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Relationship between gallstone and biliary tract neoplasm; a systematic review and meta-analysis of cohort and case-control studies

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Abstract

Introduction: As a common disease, gallstone has the potential to increase the risk of biliary tract neoplasm via inflammation, bile flow alterations, or changing the levels of metabolic hormones.
Objectives: The present systematic review intended to investigate the potential relationship between gallstone and biliary tract neoplasm.
Materials and Methods: The present study was conducted through a systematic review and meta-analysis, based on the guidelines provided by PRISMA. A comprehensive search was performed in the Web of Science, Cochrane, ProQuest, PubMed, and Google Scholar databases until February 20, 2024. Moreover, data analysis was performed using the STATA 14 software, and the significance level was set at $P<0.05$.
Results: The present systematic review included 14 case-control and 11 cohort studies. According to our results, gallstone increased the risk of biliary tract neoplasm in all studies (OR: 4.08, 95% CI: 2.82, 5.92), including cohort (OR: 4.35, 95% CI: 2.61, 7) and case-control studies (OR: 3.87, 95% CI: 2.22, 6.72). Moreover, the increased risk of biliary tract neoplasm was reported in the gallstone patients of the age groups of 40-49 years (OR: 2.97, 95% CI: 2.30, 3.84), 50-59 years (OR: 2.92, 95% CI: 2.02, 4.23), and 60-69 years (OR: 6.34, 95% CI: 4, 10.07). Furthermore, the patients with gallstones were at an increased risk of gallbladder cancer (OR: 6.24, 95% CI: 3.95, 9.85), intrahepatic bile duct cancer (OR: 4.46, 95% CI: 1.31, 15.15), extrahepatic bile duct cancer (OR: 4.19, 95), and ampulla of Vater cancer (OR: 2.47, 95% CI: 1.53, 3.99) compared to patients without gallstones.
Conclusion: Gallstones significantly increased the risk of biliary tract neoplasm, with the highest risk reported in the age group of 60-69 years.
Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024518046) and Research Registry (UIN: reviewregistry1800) website.

Introduction

As a relatively common disease (1), gallstone is more prevalent in women, patients older than 40 years, and those with a positive family history (2). Additionally, other risk factors, such as age, gender, weight, and bacterial infections play a role in the formation of gallbladder stones (3-5). Several patients with gallstone experience acute or chronic inflammation, nausea, emesis, diarrhea, and right-sided abdominal pain (biliary colic), while more serious cases may result in cholangitis, biliary pancreatitis, gallbladder cancer, and other conditions (1). Additionally, it has been shown that gallstones can increase the risk of carcinoma by causing inflammation (6,7), bile flow alterations (8), or changing the levels of metabolic hormones (9).

Bile duct cancers account for about 3% of all gastrointestinal malignancies (10) and include an extensive range of neoplasms, including the biliary tract neoplasms (CCA) arising from the gallbladder, ampulla of Vater, and intrahepatic, perihilar, and distal bile ducts (11). As a malignant bile duct tumor, gallbladder cancer accounts

Key point

The findings of our systematic review and meta-analysis of cohort and case-control studies highlighted a substantial increase in the risk of biliary tract neoplasms associated with gallstones, particularly in individuals aged 60-69 years, underscoring the critical need for targeted screening programs and heightened vigilance in this age group.

for 80%-95% of all global cases of bile duct malignancy (12). Besides, biliary tract neoplasm is an aggressive bile duct malignancy with globally increasing incidence and mortality (13). According to reports, the incidence of bile duct cancers is increasing in all 3 sub-areas of bile ducts, including gallbladder cancer, extrahepatic bile duct cancer, and ampulla of Vater cancer (14,15).

Objectives

Considering the controversial results reported by previous cohort and case-control studies (16,17), the present systematic review and meta-analysis intended to inspect the potential relationship between gallstone and biliary tract neoplasm.

Materials and Methods

Study design

The present systematic review was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (18), and the reported protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO).

Search strategy

The databases of Web of Science, Cochrane, ProQuest, PubMed, and Google Scholar were searched for the related studies until February 20, 2024, without any geographical and time limitations. Furthermore, to ensure a comprehensive search, updated Medical Subject Headings (MeSH) and their equivalents—such as "Biliary Tract Neoplasms," "Biliary Tract Cancer," "Cholangiocarcinoma," "Gallstones," and "Biliary Calculi"—were utilized. The keywords were systematically combined using the logical operators "AND" and "OR.. Not only that, but the references of the included studies were also evaluated to further strengthen the eligible data. For example, the search strategy used in PubMed was as follows: (Biliary Tract Neoplasms[Title/Abstract] OR Biliary Tract Cancer[Title/Abstract] OR Cholangiocarcinoma[Title/Abstract]) AND (Gallstones[Title/Abstract] OR Biliary Calculi[Title/Abstract])

The PICO components (Population, Intervention/Exposure, Comparison, Outcomes) of the present study were as follows: The study population included all the studies evaluating the relationship between gallstone and biliary tract neoplasm, while gallstone was considered as the exposure. On top of that, the comparison group included individuals without gallstone. Subsequently, the outcome was the relationship between gallstone and biliary tract neoplasm, which was reported using the odds ratio (OR), relative risk (RR), hazard ratio (HR), and standardized incidence ratio (SIR).

Inclusion and exclusion criteria

The inclusion criteria were the cohort and case-control studies evaluating the relationship between gallstone and biliary tract neoplasm. Conversely, the duplicated studies, reviews, studies investigating the relationship between biliary tract neoplasm and gallstone plus another variable, low-quality studies, those without any access to their full texts, the studies without necessary data for analysis, and those reporting qualitative data were all excluded from the present systematic review and meta-analysis.

Quality assessment

Two of the authors conducted a thorough qualitative assessment using the Newcastle Ottawa Scale to ensure the quality and reliability of the included studies. In the mentioned scale, each question was assigned a maximum of one star, except for the comparison question, which could be assigned two stars. Therefore, the scale was scored from 0 to 10, representing the lowest to highest quality, respectively. Studies with more than 6 scores were considered high-quality studies and were included in the analysis (19).

Data extraction

The data extraction was performed by two researchers independently and included authors' names, patients' age, study location (country), study type, sample sizes, year of the study performance, publishing time, and the relationship between gallstone and biliary tract neoplasm using the OR, RR, HR, and SIR indices. In addition, all data were thoroughly evaluated by a third researcher to ensure the accuracy and correct the potential discrepancies.

Statistical analysis

We used the logarithms of OR, RR, HR, and SIR indices for each study, and the obtained values were combined at the end. Additionally, the inter-study heterogeneity was evaluated using the I^2 index, which classifies heterogeneity into 3 levels: low heterogeneity (<25%), moderate heterogeneity (25%-75%), and high heterogeneity (>75%). Moreover, we used the random effects model due to the high level of heterogeneity. Finally, data analysis was conducted using the STATA 14 software, and the significance level was set at 0.05.

Results

During the search phase, a total of 390 studies were extracted from the mentioned databases. However, 192 studies were duplicated and were excluded from the systematic review. Then, the abstracts of the remaining

studies were evaluated, and 13 studies were excluded due to a lack of access to their full texts. Thus, there were 185 studies with available full texts, of which 29 were excluded because they lacked the necessary data for analysis. Finally, 131 out of 156 remaining studies were excluded due to fulfilling other exclusion criteria, and 25 studies were included in the final analysis (Figure 1).

The present systematic review included 25 studies, including 11 cohort and 14 case-control studies, which were conducted in different countries and were published during 1987-2023 (Table 1).

According to our findings, all included studies reported that gallstone significantly increased the risk of biliary tract neoplasm (OR: 4.08, 95% CI: 2.82, 5.92, Figure 2).

Nonetheless, both cohort (OR: 4.35, 95% CI: 2.61, 7.25) and case-control studies (OR: 3.87, 95% CI: 2.22, 6.72) reported such a significant effect. However, the risk of biliary tract neoplasm reported in cohort studies was higher than case-control studies (Figure 3).

According to age group analysis, the increased risk of biliary tract neoplasm was reported in gallstone patients of the age groups of 40-49 years (OR: 2.97, 95% CI: 2.30, 3.84), 50-59 years (OR: 2.92, 95% CI: 2.02, 4.23), and 60-69 years (OR: 6.34, 95% CI: 4, 10.07). Moreover, the risk was similar in the age groups of 40-49 and 50-59 years, while it was almost twice in the age group of 60-69-year-olds (Figure 4).

Meanwhile, the risk of biliary tract neoplasm was higher in patients with gallstones compared to those without this problem (OR: 6.24, 95% CI: 3.95, 9.85, Figure 5).

On the other hand, the patients with gallstones were at an increased risk of intrahepatic bile duct cancer (OR: 4.46, 95% CI: 1.31, 15.15), extrahepatic bile duct cancer (OR: 4.19, 95% CI: 2.40, 7.30). It is worth noting that patients with gallstones are more prone to contracting intra hepatic bile duct cancer compared with extrahepatic bile duct cancer (Figures 6 and 7).

The risk of developing ampulla of Vater cancer in patients with gallstone is more than those who do not have this disease (OR: 2.47, 95% CI: 1.53, 3.99) (Figure 8).

Finally, additional analysis using the meta-regression diagram showed no significant relationship between "gallstones plus the risk of biliary tract neoplasm" and the year of study publication (p=0.171) or sample size

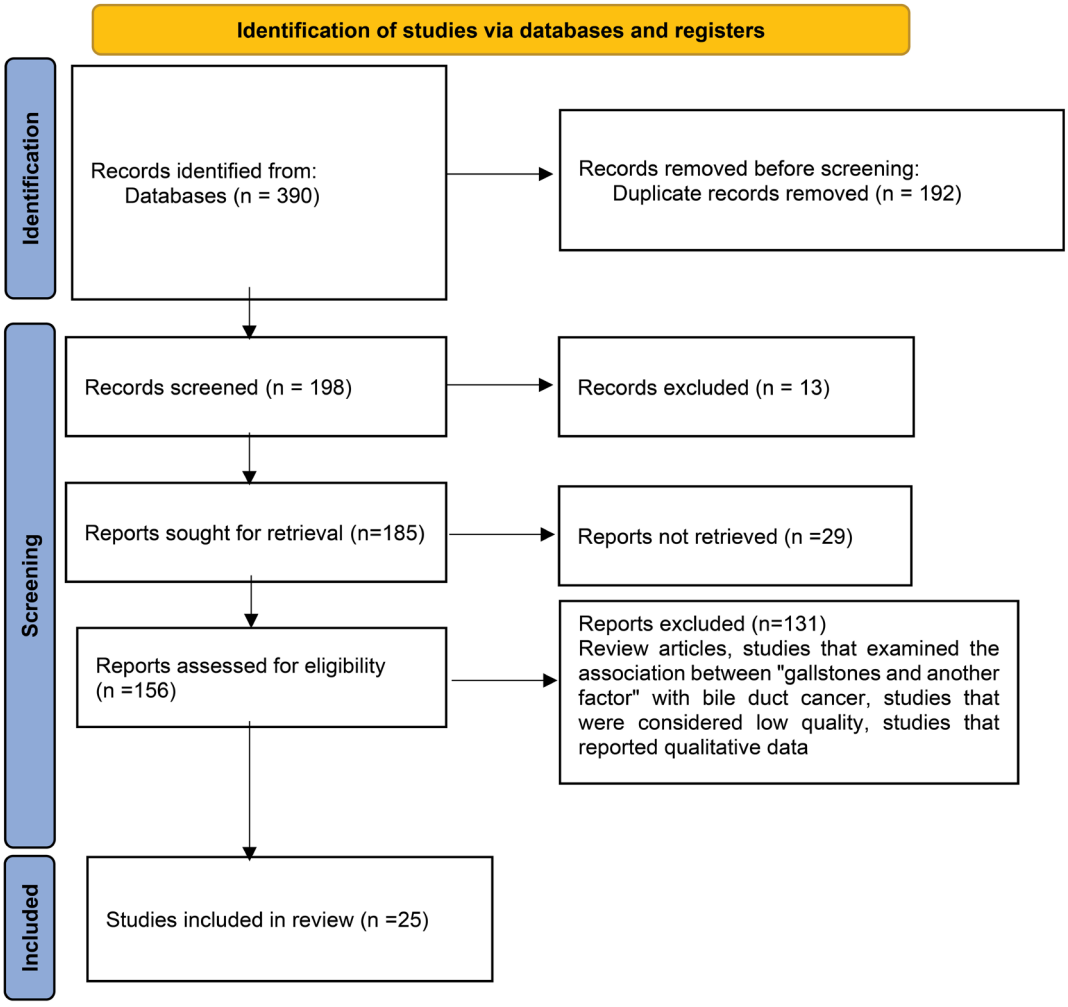

Figure 1. Flowchart illustrating the study selection process based on the PRISMA guidelines.

Table 1. Summarized information of the studies that were included in the systematic review and meta-analysis

First Author, year	Country	Type of study	Total number of people	Total age of people (year)	Number of people with gallstones	Age of people with gallstones (year)	Number of people who did not have gallstones	Age of people who did not have gallstones (year)	Duration of research
Zhu, 2023 (20)	China	Cohort	438	63	NR	NR	NR	NR	from Jan 2010 to Jun 2020
Luo, 2022 (17)	USA	Cohort	164865	NR	11559	52.5	153306	50.4	1982-2012
Ahn, 2022 (16)	Korea	Case–Control	NR	NR	958677	NR	9586770	NR	NR
Pang, 2021(21)	China	Cohort	39298		8515	54.7	30783	53.4	2004–2008
Huang, 2020 (22)	South Korea	Cohort	704437	41.7	NR	NR	NR	NR	Between 2002 and 2015
Torp, 2020 (23)	Denmark	Cohort	132771	>18	NR	NR	NR	NR	1996 to 2015
Zhu, 2020 (24)	China	Case–Control	4657	NR	1749	63	2908	61	from Aug 2008 to Aug 2018
Rosato, 2016 (25)	Italy	Case–Control	NR	NR	159	25-76	795	25-76	1983-2009
Lee, 2015 (26)	South Korea	Case–Control	NR	NR	81	66.6	162	67	between Jul 2007 and Dec 2013
Lee, 2015 (27)	South Korea	Case–Control	NR	NR	276	67.8	67.5	NR	between 2007 and 2013
Nogueira, 2014 (28)	USA	Case–Control	5310	76.5	567	76.5	NR	NR	1992–2005
Chen, 2014 (29)	Taiwan	Cohort	NR	NR	15545	NR	62180	NR	2000 to 2010
Nordenstedt, 2012 (30)	Sweden	Cohort	192960	68.1	NR	NR	NR	NR	1965–2008
Cai, 2011 (31)	China	Case–Control	NR	NR	313	56.64	608	55.58	from Jan 2000 to Dec 2005
Tao, 2010 (32)	China	Case–Control	NR	NR	190	59.4	380	59.4	between 1998 and 2008
Grainge, 2009 (33)	UK	Case–Control	NR	NR	611	NR	5760	NR	between 1987 and Mar 2002
Ishiguro, 2008 (34)	Japan	Cohort	101868	52	253	NR	NR	NR	1990–1994
Hsing, 2007 (35)	China	Case–Control	2623	>18	627	NR	1996	NR	between Jun 1997 and May 2001
Hsing, 2007 (36)	China	Cohort	959	40-75	201	NR	NR	NR	between 1997 and 2000
Ahrens, 2007 (37)	Denmark, Sweden, France, Germany and Italy	Case–Control	NR	NR	153	35–70	1421	35–70	between 1995 and 1997
Welzel, 2007 (38)	USA	Case–Control	NR	NR	1084	≥65	102782	≥65	1993–1999
Khan, 1999 (39)	USA	Case–Control	NR	NR	69	NR	138	NR	between Jan 1, 1980, and Apr 4
Chow, 1999 (40)	Denmark	Cohort	60176	70	NR	NR	NR	NR	1977 to 1989
Lowenfels, 1992 (41)	USA	Case–Control	NR	NR	131	NR	2399	NR	NR
Maringhini, 1987 (42)	USA	Cohort	2583	NR	NR	NR	NR	NR	1950-1970

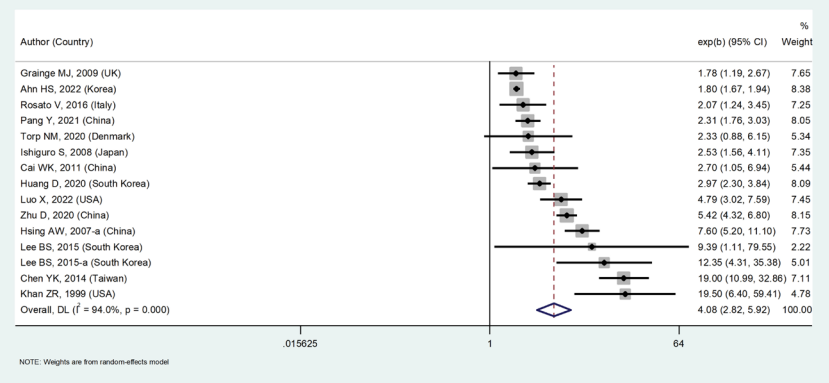

Figure 2. Forest plot showing the relationship between gallstones and the risk of biliary tract neoplasm.

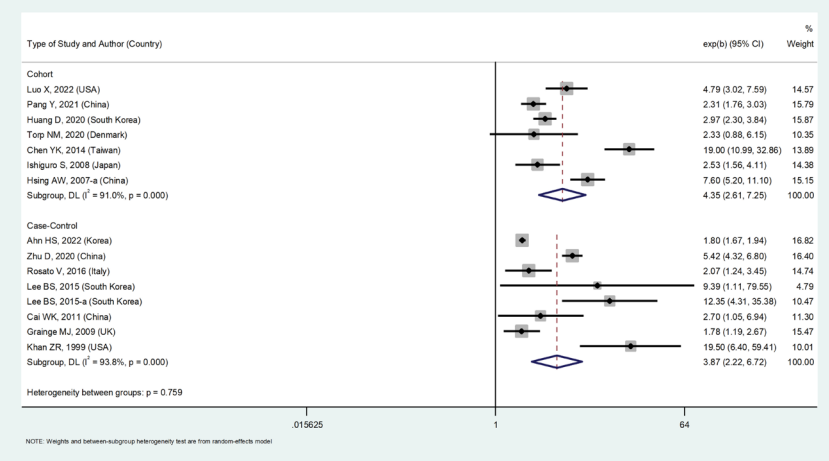

Figure 3. Forest plot showing the relationship between gallstones and the risk of biliary tract neoplasm by type of studies.

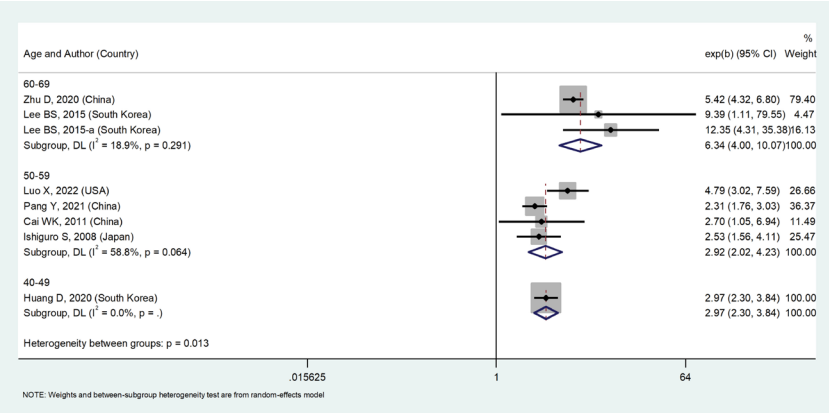

Figure 4. Forest plot showing the relationship between gallstones and the risk of biliary tract neoplasm by age of patients.

(*P*=0.505). In general, the results of the present meta-analysis were not affected by the sample sizes of the studies, and the risk did not change significantly during the past years (Figures 9 and 10).

Discussion

The present meta-analysis, which included 25 studies, showed that gallstones significantly increased the risk of biliary tract neoplasm.

Compatible with our results, a meta-analysis by Cai et al included seven case-control studies, showing that gallbladder stones could increase the risk of intrahepatic biliary tract neoplasm (OR: 17.64, 95% CI: 11.14, 27.95) (43), while another meta-analysis by Clements et al

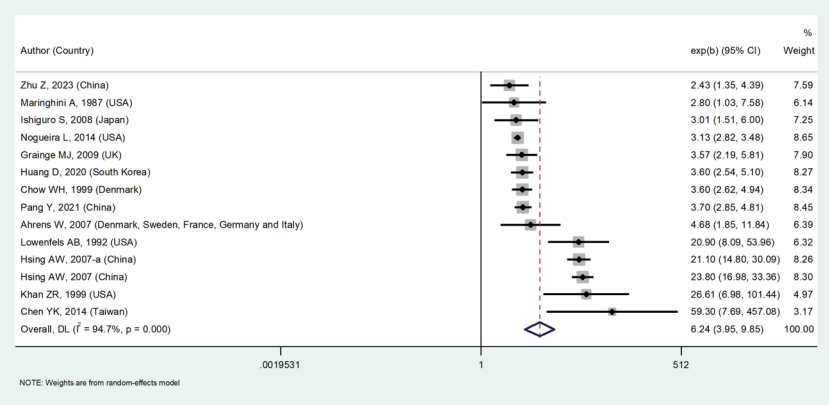

Figure 5. Forest plot showing the relationship between gallstones and the risk of gallbladder.

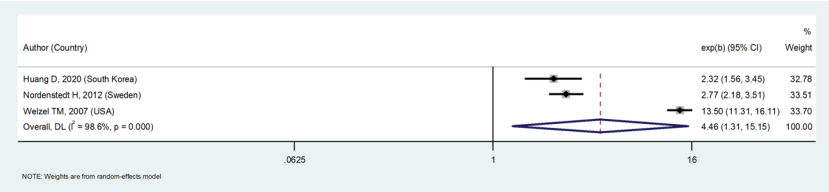

Figure 6. Forest plot showing the relationship between gallstones and the risk of intra-hepatic bile duct cancer.

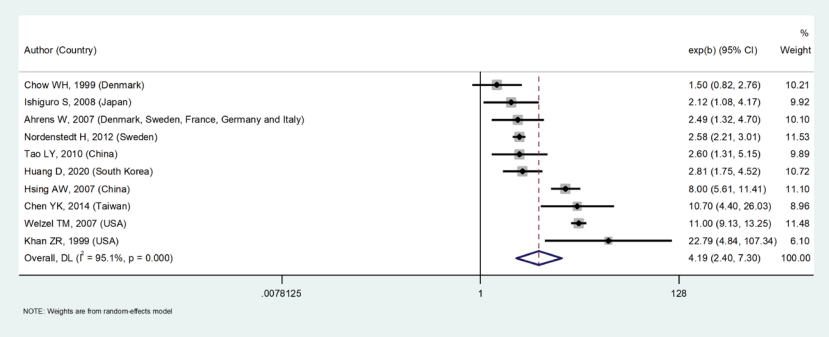

Figure 7. Forest plot showing the relationship between gallstones and the risk of extra-hepatic bile duct cancer.

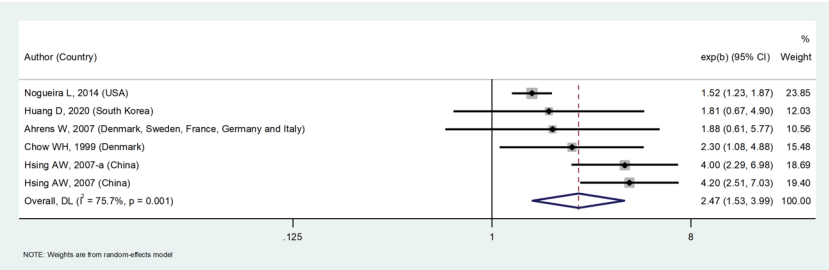

Figure 8. Forest plot showing the relationship between gallstones and the risk of ampulla of Vater cancer.

reported biliary cysts, gallstones, cirrhosis, hepatitis B, and hepatitis C as the most important risk factors for intrahepatic (OR: 3.38, 95% CI: 1.93, 5.92) and extrahepatic biliary tract neoplasm (OR: 5.92, 95% CI: 3.09, 11.32) (44). Thus, these meta-analyses reported gallstones as a significant risk factor for biliary tract neoplasm, reporting that gallstones patients were several times more at risk of developing biliary tract neoplasms compared to those without gallstones. Such a relationship can be explained by gallstones-induced chronic inflammation.

On the other hand, a meta-analysis by Chiong et al reported an increased risk of rectal cancer in patients with gallstones (OR: 1.33, 95% CI: 1.02, 1.73) (45), while another meta-analysis by the same team reported gallstones as a significant risk factor for colon adenoma (OR: 2.26, 95% CI: 1.83, 2.81) (46). Moreover, the meta-analysis by Fan

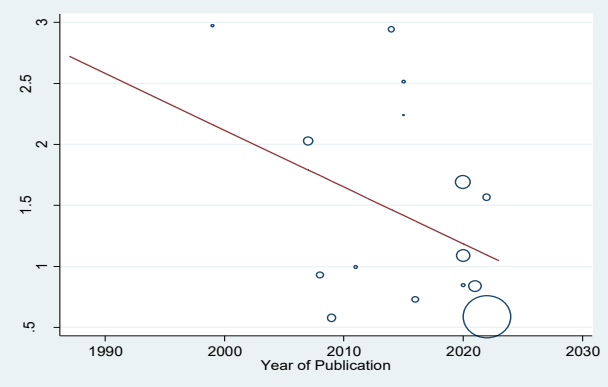

Figure 9. The meta-regression diagram showing the association between gallstones and biliary tract neoplasm by year of publication.

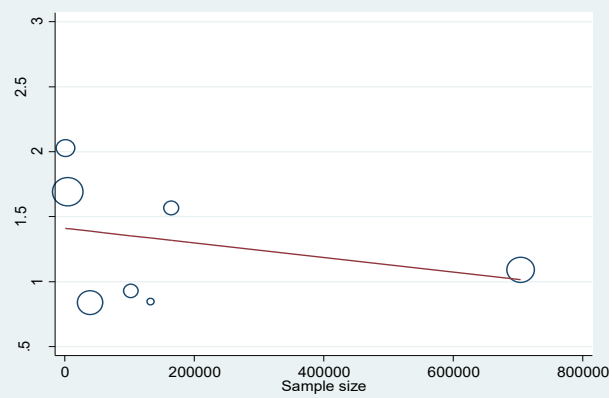

Figure 10. The meta-regression diagram showing the association between gallstones and biliary tract neoplasm by sample size.

et al showed that gallstones (RR: 1.70, 95% CI: 1.30, 2.21) and a history of cholecystectomy (RR: 1.31, 95% CI: 1.19, 1.43) could increase the risk of pancreatic cancer (47). According to a cohort study by Ward et al on 334 986 participants in Europe, gallstones significantly increased the risk of colorectal cancer in female patients (HR: 1.14, 95% CI: 0.99, 1.31), while no significant relationship was found in male patients (HR: 0.81, 95% CI: 0.63, 1.04) (48). Thus, these studies showed that gallstones could increase the risk of other gastrointestinal cancers rather than biliary tract neoplasm, including rectal, colon, pancreatic, and colorectal cancers.

These findings are somehow compatible with our results. Interestingly, gallstones can even increase the risk of prostatic cancer (RR=1.35, 95% CI: 1.17-1.56) according to a meta-analysis by Li et al that included seven studies (49).

Furthermore, a meta-analysis by Li et al evaluated the relationship between being overweight and obesity with the risk of gallbladder cancer and extra hepatic bile duct cancer, showing the increased risk of gallbladder cancer (RR: 1.17, 95% CI: 1.07, 1.28) and extra hepatic bile duct cancer (RR: 1.26, 95% CI: 1.14, 1.39) in overweight individuals. The same relationship was found between obesity and gallbladder cancer (RR: 1.62, 95% CI: 1.49, 1.75), as well as obesity and extra hepatic bile duct cancer (RR: 1.48; 95% CI: 1.21, 1.81) (50). Furthermore, the meta-analysis by Wang et al investigated the relationship between hepatitis B and C with the risk of bile duct cancers, showing that infection with hepatitis B virus (HBV) (OR: 2.16; 95% CI: 1.73–2.69) and hepatitis C virus (HCV) (OR: 2.12; 95% CI: 1.62–2.77) could increase the risk of bile duct cancers (51). According to another meta-analysis by Ren et al that included 21 studies, diabetes was significantly related to an increased risk of bile duct cancers (RRs: 1.43, 95% CI: 1.18, 1.72) (52). Thus, in addition to gallstones, other factors, such as obesity, overweight, diabetes, and infection with hepatitis B or C, play roles in the development of bile duct cancers.

Conclusion

The present meta-analysis showed that gallstones could significantly increase the risk of several types of biliary tract neoplasm, with the highest risk reported in the age group of 60-69 years. The bile duct cancers prevalent in patients with gallstones include gallbladder cancer, intra-hepatic bile duct cancer, extrahepatic bile duct cancer, biliary tract cancer, and ampulla of Vater cancer, in order of prevalence. Thus, patients with gallstones are at high risk for developing biliary tract neoplasm and are recommended to undergo necessary screening tests.

Limitations of the study

The present systematic review had some limitations. For example, the included studies did not mention the gender and underlying diseases of the patients with gallstones. Thus, it was not possible to perform a subgroup analysis based on gender and underlying disease. Moreover, only one study was performed in each of the countries evaluated in the present systematic review. Therefore, we did not perform a subgroup analysis based on the country of the study performance.

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Authors' contribution

Conceptualization: Fatma Adnan Abdullkareem and Shahab Emamieh.
Data curation: Faraz Zandiyeh and Shahrzad Ghaffariyan.
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Methodology: Sara Teihou Jorshari and Elahe Zaremoghadam.
Project management: Shahrzad Ghaffariyan.
Resources: All authors.
Supervision: Fatma Adnan Abdullkareem.
Validation: Abdul Amir Kadhum and Afsaneh Mirshekari.
Visualization: Elahe Zaremoghadam.
Writing–original draft: All authors.
Writing–reviewing and editing: All authors.

Conflicts of interest

There are no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website with (ID: CRD42024518046) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1800). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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