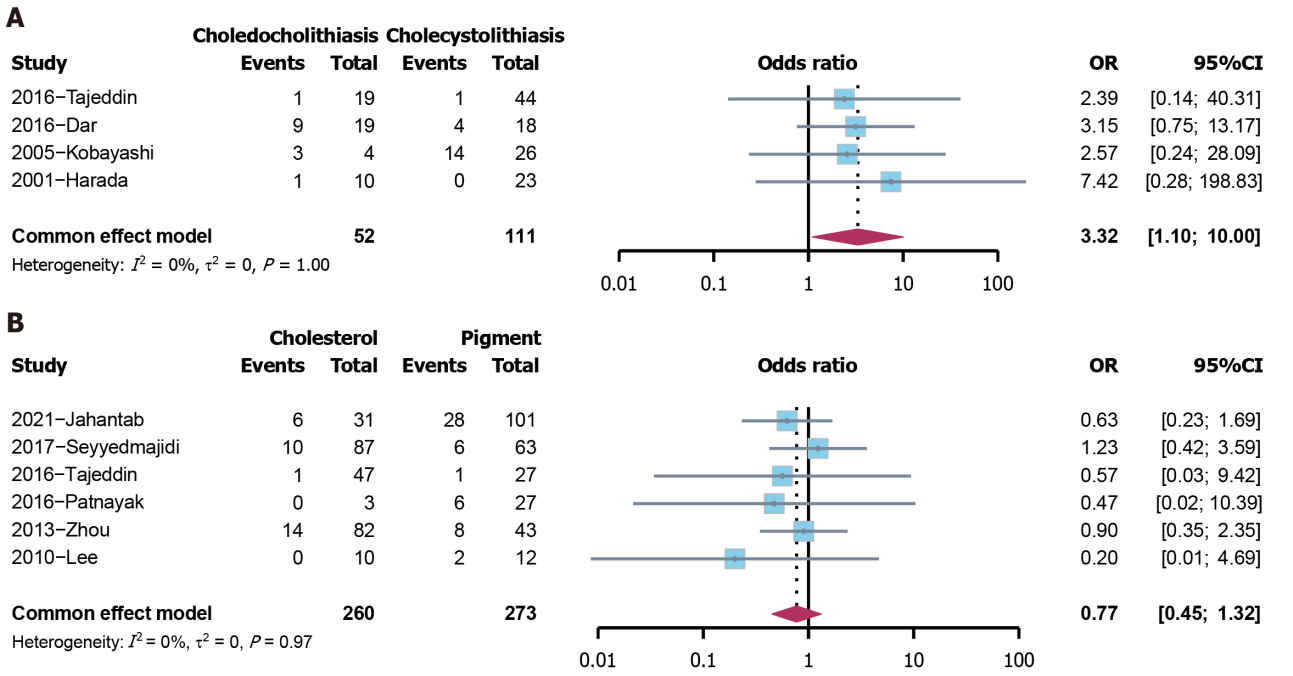

Figure 6 The results of phenotype analysis of cholelithiasis. A: The analysis of position of stones; B: The analysis of chemical components of stones. CI: Confidence interval; OR: Odds ratio.

extensive exploration.

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FOOTNOTES

Author contributions: Cai T and Li Y contributed to the methodology and resources; Yao SY and Li XM made validation and formal analysis and wrote the original draft; Yao SY, Li XM, and Cai T cured the data; Cai T, Liang LX, and Liu XM supervised the research; Wang F reviewed and edited the article; Liang LX, Liu XM, and Wang F acquired the funding; Lei YF, Zhu Y, and Wang F conceptualized and administrated the project. Zhu Y and Wang F are the co-corresponding authors of the article. Yao SY and Li XM contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

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Data sharing statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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