

***Helicobacter* Species as Possible Risk Factor in Gallbladder Cancer and Gallstones: A Meta-Analysis**

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ABSTRACT

Background: It has been long known that *Helicobacter* species are one of the leading causes in gastrointestinal diseases. Recently, it is emerging as one of the causes leading to gallbladder diseases, such as gallbladder cancer and gallstones. The aim of this study is to assess the correlation between *Helicobacter* species and gallbladder cancer and gallstones.

Method: This meta-analysis assessed case-control studies from the year 2001 to 2022. A comprehensive literature search was performed in Pubmed, Scopus, Embase, dan Plos One. Review manager 5.4.1, along with the Mantel Haenszel method, was utilized to analyze the data extraction. The methodological index was utilized to assess the risk of bias from the included studies. The odds ratio is calculated with a confidence interval of 95%. $P < 0.05$ was considered significant.

Results: Twenty case-control studies from the year 2001 to 2018 with a total number of 2,065 participants were included. We found that there is a low risk of bias and a significant difference between the control group and the experimental group; gallbladder cancer (random effect: OR = 2.38; 95% CI: 1.35–4.19; $p = 0.003$) and gallstones (fixed effect: OR = 4.17; 95% CI: 2.71–4.62; $p = 0.00001$).

Conclusion: Results of this meta-analysis demonstrated that the patients with *Helicobacter* species have an increased risk of gallbladder cancer and gallstones.

Keywords: gallbladder cancer, gallstones, *Helicobacter* sp.

ABSTRAK

Latar belakang: Telah lama diketahui bahwa spesies *Helicobacter* adalah salah satu penyebab utama penyakit gastrointestinal. Belakangan ini muncul sebagai salah satu penyebab penyakit kandung empedu, seperti kanker kandung empedu dan batu empedu. Tujuan dari penelitian ini adalah untuk menilai hubungan antara spesies *Helicobacter* dan kanker kandung empedu dan batu empedu.

Metode: Meta-analisis ini menilai studi kasus-kontrol dari tahun 2001 hingga 2022. Pencarian literatur yang komprehensif dilakukan di Pubmed, Scopus, Embase, dan Plos One. Review manager 5.4.1, bersama dengan metode Mantel Haenszel, digunakan untuk menganalisis ekstraksi data. Indeks metodologi digunakan untuk menilai risiko bias dari studi yang disertakan. Odds ratio dihitung dengan confidence interval 95%. $P < 0,05$ dianggap signifikan.

Hasil: Dua puluh studi kasus-kontrol dari tahun 2001 hingga 2018 dengan jumlah total 2.065 peserta dimasukkan. Kami menemukan bahwa ada risiko bias yang rendah dan perbedaan yang signifikan antara kelompok kontrol dan kelompok eksperimen; kanker kandung empedu (efek acak: OR = 2,38; 95% CI: 1,35–4,19; $p = 0,003$) dan batu empedu (efek tetap: OR = 4,17; 95% CI: 2,71–4,62; $p = 0,00001$).

Simpulan: Hasil meta-analisis ini menunjukkan bahwa pasien dengan spesies *Helicobacter* memiliki peningkatan risiko kanker kandung empedu dan batu empedu.

Kata Kunci: kanker kandung empedu, batu empedu, *Helicobacter sp.*

INTRODUCTION

In most developed countries, bile duct malignancies, including intrahepatic, perihilar, distal bile duct, and gallbladder malignancies, have a low incidence. However, they represent a significant health problem in endemic areas.¹ The most common type of biliary tract cancer is gallbladder cancer. According to Global burden of cancer study (GLOBOCAN) 2020 data, gallbladder cancer accounts for 115,949 new cases, including all genders and ages, and the number of deaths is estimated 84,695 cases.^{2,3} The American Cancer Society estimates that in 2022, gallbladder and bile duct cancers in the United States will reach approximately 12,130 new diagnoses, 5,710 in men and 6,420 in women, and around 4,400 deaths from these cancers, 1,830 in men and 2,570 in women.⁴ Although breast cancer is still the leading cause of cancer-related death, the rising number of deaths caused by gallbladder cancer should also be of particular concern.^{2,3}

It is vital to treat existing risk factors to deliver the appropriate treatments as soon as possible when dealing with cancer. Gallstone is recognized as significant risk factor of gallbladder cancer (RR = 3.01-23.8). The duration for having gallstones is linearly associated with greater chance for having gallbladder cancer.^{5,6} Another significant risk factor is *Helicobacter* species infection, and this infection impacts the development of gallbladder cancer and the formation of stones in the gallbladder.

This meta-analysis assesses the correlation between *Helicobacter* species and gallbladder stone and cancer.

METHOD

There were two research questions. First, is whether there is a difference between bile duct malignancy

patients and bile duct stones, both of which have been shown to have *Helicobacter spp.* infection? Second, is there a difference between patients with gallbladder duct stones and patients without any problems with the gallbladder duct, both of which had proven *Helicobacter spp.* infection? These two research questions were related to the main outcome and secondary outcome of this research. In order to analyze this research question quantitatively, it was necessary to convert them into population, intervention, comparison, outcome (PICO). For the intervention part is none, because these research questions aims to assess risk factors, not therapeutic effectiveness.

Table 1. Both research questions in the form of PICO

First question	
Population	Patients with bile duct malignancy and proven infection with <i>Helicobacter</i> species
Intervention	-
Comparison	Patients without malignancy in the biliary tract, but with biliary tract disorders and proven infection with <i>Helicobacter</i> species
Outcome	Association between malignancy of the biliary tract and <i>Helicobacter</i> species infection
Second question	
Population	Patients with gallbladder stones/infection and proven infection with <i>Helicobacter</i> species
Intervention	-
Comparison	Patients without any problems with the gallbladder, but proven infection with <i>Helicobacter</i> species
Outcome	Association between gallbladder disease and <i>Helicobacter</i> species

The research team consisted of five people. One person acted as data manager (JAT) and team leader, the remaining four people acted as reviewers (DNE, KPH, DD, JAJMNL). The criteria agreed upon by the team were to be the team leader, must have experience and high experience related to data analysis. In practice, if there was a difference of opinion, it would be discussed and decided by the team leader.

Search Strategy

The literature search was performed in medical databases such as Pubmed, Scopus, Embase, dan Plos One. The search string used was "*Helicobacter* AND gallbladder cancer", "*Helicobacter* species AND gallbladder cancer", "*Helicobacter* AND gallbladder stones", "*Helicobacter* species AND gallstones", "*Helicobacter* AND gallstone", "*Helicobacter* AND cholelithiasis", "*Helicobacter* species AND cholelithiasis", "*Helicobacter* species AND benign gallbladder diseases". In searching the literature, the research team agreed to use the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Eligibility Criteria

Inclusion criteria: (1) the study design was an observational study (case-control, cohort, and cross-sectional); (2) there was a standard modality for detecting *Helicobacter* species and establishing a diagnosis related to the gallbladder, either cholelithiasis, cholecystitis, or malignancy; (3) the research subjects were patients with biliary tract disorders (which include stones, infections, and malignancies); (4) the results of the research used in the period 2001 to 2022. Exclusion criteria: (1) the study design was a clinical trial; (2) the data presented were incomplete; (3) the language used was not comprehensible by the authors, other than English and Indonesian.

Data Extraction and Quality Assessment

There are two data analyses in this meta-analysis. For the first data analysis, the case group consisted of gallbladder cancer patients with *Helicobacter spp.* infection. Meanwhile, the control group consisted of cholelithiasis and/or cholecystitis patients with *Helicobacter spp.* infection. The case group for the second data analysis consisted of cholelithiasis and/or cholecystitis patients with *Helicobacter spp.* infection. Meanwhile, the control group consisted of patients with *Helicobacter spp.* infection but without gallbladder diseases.

Assessment of Bias

In this meta-analysis, the team did not involve independent reviewers. The research team used methodological index for non-randomized studies (MINORS) to assess the quality and risk of bias of the studies. There are 12 items in MINORS, namely:

(1) a clearly stated aim; (2) inclusion of consecutive patients; (3) prospective collection of data; (4) endpoint appropriate to the aim of the study; (5) unbiased assessment of the study endpoint; (6) follow-up period appropriate to the aim of the study; (7) loss to follow up less than 5%; (8) prospective calculation of the study size; (9) an adequate control group; (10) contemporary groups; (11) baseline equivalence of groups; and (12) adequate statistical analyses.⁷

Statistical Analysis

In data processing, the research team used the review manager application, version 5.4.1. This version was released in 2020. In the data analysis, 95% confidence interval was used. Provisions for receiving a significant result is a probability value < 0.05 . An assessment of heterogeneity was also carried out with the Q statistic or chi squared test, as well as I^2 . Also included the Mantel–Haenszel test in categorizing data.

RESULTS

From the literature search, we obtained 1,138 studies. We procured 20 studies that matched the research questions, inclusion criteria, and exclusion criteria through critical appraisal.⁸⁻²⁷ There are two research questions, as shown in table 1. The first research question is whether there is a relationship between *Helicobacter spp.* infection in patients with gallbladder cancer? The second research question is whether there is a relationship between *Helicobacter spp.* infection in patients with cholelithiasis?

Data analysis showed a relationship between the two. The first outcome, *Helicobacter* infection was an associated risk of malignancy in gallbladder cancer ($p = 0.003$, OR = 2.38, 95% CI: 1.35–4.19). The second outcome, *Helicobacter* infection was also a risk for cholelithiasis ($p < 0.00001$), OR = 4.20, 95% CI: 2.67–6.61). It is also seen that the first output and the second output are related to each other. The risk assessment of bias also shows the majority is green, so the quality of the study is good.

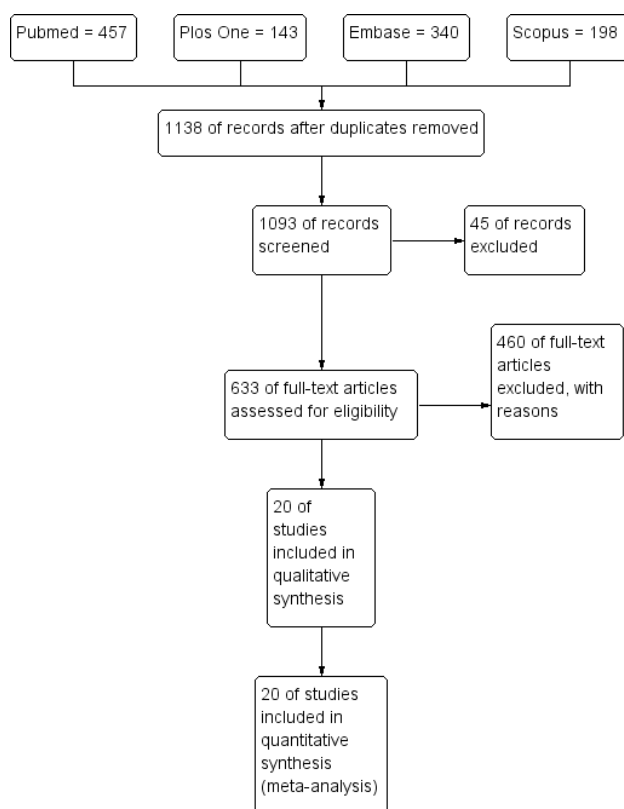


Figure 1. Flow chart of studies

Table 2. The characteristic study that assessed *Helicobacter* species and gallbladder cancer association

Author	Country	Type of gallbladder disorder	Type of malignancy	Species
Fukuda K, et al (2002) ⁸	Japan	Cholelithiasis, adenomyomatosis and polyps	Extrahepatic bile duct cancer, intrahepatic bile duct cancer, gallbladder cancer, cancer of the papilla of Vater	<i>H. bilis</i> , <i>H. hepaticus</i> , <i>H. pylori</i>
Matsukura N, et al (2002) ⁹	Japan, Thai & USA	Cholelithiasis and or cholecystitis	Bile duct or gallbladder cancer	<i>H. bilis</i>
Bulajic M, et al (2002) ¹⁰	Germany	Cholelithiasis without tumor and biliary tumors	Biliary tumor	<i>H. pylori</i>
Murata H, et al (2004) ¹¹	Japan	Cholelithiasis	Gallbladder cancer, common bile duct cancer (biliary tract cancer), pancreatic cancer	<i>H. bilis</i>
Kobayashi T, et al (2005) ¹²	India	Cholecystolithiasis and choledochocystolithiasis	Gallbladder cancer and common bile duct cancer	<i>H. pylori</i> , <i>H. hepaticus</i> , <i>H. bilis</i>
Leelawat K, et al (2007) ¹³	Thailand	Intrahepatic duct stones	Liver metastases, cholangiocarcinoma, hepatocellular carcinoma	<i>H. pylori</i>
Bohr URM, et al (2007) ¹⁴	Germany	Cholelithiasis	Gallbladder carcinoma	<i>H. ganmani</i>
Al-Soud WA, et al (2008) ¹⁵	Sweden	Focal nodular hyperplasia, liver adenoma, focal fatty lesion, hepatoma	Cholangiocarcinoma, hepatocellular carcinoma	<i>H. muridarum</i> , <i>H. bilis</i> , <i>H. pullorum</i> , <i>H. pylori</i> , <i>Helicobacter</i> sp. <i>flexispira</i> taxon, <i>H. hepactius</i> and <i>H. bizzozeronii</i>
Sherafat SJ, et al (2012) ¹⁶	Iran	Cholelithiasis	Biliary– pancreatic malignancy	<i>H. pylori</i>
Avilés-Jiméne F, et al (2015) ¹⁷	Mexico	Benign biliary pathology	Biliary tract cancer or extrahepatic cholangiocarcinoma	<i>H. pylori</i>
Yakoob J, et al (2016) ¹⁸	India	Chronic cholecystitis with cholelithiasis, gallbladder polyps	Gallbladder cancer	<i>H. pylori</i>
Tsuchiya Y, et al (2018) ¹⁹	India	Gallbladder cancer & cholelithiasis	Gallbladder cancer	<i>H. pylori</i>

Table 3. The characteristic study that assessed *Helicobacter* species and gallstone association

Author	Country	Type of gallbladder disorder	Type of control group	Species
Matsukura N, et al (2002) ⁹	Japan, Thai & USA	Cholelithiasis and/or cholecystitis	Not cancer and not gallstone	<i>H. bilis</i>
Bulajic M, et al (2002) ¹⁰	Germany	Cholelithiasis	Not cancer and not gallstone	<i>H. pylori</i>
Silva CP, et al (2003) ²⁰	Brazil	Cholelithiasis	Not cancer and not gallstone	<i>H. pylori</i>
Chen W, et al (2003) ²¹	New Zealand	Asymptomatic cholelithiasis and symptomatic cholelithiasis	Not cancer and not gallstone	<i>H. pylori</i>
Farshad, et al (2004) ²²	Iran	Mild chronic cholecystitis and asymptomatic Cholelithiasis	Not cancer and not gallstone	<i>H. pylori</i>
Kobayashi T, et al (2005) ¹²	India	Cholecystolithiasis and choledochocystolithiasis	Not cancer and not gallstone	<i>H. pylori</i> , <i>H. hepaticus</i> , and <i>H. bilisus</i>
Bohr URM, et al (2007) ¹⁴	Germany	Cholelithiasis	Not cancer and not gallstone	<i>H. ganmani</i>
Griniatsos J, et al (2009) ²³	India	Cholelithiasis	Not cancer and not gallstone	<i>H. pylori</i>
Bansal VK, et al (2012) ²⁴	India	Benign/cholelithiasis	Not cancer and not gallstone	<i>H. pylori</i>
Dar MY, et al (2016) ²⁵	India	Cholelithiasis	Hydatid cyst disease of liver and right colonic growth.	<i>H. pylori</i>
Fatemi SM, et al (2017) ²⁶	Iran	Acute and chronic cholecystitis	Not cancer and not gallstone	<i>H. pylori</i> , <i>H. bilis</i>
Isaeva G (2018) ²⁷	Rusia	Chronic non-calculous cholecystitis dan chronic calculous cholecystitis	Not cancer and not gallstone	<i>H. pylori</i>

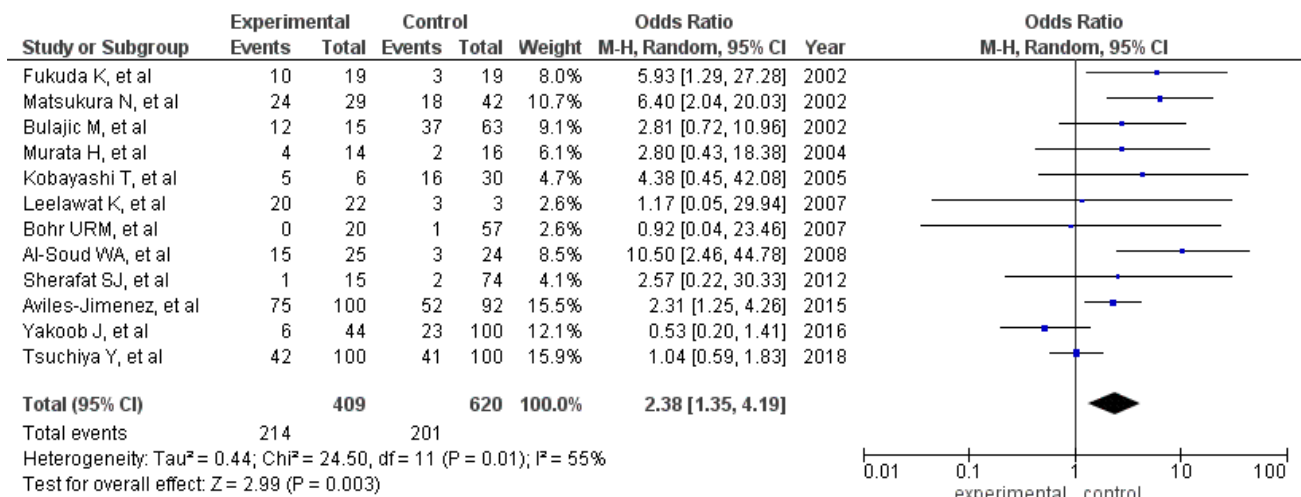


Figure 2. Forest plot of gallbladder cancer

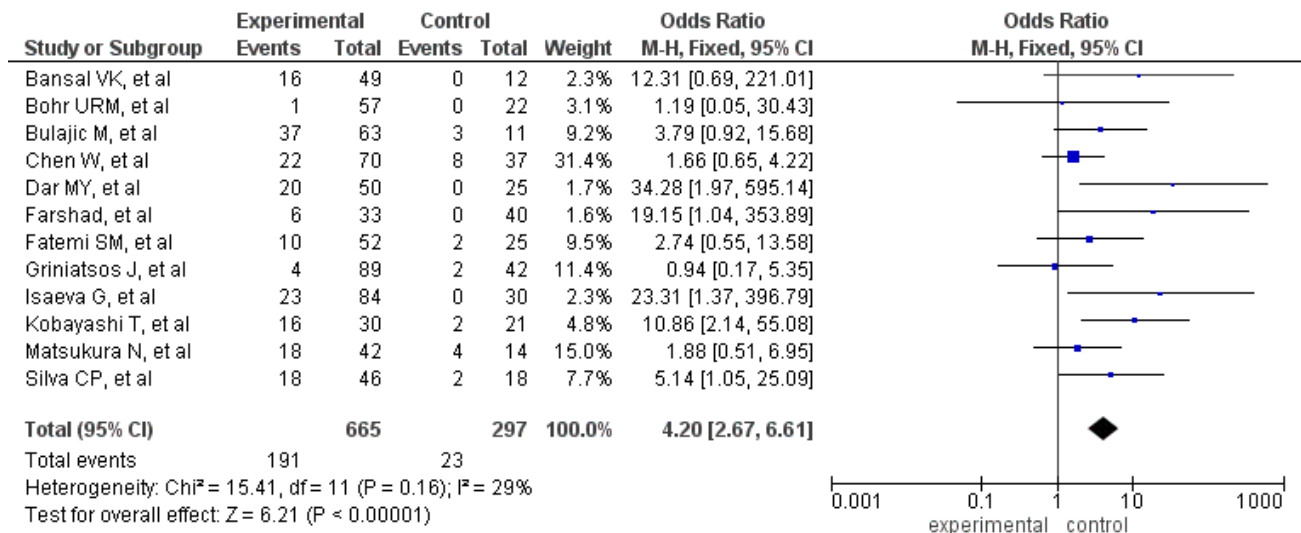


Figure 3. Forest plot of cholelithiasis

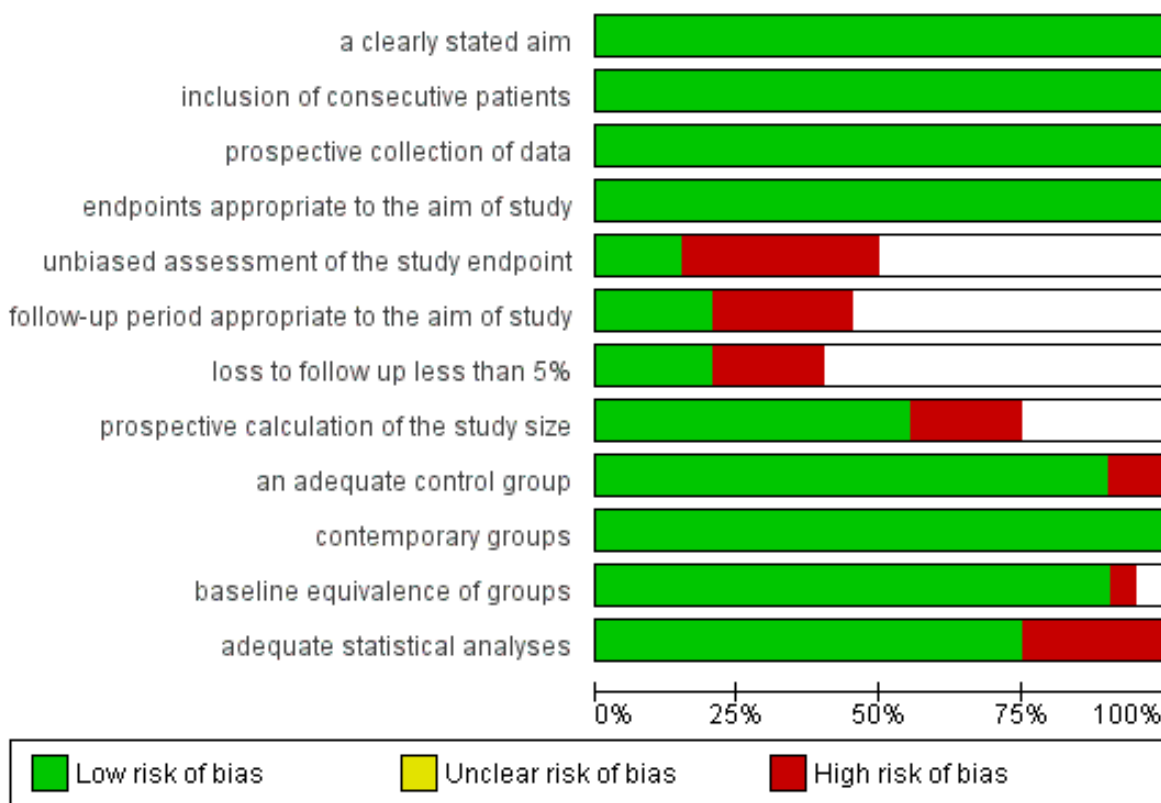


Figure 4. Risk of bias graph

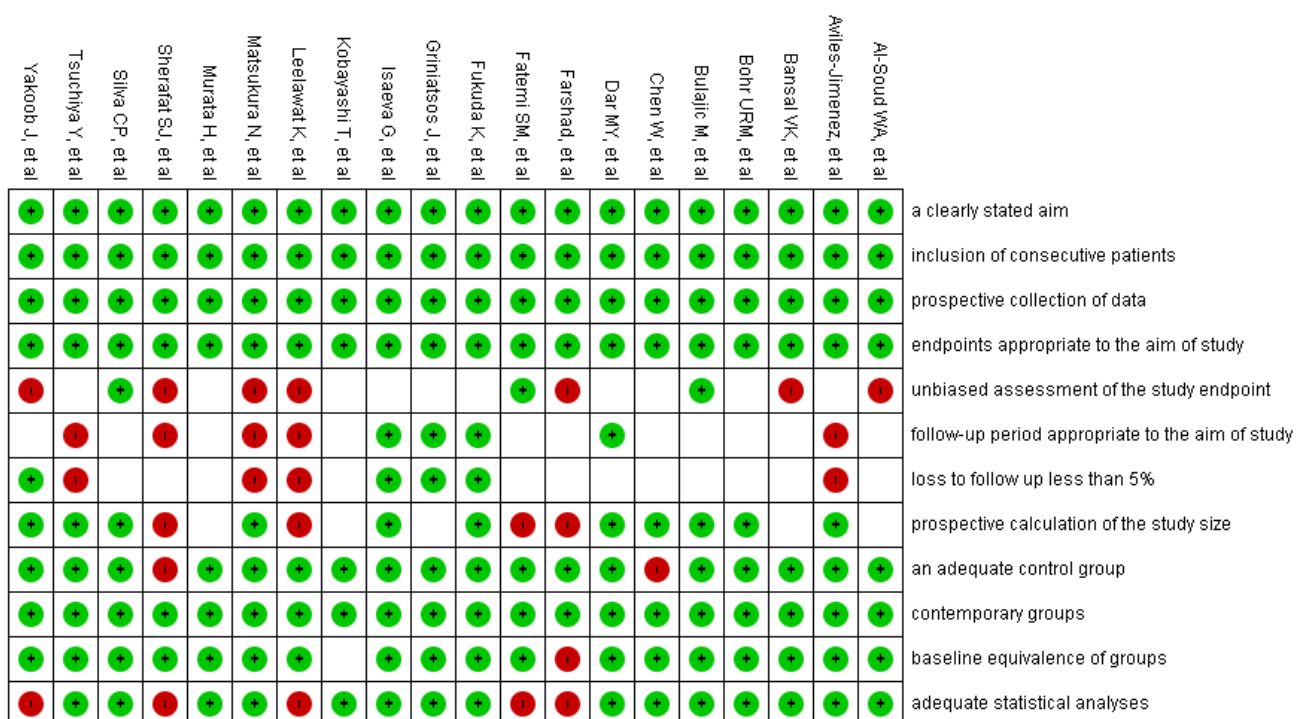


Figure 5. Risk of bias summary

DISCUSSION

Similar to the meta-analysis conducted by Cen L et al in 2017. This study showed that helicobacter infection of the gallbladder is strongly associated with cholelithiasis and chronic cholelithiasis.³¹ Also supported by a meta-analysis compiled by Wang L et al in 2021. This study also showed a positive correlation between *Helicobacter spp* infection and stones in the gallbladder tract.³² Likewise, a study conducted by Cherif S et al in 2020. In addition to stones in the gallbladder, *Helicobacter spp* is also a risk factor for cancer in the bile ducts.³³

The strength of this meta-analysis over others is that it combines exposure to *Helicobacter spp*, with the incidence of gallbladder duct stones and gallbladder malignancy. It can be seen that if early screening for gallbladder stones can be carried out, of course it will be better in preventing malignancy in the gallbladder tract. Gallbladder stones are also a risk factor for malignancy.

Of all the studies used, there was no significant difference in the number of female and male patients. There is also no clear explanation regarding genetic factors.³⁴ However, in 2022 there is an opinion stating the role of genetic factors. None of the studies used in this meta-analysis were published in 2022.³⁵

The relationship between *Helicobacter spp*. with cancer and biliary tract stones is still disputed.⁶ However, this meta-analysis shows that *Helicobacter spp*. does play a role in the occurrence of gallbladder cancer and gallstones. When *Helicobacter spp*. moves, they can express epidermal growth factor (EGF), accelerating biliary cell kinetics or the energy possessed by biliary cells. Which then results in the formation of hepatobiliary cancer. This mechanism is more common with *H. bilis* and *H. hepaticus* than *H. pylori*.⁸ Besides playing a role in expressing inflammatory mediators, this group of bacteria can also produce toxins that damage surrounding tissues.¹³

If an obstruction occurs, this group of bacteria can also form gallstones, especially if it blocks the valve or sphincter of Oddi. This sphincter controls bile and pancreatic fluids so that when there is obstruction, retrograde reflux of bacteria can occur towards the biliary tract. These bacteria can also spread to the liver hematogenously to cause liver cancer.¹⁷ In addition, some sources say that these bacteria can migrate from the duodenum through the sphincter of Oddi. Furthermore, it can also spread to the liver, in which it will be excreted along with bile.²⁶

Not only can *Helicobacter spp*. survive in the gastric mucosa, but they can also live and settle in bile acids despite its toxicity, with building blocks being deoxycholic acid and chenodeoxycholic acid.¹⁸ Most bacteria can barely survive and multiply in the bile. This statement shows that some *Helicobacter* species tolerate bile and even colonize it.¹²

In addition to acting as a risk factor for gallbladder cancer, *Helicobacter spp*. also increase the risk of stone formation as the bacteria acts as a foreign body to form a nidus where stones can form. The nidus can also produce hydrolyzing enzymes or nucleating proteins with structures such as immunoglobulins. The CagA protein from *H. pylori* bacteria is homologous to aminopeptidase so it can increase the risk of gallstone formation.¹⁶

Helicobacter spp. infection is a risk factor for gallbladder cancer but can be exacerbated by the consumption of alcohol.¹⁰ In cases of cholelithiasis and/or cholecystitis, the antibiotics given are broad-spectrum antibiotics such as quinolones and cephalosporins.⁴ On the other hand, there is an opinion that the antibiotic regimens that can be given to treat *Helicobacter spp*. infection are amoxicillin or a combination of antibiotics such as clarithromycin and metronidazole.³ Unfortunately, there is still no evidence of an effective antibiotic for *Helicobacter spp*. infection in cholecystitis or cholelithiasis patients.

Therefore, it is necessary to conduct clinical trials to prove whether broad-spectrum antibiotics, such as quinolones and cephalosporins, can treat *Helicobacter spp*. infections. Additionally, there is a need for clinical trials to assess whether the administration of an antibiotic regimen for *Helicobacter spp*. can be used in patients with cholecystitis and/or cholelithiasis. With this, we hope that further and more extensive research will minimize the risk of gallbladder cancer.^{28,29}

This study also shows that it is essential to find the presence of *Helicobacter spp*. early. It is necessary to carry out examinations, such as endoscopy, to detect *Helicobacter spp*. infection. However, endoscopy is still not readily available in some areas in Indonesia, especially in Eastern Indonesia. A simple non-invasive examination, the urea breath test (UBT), can be utilized instead.³⁰

The weakness of this study would be the lack of discussion regarding the method of examining the *Helicobacter spp*. which is undoubtedly different for each study. The research team hopes that in the future there will be large-scale studies to assess the role of *Helicobacter spp*. Infection.

CONCLUSION

Results of this meta-analysis demonstrated that the patients with *Helicobacter spp.* have an increased risk of gallbladder cancer and gallstones. Large-scale clinical trial studies are needed to assess antibiotic administration

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