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Comparison of pathogen patterns in benign and malignant obstruction in cholangitis patients: A systematic review

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ABSTRACT

Background: Cholangitis is a serious bile duct infection caused by obstruction that permits bacterial growth and may progress to sepsis. Management includes antibiotics and biliary drainage, but selection is challenged by antibiotic resistance and differing pathogen patterns between benign and malignant obstruction. This systematic review aimed to compare the prevalence and distribution of pathogens identified in bile, blood, and biliary stent cultures between benign and malignant biliary obstruction in patients with cholangitis.

Methods: A systematic search of PubMed, Scopus, and ScienceDirect (January 1, 2014-October 17, 2024) identified cohort, case-control, and cross-sectional studies comparing microbial profiles in benign versus malignant cholangitis. Non-English articles, case reports, randomized trials, and reviews were excluded.

Results: Eight studies involving 3,575 patients were included. Culture positivity was generally higher in benign obstruction (bile 55.7% vs. 44.3%; blood 19.6% vs. 14.2%). *Escherichia coli* was most frequently isolated, followed by *Enterococcus* spp., *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Malignant cases more often yielded *Candida* spp. and *viridans-group streptococci* from stents.

Conclusion: Distinct pathogen patterns may inform empirical therapy, though further research is needed.

Keywords: benign obstruction, cholangitis, malignant obstruction, pathogen pattern

INTRODUCTION

Cholangitis is an inflammatory infection of the bile ducts, usually caused by obstruction from gallstones, tumors, strictures, or other conditions [1]. Obstruction increases intraductal pressure, compromising the mucosal barrier and allowing bacteria that are often derived from the gastrointestinal tract to enter by ascending infection or bacterial translocation [1, 2]. Reduced bile flow to the intestine also disrupts gut microbiota and damages tight junctions, further promoting translocation. Without treatment, cholangitis may lead to sepsis, organ failure, and death, with mortality rates around 5-10% in patients receiving drainage and over 50% in untreated cases [3, 4].

Based on the obstruction type, cholangitis is classified as benign or malignant. Benign causes include gallstones and primary sclerosing cholangitis, which partially block bile flow and promote ascending infection. Otherwise, malignant obstructions often cause total obstruction, which makes ascending infection less likely. In this case, cholangitis might be caused by enteric bacterial translocation, which can lead to more severe conditions such as sepsis. Common pathogens include gram-negative and anaerobic bacteria such as *Escherichia coli, Klebsiella spp., Enterobacter spp., Pseudomonas spp.,* and *Citrobacter spp* [2, 5].

Management relies on prompt biliary drainage and empirical antibiotics while awaiting culture results [5, 6]. However, antibiotic resistance is a growing concern, especially in patients with prior antibiotic exposure [7]. Past studies suggest differences in bacterial patterns between benign and malignant cholangitis, raising the potential for more targeted empirical antibiotic choices [6].

Research comparing these patterns remains limited. While previous studies have described microbiological profiles in acute cholangitis (AC), a direct comparative synthesis of pathogen patterns between benign and malignant biliary obstruction across different culture sources (bile, blood, and biliary stents) remains limited. This review uniquely integrates evidence from multiple clinical settings to identify consistent differences and overlaps in pathogen distribution, which may help refine empiric antimicrobial strategies. Therefore, this systematic review aimed to compare the prevalence and distribution of pathogens identified in bile, blood, and biliary stent cultures between benign and malignant biliary obstruction in patients with cholangitis. Understanding these differences may support more informed empirical antibiotic selection while awaiting microbiological culture results.

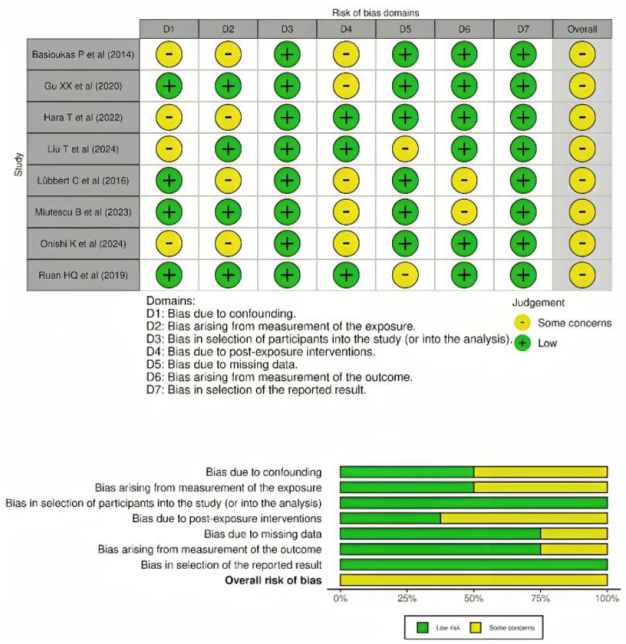

Figure 1. ROBINS-E tool for bias assessment (Source: Created by the authors based on included studies)

MATERIALS AND METHODS

Protocol and Registration

This review was conducted and reported in accordance with the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA). The review was registered with the open science framework with registration DOI: https://doi.org/10.17605/OSF.IO/QNECX.

Information Sources and Search Strategy

Studies were retrieved from multiple electronic databases, including PubMed, Scopus, and Science Direct, for studies published from January 1, 2014, to October 17, 2024. Boolean operators were utilized among the keywords. The search included the following keywords: (“cholangitis” OR “acute cholangitis”) AND (“malignant” OR “malignant disease”) AND (“benign” OR “benign disease”) AND (“bacterial” OR “pathogen” OR “microbial”). The last date the databases were searched was October 17, 2024. Studies published before 2014 were excluded to ensure that the microbiological patterns and antimicrobial resistance profiles reflected contemporary clinical practice, as pathogen distribution and resistance patterns may change over time.

Study Selection

Eligible studies included patients with cholangitis and compared the microbial pattern between the benign and malignant group (at least one of these: positive culture result and microbial species) based on the culture result (blood culture, bile culture, or other forms of culture). A positive culture refers to the microbiological detection of bacterial or fungal growth from bile, blood, or biliary stent samples reported in the included studies. Cohort and case-control studies were included, while case reports, case series, systematic reviews, meta-analyses, and clinical guidelines were excluded. The studies with languages other than English were excluded. The reviewers included studies that were available in full-text form.

Two reviewers independently screened all retrieved records. First, titles and abstracts were assessed for relevance. Potentially eligible articles were then evaluated through full-text review. Disagreements between reviewers were resolved through discussion, and if consensus was not reached, a third reviewer was consulted. Duplicates were excluded from the initial search results, and all potentially relevant study titles and abstracts were screened to assess their eligibility. Any disagreements were settled by discussion or consulting a third reviewer.

Data Collection

After the final screening, the pertinent information from the studies was retrieved and entered into a Google Spreadsheet. All three authors recorded and validated data into columns: author, year, country, study design, sample, sample size, age, comparison, and outcomes of interest, such as comparison of positive culture results and pathogen species between benign and malignant diseases. In the outcome columns, especially in the pathogen species column, authors extracted narrative descriptions of findings from published reports. The disagreements between reviewers were resolved by comprehensive discussions.

Risk of Bias Assessment

The risk of bias in non-randomized studies-of exposures (ROBINS-E) tool was employed by three independent reviewers to assess each study included in this analysis. Any initial disagreements were discussed and resolved among the reviewers, and we opted to exclude studies that received a critical overall bias rating based on the ROBINS-E criteria. Using the ROBINS-E, we evaluated each study for potential bias across several domains: confounding factors, participant selection, exposure classification, deviations from intended exposures, missing data, outcome measurement, and selective reporting of results. For each domain, reviewers assigned low, moderate, high, serious, or critical ratings, following the specific criteria outlined in **Figure 1**.

Domain-level assessments were conducted for each included study. Most studies were judged to have “some concerns” primarily due to potential confounding factors, retrospective study designs, and incomplete reporting of participant characteristics or exposure classification. However, none of the studies included were rated as having a critical risk of bias; therefore, all studies were retained in the qualitative synthesis.

Synthesis Methods

Studies that met the inclusion criteria were tabulated in Google Spreadsheet according to key characteristics, which included study design, patient demographics, the Tokyo guidelines 2018 (TG18) classification for cholangitis, type of obstruction (benign or malignant), type of microbiological culture made, whether there was growth of culture, and the bacterial pathogens identified. In cases where summary measures or relevant information were unavailable, attempts were made to contact the authors for clarification. Studies with unresolvable missing data were excluded from relevant analyses. The results from individual studies were summarized and presented in tables, categorizing the bacterial patterns observed in both benign and malignant obstruction groups. A qualitative approach was employed to synthesize the data, focusing on identifying and describing patterns in bacterial

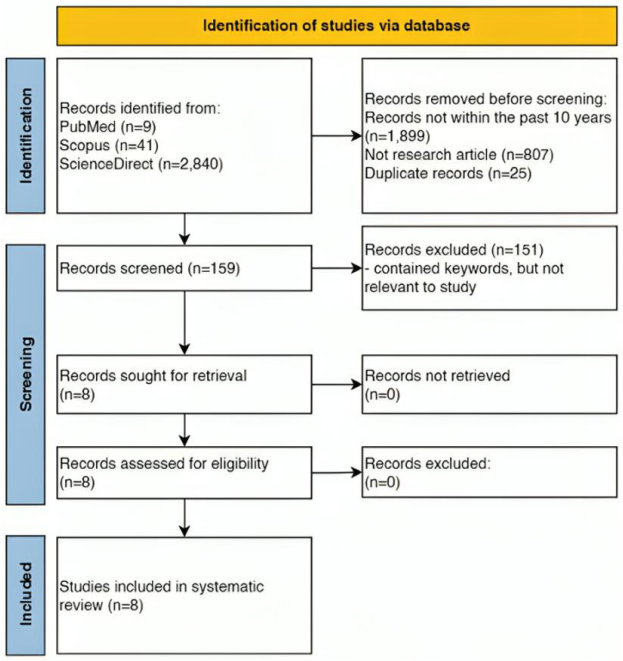

Figure 2. PRISMA flowchart of study selection (Source: Created by the authors based on included studies)

distribution between the two groups. The synthesis focused mainly on a narrative comparison of the different bacterial species identified in each group, with attention to variations in culture methods, diagnostic criteria, and study demographics.

A quantitative meta-analysis was not performed because of substantial heterogeneity among the included studies. The studies differed in terms of study design, patient populations, types of cultures analyzed (bile, blood, or biliary stent cultures), microbiological reporting methods, and outcome definitions. Due to this variability, a narrative synthesis approach was considered more appropriate to summarize the findings.

RESULTS

Study Characteristics

The database search yielded 2,890 records (PubMed: 9, Scopus: 41, ScienceDirect: 2,840). After removing 1,899 records published over 10 years ago, 807 non-research articles, and 25 duplicates, 159 records were screened. Of these, 151 were excluded for lack of relevance, leaving eight records for eligibility assessment. No further exclusions were made, resulting in 8 studies included in this systematic review. Of the eight studies, six were retrospective cohort studies [1-5], and the remaining two were one prospective cohort studies [6] and one cross-sectional studies [7]. A PRISMA flowchart is presented in **Figure 2**.

Risk of Bias

The risk of bias assessment was conducted by three independent authors using validated tools. For analyzing the quality of included studies we used a tool from Cochrane collaborations, namely ROBINS-E, which contains a methodological assessment of 7 domains:

(a) D1: bias due to confounding,

(b) D2: bias arising from measurement of the exposure,

(c) D3: bias in selection of participants into the study (or into the analysis),

(d) D4: bias due to post-exposure interventions,

(e) D5: bias due to missing data,

(f) D6: bias arising from measurement of the outcome, and

(g) D7: bias in selection of the reported result.

The result is shown in **Figure 1**. The authors' evaluations were categorized as "low" or "some concerns" of bias. Based on the bias assessment, all included studies were remarked with some concerns.

Results of Individual Studies

Demographic characteristics of subjects

In total, 3,575 cholangitis patients participated in 8 studies included in this systematic review. Five studies were conducted in Asia, three in China, and two in Japan. The other three were conducted in Europe, including Romania, Germany, and Greece. All studies reported the mean and median age of cholangitis patients to be over 55, indicating an older age range (58.4-83.0 years). Four studies [1, 3, 5, 7] indicated that females constituted the majority, while the other four studies [2, 4, 6, 8] reported males as the predominant gender.

Regarding patient condition characteristics, only three studies provided the TG18 classification of cholangitis severity. The studies in [1, 4] reported that grade I was the most prevalent among participants, whereas the study in [2] found that grade II and grade III were more commonly observed. Among the eight studies, only two [2, 6] reported data on total bilirubin and white blood cell (WBC) counts. The study in [2] showed that 21.2% of participants had total bilirubin ≥ 5 mg/dL. Meanwhile, the study in [6] revealed that 12.7% of participants had total bilirubin levels below 1.0 mg/L. The study in [2] showed that 40% of participants had WBC of ≤ 4,000 or ≥ 12,000 cells/mm [3]. Meanwhile, the study in [6] showed 7.05% of their participants had WBC counts ranging from 3,500 to 9,800 cells/mm [3]. The complete study characteristics of each study are stated in **Table 1**.

Table 1. Summary of the studies included in this systematic review

Reference	Location	Population	Age	Male: n (%)	TG18 classification	TB	WBC	BEM	Culture method
Miutescu et al. (2023)	Romania	262 patients diagnosed with AC using TG18 criteria. Patients were included only on their first admission during the data collection period, even if they experienced multiple episodes of AC.	67.6± 14.1 years	128 (48.90)	Grade I: 103/262; 39.3%, grade II: 95/262; 36.3%, grade III: 64/262; 24.4%	N/A	N/A	Endoscopic	Bile culture (n=262) , blood culture (n=141)
Onishi et al. (2024)	Japan	288 patients diagnosed with AC using TG18 criteria (165 with positive culture results).	83 (75-87) years	178 (61.80)	Grade I: 39/165; 23.6%, grade II: 76/165; 46.1%, grade III: 50/165; 30.3%	≥5 mg/dL (35/165; 21.2%)	WBC ≤ 4,000 or ≥ 12,000 cells/mm^3 (66/165; 40%)	Percutaneous, endoscopic, & intraoperative	Bile culture (n=274), blood culture (n=198)

Table 1 (Continued).

Reference	Location	Population	Age	Male: n (%)	TG18 classification	TB	WBC	BEM	Culture method
Liu et al. (2024)	China	317 patients with definite AC and bacteremia diagnosed using TG18 criteria.	62.7 (18-97) years	136 (42.90)	N/A	N/A	N/A	Percutaneous, endoscopic, & intraoperative	Bile culture (n=317)
Hara et al. (2022)	Japan	251 patients diagnosed with AC who underwent biliary drainage.	78 (37-96) years	64 (58.60)	Grade I: 0/109;55.0%, grade II: 32/109;29.4%, grade III: 17/109;15.6%	N/A	N/A	Percutaneous and endoscopic	Bile culture (n=69), blood bulture (n=95) *using sheep blood agar and Columbia agar
Gu et al. (2020)	China	1,339 patients underwent ERCP, percutaneous transhepatic cholangiodrainage, and other biliary surgeries.	62.42± 14.90	653 (48.75)	N/A	N/A	N/A	Percutaneous, endoscopic, & intraoperative	Bile culture (n=1,339)
Ruan et al.(2019)	China	956 patients with biliary or pancreatic disorders who underwent ERCP procedures.	58.4± 15.0 years	586 (61.30)	N/A	N/A	N/A	Endoscopic	Bile culture (n=956)
Lübbert et al. (2016)	Germany	120 patients with biliary strictures who underwent elective or emergency stent exchanges (213 biliary stent cultures).	64 years	75 (62.50)	N/A	<1.0 mg/L (127/213 ;2.7%)	WBC 3,500-9,800 cell/mm^3 (7.05%)	Endoscopic	Biliary stent culture
Basioukas et al. (2014)	Greece	42 patients with biliary stents, some presenting with symptoms of stent occlusion such as AC, recurrent jaundice, or biliary colic accompanied by elevated liver function tests (51 plastic biliary stent cultures).	71 (39-92) years	17 (40.50)	N/A	N/A	N/A	Endoscopic	Biliary stent culture *using blood agar, McConkey agar, and Columbia agar with rabit blood

Note. Age: Mean (standard deviation) or median (range); TB: Total bilirubin; BEM: Bile extraction methods

Table 2. The comparison between benign vs. malignant obstruction in positive growth

Reference	Positive growth (%)		
	Total	Benign	Malignant
Miutescu et al. (2023)	Bile culture: 73.3% (192/262)	Bile culture: 55.7% (107/192)	Bile culture: 44.3% (85/192)
	Blood culture: 31.0% (45/141)	Blood culture: 19.6% (29/138)	Blood culture: 14.2% (16/127)
Onishi et al. (2024)	Bile culture: 57.6% (95/165) of bacteremia patients	N/A	N/A
	Blood culture: 57.3% (165/288) of patients included	N/A	N/A
Liu et al. (2024)	Bile culture: 100% (317/317)	Bile culture: 100% (247/247)	Bile culture: 100% (70/70)
Hara et al. (2022)	Bile culture: 97.1% (67/69)	Bile culture; 100% (28/28)	Bile culture: 95.1% (39/41)
	Blood culture: 51.6% (49/95)	Blood culture; 37.1% (35/95)	Blood culture: 61.6% (60/95)
Gu et al. (2020)	Bile culture: 55.1% (738/1339)	Bile culture: 57.8% (554/959)	Bile culture: 48.4% (184/380)
Ruan et al.(2019)	Bile culture: 38.0% (363/956)	Bile culture: 38.0% (322/847)	Bile culture: 38.0% (41/108)
Lübbert et al. (2016)	Biliary stent culture: 100% (213/213)	Biliary stent culture: 100% (137/137)	Biliary stent culture: 100% (76/76)
Basioukas et al. (2014)	Biliary stent culture: 100% (51/51)	N/A	N/A

Comparison of culture results

Three studies (A, B, and D) conducted bile and blood cultures, while another three (C, E, and F) performed only bile cultures. The remaining two studies (G and H) analysed biliary stent cultures. Only two studies (A and D) compared culture results between benign and malignant cholangitis. It was found that benign cases had a higher rate of positive results than malignant cases in both bile cultures (55.7% vs. 44.3%) and blood cultures (19.6% vs. 14.2%) [1]. In contrast, the study in [4] reported that while benign cases had a higher percentage of positive bile cultures (100% vs. 95.1%), malignant cases showed a greater prevalence of positive blood cultures (61.6% vs. 37.1%) in patients with the second episode of AC. The detailed results are stated in **Table 2**.

Comparison of pathogen species

Across the included studies, several consistent patterns emerged despite variations in study design and population. Gram-negative bacteria, particularly *Escherichia coli* and *Klebsiella pneumoniae*, were the dominant pathogens in both benign and malignant obstruction. However, benign obstruction tended to show higher proportions of typical enteric organisms, while malignant obstruction was more frequently associated with a broader and more heterogeneous microbial profile, including opportunistic pathogens. Based on bile culture findings, it was reported that *Escherichia coli* was significantly more prevalent in bile cultures from patients with benign obstructions (56.1%) compared to malignant obstructions (37.6%) (p = 0.003) [1]. Similarly, it was identified *Escherichia coli* (26.4%), *Enterococcus faecium* (12.8%), *Enterococcus faecalis* (11.0%), *Klebsiella pneumoniae* (10.1%), and *Pseudomonas aeruginosa* (7.7%) as the most frequently detected bacteria in bile cultures from patients with benign conditions [3]. In addition, malignant conditions showed similar but lower rates in bacteria composition. The predominant bacteria were *Escherichia coli* (17.8%), *Enterococcus faecalis* (12.2%), *Enterococcus faecium* (8.9%), *Klebsiella pneumoniae* (7.8%), and *Pseudomonas aeruginosa* (4.4%), though no significant differences were observed between the groups [3]. In the study in [4], *Enterococcus* spp. emerged as the most common pathogens in malignant and benign AC cases [4]. It was reported that in patients with benign diseases (n = 554), the most prevalent strains were *E. coli*

(41.7%), *P. aeruginosa* (9.93%), *K. pneumoniae* (9.93%), and *E. faecium* (7.04%). Among patients with malignant diseases (n = 184), *E. coli* (44.02%), *K. pneumoniae* (16.30%), *P. aeruginosa* (10.33%), and *E. faecium* (6.52%) were the dominant strains [5]. Although the prevalence of these strains was generally similar between the groups, *K. pneumoniae* was significantly more common in benign conditions (55 vs. 30, p = 0.019) [5]. Conversely, it was found that *K. pneumoniae* strains were more frequently identified in malignant diseases than benign ones (24.4% vs. 11.8%, p = 0.046) [8]. However, there were no significant differences in the prevalence of *E. coli* (58.7% vs. 51.2%, p = 0.456), *Enterococcus* spp. (10.9% vs. 19.5%, p = 0.175), or fungi (5.0% vs. 7.3%, p = 0.792) between the two groups [8].

Based on blood culture results, it was reported no significant differences in the bacterial species identified between benign and malignant obstructions (p > 0.05) [1]. It was observed that cefmetazole-susceptible bacteria, including *Streptococcus* species, *E. coli*, and *Klebsiella* species, were more commonly isolated from blood cultures in patients with AC and bile duct stones (benign obstruction) (86.7%, 111/128) compared to those with malignant biliary obstruction (54.3%, 38/70) [2]. The study in [4] noted that *Streptococcus* spp. were more frequently isolated in blood cultures from patients with malignant tumors than those with benign conditions (10.2% vs. 0%, p = 0.043). Additionally, their findings indicated that patients with AC caused by malignant tumors had a higher prevalence of *Klebsiella* bacteremia (26.6% vs. 8.5%, p = 0.036) but a lower prevalence of *Aeromonas hydrophile* bacteremia (0.0% vs. 8.5%, p = 0.036) [4].

It was reported that in biliary stent cultures, there were statistically significant differences in colonization between malignant and benign biliary strictures for *Candida spp.* (67.1% vs. 49.6%, p = 0.015), viridans-group *streptococci* (40.8% vs. 26.3%, p = 0.032), and *Pseudomonas aeruginosa* (1.3% vs. 8.8%, p = 0.035) [6]. However, it was found that the most common organisms in biliary stent culture were *Enterococcus sp.* (74%), *E. coli* (62%), and *Klebsiella sp.* (58%). *E. coli* was more frequently identified in benign diseases compared to malignant diseases (78% vs. 43%, p < 0.05) [7]. The detailed results are presented in **Table 3**.

Table 3. The comparison of pathogen species between benign vs. malignant obstruction

Reference	Pathogen species		
	Total	**Benign**	**Malignant**
Miutescu et al. (2023)	**Bile culture (n = 192):** *Escherichia coli* (47.9%), *Klebsiella spp.* (26.6%), *Pseudomonas spp.* (13%), *Enterobacter spp.* (5.2%), *Acinetobacter spp.* (3.1%), *Citrobacter spp.* (5.7%), *Enterococcus spp.* (21.6%), *Streptococcus spp.* (3.1%), *Staphylococcus spp* (1.6%).	**Bile culture (n = 107):** *Escherichia coli* (56.1%), *Klebsiella spp.* (24.3%), *Pseudomonas spp.* (10.3%), *Enterobacter spp.* (5.6%), *Acinetobacter spp.* (0.9%), *Citrobacter spp.* (4.7%), *Enterococcus spp.* (18.7%), *Streptococcus spp.* (4.8%), *Staphylococcus spp.* (0.9%).	**Bile culture (n = 85):** *Escherichia coli* (37.6%), *Klebsiella spp.* (29.4%), *Pseudomonas spp.* (14.1%), *Enterobacter spp.* (4.7%), *Acinetobacter spp.* (5.9%), *Citrobacter spp.* (7.1%), *Enterococcus spp.* (24.7%), *Streptococcus spp.* (1.2%), *Staphylococcus spp.* (2.4%).
	Blood culture (n = 45): *Escherichia coli (31.3%), Klebsiella spp.* (25.0%), *Pseudomonas spp.* (6.3%), *Enterobacter spp.* (6.3%), *Acinetobacter spp.* (6.3%), *Citrobacter spp.* (0.0%), *Enterococcus spp.* (6.3%), *Staphylococcus spp.* (18.8%), *Streptococcus spp.* (0.0%).	**Blood culture (n = 29):** *Escherichia coli* (55.2%), *Klebsiella spp.* (17.2%), *Pseudomonas spp.* (3.4%), *Enterobacter spp.* (10.3%), *Acinetobacter spp.* (0.0%), *Citrobacter spp.* (3.4%), *Enterococcus spp.* (3.4%), *Streptococcus spp.* (3.4%), *Staphylococcus spp. (*3.4%).	**Blood culture (n = 16):** *Escherichia coli* (31.3%), *Klebsiella spp.* (25.0%), *Pseudomonas spp.* (6.3%), *Enterobacter spp.* (6.3%), *Acinetobacter spp.* (6.3%), *Citrobacter spp.* (0.0%), *Enterococcus spp.* (6.3%), *Streptococcus spp.* (0.0%), *Staphylococcus spp.* (18.8%).
Onishi et al. (2024)	**Bile culture (n = 274):** *Escherichia coli* (15.7%), *Klebsiella spp.* (21.5%), *Enterococcus spp.* (23.7%), *Streptococcus spp.* (10.9%), *Citrobacter spp.* (3.3%), *Pseudomonas aeruginosa* (3.6%), *Enterobacter spp.* (7.3%), *Bacteroides spp.* (1.1%), *Staphylococcus spp.* (2.2%).	**Bile culture (n = 142):** *Escherichia coli* (23.2%), *Klebsiella spp.* (23.9%), *Enterococcus spp.* (21.1%), *Streptococcus spp.* (8.5%), *Citrobacter spp.* (2.8%), *Pseudomonas aeruginosa* (1.4%), *Enterobacter spp.* (2.8%), *Bacteroides spp.* (1.4%), *Staphylococcus spp.* (2.8%).	**Bile culture (n = 132):** *Escherichia coli* (7.6%), *Klebsiella spp.* (18.9%), *Enterococcus spp.* (26.5%), *Streptococcus spp.* (13.6%), *Citrobacter spp.* (3.8%), *Pseudomonas aeruginosa* (6.1%), *Enterobacter spp.* (12.1%), *Bacteroides spp.* (0.8%), *Staphylococcus spp.* (1.5%).
	Blood culture (n = 198): *Escherichia coli* (41.4%), *Klebsiella spp.* (27.8%), *Enterococcus spp.* (10.1%), *Streptococcus spp.* (2.5%), *Citrobacter spp.* (1.5%), *Pseudomonas aeruginosa* (3.0%), *Enterobacter spp.* (9.1%), *Bacteroides spp.* (3.0%), *Staphylococcus spp.* (0.0%).	**Blood culture (n = 128):** *Escherichia coli* (49.2%), *Klebsiella spp.* (28.9%), *Enterococcus spp.* (7.0%), *Streptococcus spp.* (3.1%), *Citrobacter spp.* (0.0%), *Pseudomonas aeruginosa* (0.8%), *Enterobacter spp.* (3.9%), *Bacteroides spp.* (4.7%), *Staphylococcus spp.* (0.0%).	**Blood culture (n = 70):** *Escherichia coli* (27.1%), *Klebsiella spp.* (25.7%), *Enterococcus spp.* (15.7%), *Streptococcus spp.* (1.4%), *Citrobacter spp.* (4.3%), *Pseudomonas aeruginosa* (7.1%), *Enterobacter spp.* (18.6%), *Bacteroides spp.* (0.0%), *Staphylococcus spp.* (0%).
Liu et al. (2024)	**Bile culture (n = 317):** *Escherichia coli* (24.6%), *Klebsiella pneumoniae* (9.6%), *Pseudomonas aeruginosa* (7.0%), *Enterococcus faecium* (11.9%), *Enterococcus faecalis* (11.2%), *Enterococcus casseliflavus* (4.2%).	**Bile culture (n = 247):** *Escherichia coli* (26.4%), *Klebsiella pneumoniae* (10.1%), *Pseudomonas aeruginosa* (7.7%), *Enterococcus faecium* (12.8%), *Enterococcus faecalis* (11.0%), *Enterococcus casseliflavus* (4.5%).	**Bile culture (n = 70):** *Escherichia coli* (17.8%), *Klebsiella pneumoniae* (7.8%), *Pseudomonas aeruginosa* (4.4%), *Enterococcus faecium* (8.9%), *Enterococcus faecalis* (12.2%), *Enterococcus casseliflavus* (3.3%).
Hara et al. (2022)	*N/A*	**Bile culture (n = 28):** *Enterococcus spp.* (53.6%), *Klebsiella spp.* (28.6%), *Escherichia coli* (21.4%), *Enterobacter spp.* (25.0%), *Citrobacter spp.* (7.1%), *Clostridium spp.* (10.7%), *E. coli ESBL* (3.6%), *Serratia mercescenes* (3.6%),	**Bile culture (n = 39):** *Enterococcus spp.* (43.9%), *Klebsiella spp.* (21.9%), *Escherichia coli* (19.5%), *E. coli ESBL* (2.4%), *Streptococcus spp.* (9.7%), *Enterobacter spp.* (21.9%), *Aeromonas hydrophile* (4.8%), *Pseudomonas*

Table 3. The comparison of pathogen species between benign vs. malignant obstruction

Reference	Pathogen species		
	Total	**Benign**	**Malignant**
		Pseudomonas aeruginosa (3.6%), *Aeromonas hydrophilia* (7.1%), *Clostridium spp.* (10.7%).	*aeruginosa* (4.8%), *Clostridium spp.* (2.4%), *Staphylococcus spp.* (4.8%), *Citrobacter spp.* (2.4%), *Serratia mercescenes* (2.4%).
	N/A	**Blood culture (n = 35):** *Escherichia coli* (11.4%), *Escherichia coli ESBL* (2,8%), *Klebsiella spp.* (8,5%), *Enterobacter spp.* (2,8%), *Pseudomonas aeruginosa* (2,8%), *Enterococcus spp.* (8.5%), *Aeromonas hydrophile* (8.5%).	**Blood culture (n = 60):** *Klebsiella* spp. (26.6%), *Escherichia coli* (10.0%), *Enterobacter* spp. (15.0%), *Enterococcus* spp. (8.3%), *Streptococcus* spp. (5.0%), *Pseudomonas aeruginosa* (1.6%), *Staphylococcus* spp. (1.6%), *Escherichia coli* ESBL (1.6%), *Serratia marcescens* (3.3%).
Gu et al. (2020)	**Bile culture (n = 738):** *Escherichia coli* (42.28%), *Enterococcus faecium* (6.91%), *Klebsiella pneumoniae* (11.52%), *Pseudomonas aeruginosa* (10.03%), *Proteus mirabilis* (2.85%), *Staphylococcus sp.* (8.27%).	**Bile culture (n = 554):** *Escherichia coli* (41.7%), *Enterococcus faecium* (7.04%), *Klebsiella pneumoniae* (9.93%), *Pseudomonas aeruginosa* (9.93%), *Proteus mirabilis* (2.53%), *Staphylococcus sp.* (7.22%).	**Bile culture (n = 184):** *Escherichia coli* (44.02%), *Enterococcus faecium* (6.52%), *Klebsiella pneumoniae* (16.30%), *Pseudomonas aeruginosa* (10.33%), *Proteus mirabilis* (3.8%), *Staphylococcus* sp. (11.41%).
Ruan et al.(2019)	**Bile culture (n = 363):** *Escherichia coli* (57.9%), *Klebsiella spp.* (13.2%), *Enterococcus spp.* (11.8%), *and* Fungi (*Candida albicans and Candida tropicalis*) (5.2%).	**Bile culture (n = 322):** *Escherichia coli* (58.7%), *Klebsiella spp.* (11.8%), *Enterococcus spp.* (10.9%), *and* Fungi (*Candida albicans and Candida tropicalis*) (5.0%).	**Bile culture (n = 41):** *Escherichia coli* (51.2%), *Klebsiella* spp. (24.4%), *Enterococcus* spp. (19.5%), and Fungi (*Candida albicans* and *Candida tropicalis*) (7.3%).
Lübbert et al. (2016)	**Biliary stent culture (n = 213):** *Enterococci* (78.95%), *Candida spp.* (58.35%), *Enterobacteriaceae* (73.7%), *Streptococci* (33.5%), *Staphylococci* (11.7%), *Pseudomonas spp.* (5.05%), *Anaerobes* (22.8%).	**Biliary stent culture (n = 137):** *Enterococci* (80.3%), *Candida spp.* (49.6%), *Enterobacteriaceae* (73.7%), *Streptococci* (26.3%), *Staphylococci* (10.2%), *Pseudomonas spp.* (8.8%), *Anaerobes* (21.9%).	**Biliary stent culture (n = 76):** *Enterococci* (77.6%), *Candida* spp. (67.1%), Enterobacteriaceae (73.7%), *Streptococci* (40.8%), *Staphylococci* (13.2%), *Pseudomonas* spp. (1.3%), Anaerobes (23.7%).
Basioukas et al. (2014)	**Biliary stent culture (n = 51):** *Enterococcus spp., Klebsiella spp., Pseudomonas spp., Candida spp., Escherichia coli,* and *Enterobacter spp.*	**Biliary stent culture (n = 28):** *Enterococcus spp.* (64%), *Klebsiella spp.* (67%), *Pseudomonas spp.* (10%), *Candida spp.* (25%), *Escherichia coli* (78%), and *Enterobacter spp.* (35%).	**Biliary stent culture (n=23):** *Enterococcus spp.* (82%), *Klebsiella spp.* (47%), *Pseudomonas spp.* (21%), *Candida spp.* (34%), *Escherichia coli* (43%), and *Enterobacter spp.* (17%).

Overall, although individual studies reported varying proportions, the general trend suggests substantial overlap in core pathogens, with subtle shifts toward more diverse and potentially resistant organisms in malignant obstruction.

DISCUSSION

Summary of Main Findings

Across multiple studies comparing benign and malignant obstructions, variations in culture results and pathogen prevalence were identified. It was found to have higher positive rates in benign cases [1, 4, 5]. Benign obstruction causes partial or intermittent obstructions that promote bile stasis and allow bacteria to ascend into the bile duct system. This obstruction also creates an environment conducive to bacterial colonization [1, 4]. In contrast, malignant obstruction typically occurs progressively. This complete obstruction limits bacterial ascending and reduces bile flow to the intestine, which leads to gut dysbiosis, disrupts gut tight junctions, and promotes bacterial translocation [1, 9]. Another reason is biofilm formation, which is common in benign conditions and allows bacteria to adhere to stones or duct walls, increasing culture positivity. In contrast, malignant obstructions are less likely to support such biofilm formation, reducing the chance of positive cultures [10].

Regarding blood culture results, the study in [1] found a higher prevalence of positive cultures in benign cases. In contrast, the study in [4], studying patients with recurrent AC, reported the opposite trend, with malignant cases showing greater positivity. Malignant cholangitis tends to have higher rates of positive blood cultures due to its more severe and prolonged obstruction. The complete bile stasis increases the risk of bacterial translocation into the bloodstream through gut dysbiosis and mucosa damage. The tumor microenvironment also compromises local immune responses, facilitating systemic infections [11]. Additionally, delayed diagnosis and treatment in malignant cases often allow sepsis to develop [12]. Thus, malignant cases with positive blood cultures tend to have more severe infections than benign ones. However, these results may vary across studies.

Bile culture studies revealed that *Escherichia coli* was more prevalent in benign obstructions, as reported by [1, 5]. Meanwhile, the study in [4] noted that *Enterococcus* spp. were the most common pathogens in both benign and malignant AC. On the other hand, *Klebsiella pneumoniae* showed mixed results, being more common in benign cases according to [5], but more prevalent in malignant cases, as reported by [8], and they found no significant differences in *E. coli*, *Enterococcus* spp., or fungi prevalence between the groups. However, contradictory findings were observed across studies. For example, it was reported that there was a higher prevalence of *Klebsiella pneumoniae* in benign obstruction [5], whereas it was found to have a higher prevalence in malignant cases [8].

These discrepancies may be explained by differences in study populations, regional microbiological patterns, and variations in clinical settings or previous interventions. Those results showed that in both benign and malignant cases, Gram-negative bacteria are common pathogens to be found. Many Gram-negative bacteria are part of the normal gastrointestinal tract flora, which can translocate into the biliary system, especially in cases of biliary obstruction or infection [13]. The increased pressure in the biliary ducts due to obstruction will facilitate the translocation [14]. Obstruction leads to bile stasis, reducing bile flow and impairing its natural flushing and antimicrobial effects, which diminishes its typical antibacterial properties and creates a conducive environment for bacterial growth; this allows Gram-negative bacteria, which have lipopolysaccharide-rich outer membranes that may offer an advantage in the lipid-rich bile, to colonize more easily [15]. The high isolation rate of enterococci in [4] could be attributed to a history of biliary interventions. It has been reported that *Enterococcus* spp. were the predominant pathogens isolated from biofilms in biliary stents during elective or emergency stent exchange [4].

E. coli and *K. pneumoniae* were significantly found in benign disease due to several factors, such as they are part of the normal gut flora and can ascend into the biliary tract from the duodenum, especially when there is an intermittent obstruction that allows for retrograde infection [13, 14]. In contrast, complex tumor growth in malignant cholangitis alters the microbial environment, often creating anaerobic conditions. Patients with malignant biliary obstruction show higher rates of antibiotic-resistant bacteria, including fewer common strains in benign cases [15, 16]. Therefore, *E. coli* or *K. pneumoniae* will be less common, though variation may exist, like the study in [8]. These findings are important as they can help guide appropriate empirical antibiotic therapy for patients with AC, according to the underlying cause of their biliary obstruction [1]. Moreover, identifying the most frequently encountered microorganisms in bile culture, such as *E. coli, K. pneumoniae*, or *Enterococcus spp.,* can help develop targeted therapies.

According to blood cultures, The study in [2] found that benign obstructions were more likely to yield cefmetazole-susceptible bacteria, such as *Streptococcus* spp., *E. coli*, and *Klebsiella* spp. In contrast, the study in [4] reported that malignant cases had higher rates of *Klebsiella* bacteremia but lower *Aeromonas hydrophila* bacteremia. Those results represent how the pathogen pattern of benign vs. malignant cholangitis varies across studies. Bacteria can be found in blood because of a mechanism called portal translocation. It occurs when the intestinal barrier is compromised, allowing gut bacteria, particularly gram-negative species like *E. coli* and *Klebsiella spp.*, to enter the portal circulation [17]. *Streptococcus spp.* was reportedly found in several studies on cholangitis patients, like the case report in [18] and case series in [19]. On the other hand, malignant cases with structural and immune dysfunction raises the risk of bacteremia, especially from *Klebsiella pneumoniae*, a virulent that can produce extended-spectrum beta-lactamases. *Klebsiella pneumoniae* bacteremia is associated with higher mortality and complications. Therefore, malignant cholangitis patients often require urgent interventions like ERCP [20-22].

In biliary stent cultures, it was reported that *Candida spp.* and viridans-group *streptococci* were more common in malignant cases [6]. Meanwhile, *Pseudomonas aeruginosa* was more common in benign cases. It was shown that *E. coli* was more common in benign obstruction [7]. Immune suppression in malignancy may promote the overgrowth of fungi like *Candida spp.* and the colonization of viridans-group *streptococci* [11]. Besides, malignant obstructions more often involve highly invasive interventions, which carry a high risk of introducing these pathogens [3]. Conversely, benign obstructions, such as those from gallstones or strictures, are associated with less severe bile stasis and immune suppression, favoring the growth of common bacteria such as *E. coli* [15]. The higher prevalence of *Pseudomonas aeruginosa* in benign cases may be due to nosocomial infection after procedures such as ERCP or stent placement, which introduce resistant gram-negative bacteria [3, 6]. Overall, while certain pathogens exhibited distinct patterns, significant overlaps were observed between benign and malignant conditions.

Clinical Implication

Based on findings reported in various studies, benign cholangitis tended to show a higher prevalence of gram-negative bacteria, such as *E. coli*, *Klebsiella*, and *Enterococcus* spp., in bile cultures, blood cultures, and biliary stent cultures. Meanwhile, malignant cholangitis exhibits more diverse and often resistant pathogens, including *Klebsiella*, *Candida* spp., and *Streptococcus* spp. These findings may provide supportive information for empirical antibiotic selection; however, treatment decisions should still consider local antimicrobial resistance patterns, patient characteristics, and current clinical guidelines. The current guidelines for AC address Gram-negative bacteria first, but according to the clinical manifestations and severity of the disease, Gram-positive infections also need to be considered [23].

In benign cholangitis, the emphasis is on common Gram-negative pathogens, and recommended antibiotics include cephalosporin-based and penicillin-based antibiotics. For example, piperacillin/tazobactam yields more than 80% efficacy in biliary infections [24], ampicillin with an aminoglycoside, which has a historical record of effectiveness, and third-generation cephalosporins because they are very effective against Enterobacteriaceae [25]. On the other hand, malignant cholangitis requires addressing multidrug-resistant organisms. The piperacillin-based antibiotic is, again, a reliable choice due to its broad-spectrum activity [24], while carbapenems are reserved for severe cases or suspected resistance [1, 25]. Fluoroquinolones and monobactams can also be considered for benign and malignant cases based on local resistance patterns and patient history [26].

Strengths and Limitations

This systematic review offers several strengths. It provides an up-to-date comparison of bacterial patterns in benign and malignant cholangitis by analyzing studies published between 2014 and 2024. Including cohort and cross-sectional studies from different regions and examining various culture types (bile, blood, and biliary stent cultures) helps present a comprehensive view of pathogen distribution across diverse clinical settings.

Nevertheless, there are limitations, as many studies were retrospective in nature and did not fully adjust for potential confounders such as prior antibiotic exposure, comorbidities, or the severity of cholangitis at baseline. Some studies included patients who had undergone prior interventions such as ERCP or stent placement, which may influence bacterial

profiles. The inclusion of biliary stent cultures in two studies could affect generalizability. Geographic and demographic differences, as well as variations in sample collection and culture methods, add heterogeneity that may limit the ability to draw consistent conclusions across populations. Another limitation is that only a few included studies reported cholangitis severity based on the TG18 classification. Differences in disease severity may influence microbiological findings and culture positivity rates.

CONCLUSIONS

In conclusion, benign and malignant cholangitis demonstrate partially distinct microbiological patterns, although substantial overlap exists between the two conditions. Gram-negative bacteria such as Escherichia coli and Klebsiella species remain the most frequently isolated pathogens in both groups. Malignant obstruction may be associated with a broader range of organisms, including opportunistic pathogens such as Candida species. These findings highlight the importance of considering the underlying cause of biliary obstruction when interpreting microbiological results.

This systematic review provides a comparative synthesis of pathogen patterns across benign and malignant biliary obstruction, highlighting both shared core microbiota and clinically relevant differences in pathogen distribution. These findings may support more tailored empiric antibiotic selection based on the underlying etiology of obstruction. Future studies are needed to further clarify these differences and integrate microbiological patterns with clinical severity and antimicrobial resistance to optimize treatment strategies.

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