ORIGINAL ARTICLE

Multifactorial Analysis of Biliary Infection in Patients with Hepato-pancreatico-biliary and Associated Intraabdominal Malignancies Admitted to a Teaching Hospital in Northern India

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Abstract

Background: Blockage of the biliary tract is commonly caused by malignant tumors leading to deranged liver function, responsible for poor prognosis and a high rate of *bacteriobilia* leading to mortality.

Material and methods: We collected retrospective data from the hospital information system and laboratory registers in our department from 2021 to 2022 to evaluate biliary infections in patients with hepato-pancreatico-biliary and associated intraabdominal malignancies.

Result: A total of 118 (118/234, 50.43%) patients' bile samples were estimated in this study. Patients' average age was 53.02 ± 13.49 years, with more patients below the age of 65 years among those with infected bile samples. Eight patients were infected by 102 pathogenic microorganisms. The most common pathogenic microorganism responsible for biliary infection in patients with abdominal malignancies was *Escherichia coli* (38/102, 37.25%) followed by *Klebsiella pneumoniae* (21/102, 20.59%) and *Enterococcus* spp. (18/102, 17.65%). Underlying comorbidities like diabetes mellitus, hypothyroidism, hypoproteinemia, chronic liver disease, immunosuppression, chronic kidney disease, increased hospital stay, admission to the intensive care unit (ICU), and presence of percutaneous transhepatic biliary drain were statistically significant risk factors for isolation of multidrug-resistant pathogenic bacteria.

Conclusion: Our study guided physicians in identifying the associated demographic characteristics, risk factors, and the spectrum of pathogens responsible for *bacteriobilia* in abdominal cancer patients along with the antibiotic resistance pattern among these isolates and better selection of antibiotics and antibiotic prophylaxis for patients at risk of developing biliary tract infections with multidrug-resistant pathogens.

Keywords: Antibiotic prophylaxis, Bile, Biliary tract, Cholelithiasis, Chronic kidney disease.

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Highlights

- It determines the annual incidence of patients undergoing surgical procedures for hepato-pancreatico-biliary malignancies and it also identifies the associated demographic characteristics and risk factors.
- Identification and resistance of drug of the pathogenic microorganisms isolated from biliary infections in hepatobiliary malignancy patients.

Background

Malignant obstruction of the biliary tract is commonly caused by malignant tumors leading to deranged liver function, which can be attributed to poor prognosis.[1,2] The two major causes of malignant biliary obstruction are pancreatic adenocarcinoma which accounts for 70% of cases of malignant biliary obstruction and cholangiocarcinoma. A majority (~80%) of pancreatic adenocarcinoma is deemed unresectable and needs palliative drainage.[3,4] Biliary tract Infection is attributable to severe complications and morbidity. The increased mortality rate in patients with infected biliary secretions makes timely diagnosis and treatment of biliary tract infection imperative.[5,6]

Neoplasms contributed to 9.6 million deaths and 121.2 per 100,000 age-standardized death rates (ASDRs) "according to the global burden of diseases (GBD), injuries, and risk factors study 2017". Overall mortality in gastrointestinal cancers accounted for 36.2 percent of neoplasms-related deaths.[7] While the most recent estimates recorded in literature from the According to the global burden of disease research, there were 139,500 fatalities from biliary tract cancer in 2013, up from an estimated 115,400 deaths in 1990, or ASDRs of 2.3 per 100,000 and 3.4 per 100,000, respectively.[8] The incidence of biliary tract cancers (mainly gallbladder cancer) in North India is 10–22 per 100,000 population, with a female preponderance, and is similar to other high-incidence nations like South America.[9]

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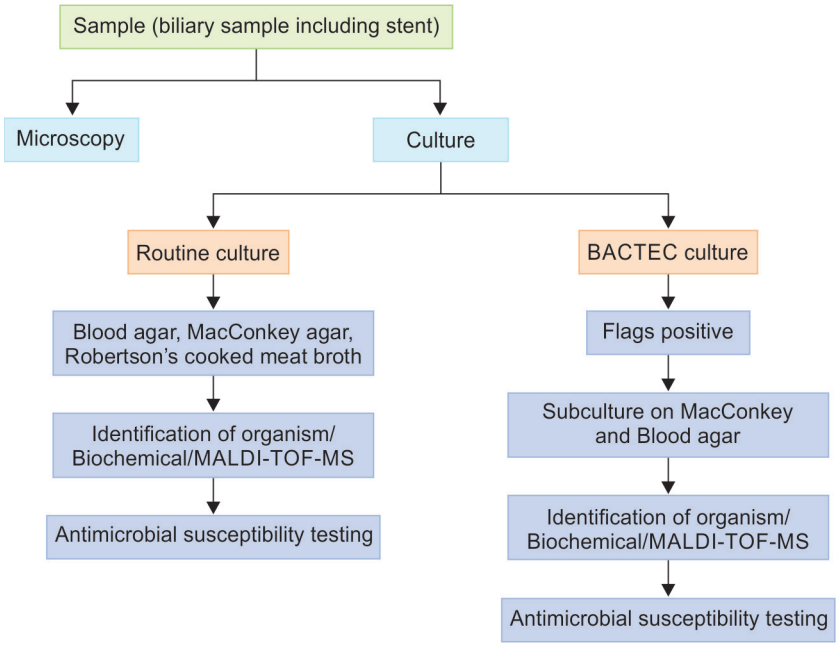
Flowchart 1: Flowchart of the workflow followed in our laboratory



Rationale for Investigation

Insufficient research has been done on patients with malignant biliary obstruction. Few studies have been done that had reported the emerging incidence of multidrug-resistant bacteria, while the presence of enteric bacteria in biliary secretions reports a negative prognostic impact on liver transplants failing the procedure.[10–13]

Objectives

We aimed to determine the annual incidence of patients undergoing surgical procedures for hepato-pancreatico-biliary malignancies at a Tertiary Care Center.

The objectives of this study include:

- Identification of the risk factors and underlying comorbidities in hepatobiliary cancer and associated cancer patients who developed infections and
- Identification and drug resistance of the pathogenic microorganisms isolated from biliary infections in hepatobiliary malignancy patients.

Material and Methods

Study Design

We retrospectively performed this study in the Microbiology Department at a University Hospital in Northern India from July 2021 to July 2022 for 1 year. Our patient group included all adults admitted to the post-operative ward of the Department of Surgical Gastroenterology who underwent surgical procedures related to the biliary tract and associated organ systems.

Setting

This study was done in the Department of Microbiology in the Trauma Center of a University Hospital in Northern India from December 2018 to September 2022. Our study cohort included patients who underwent intraabdominal surgery and were further diagnosed with hepatic-pancreaticobiliary cancers. The institute ethics committee approved this study (2021-48-EMP-EXP dated 29/11/2021). All procedures were carried out in conformity with the 1975 Helsinki Declaration and the institutional or regional relevant committee on human experimentation's ethical requirements. Informed consent was waived off as there was no intervention and no privacy data were obtained.

Participants

The study included all patients who underwent intraabdominal surgery and were further diagnosed with hepatic-pancreaticobiliary cancers.

Inclusion Criteria

All bile samples from a patient undergoing intraabdominal surgery were collected and sent to the laboratory within two hours of the procedure.

Exclusion Criteria

All skin contaminants and commensals were excluded from the study while analyzing the infective microorganisms. All samples that were not labeled properly were also excluded.

Variables

All clinical data of hepato-pancreatico-biliary cancer patients extracted from the hospital's information system were reviewed for underlying comorbidities, risk factors and length of hospital stay. A total of 234 bile samples were contained in our study and processed according to laboratory protocol. Flowchart 1 explains the flow of sample processing performed at our laboratory. Initially, a Grams' stained smear was prepared for all the samples, and Mac Conkey Agar and Blood agar plates were inoculated and further incubated for 48 hours at 37°C. Microscopic features, characteristics of the colony obtained on culture plates, and biochemical tests were used to identify and characterize the bacterial isolates.[10] Antibiotic discs containing Amikacin (30 µg), Ampicillin (10 µg), Ampicillin-Sulbactam (10/10 µg), Aztreonam (30 µg), Ceftazidime

(30 µg), Ceftriaxone (30 µg), Cefoperazone-sulbactam (75/10 µg), Ciprofloxacin (5 µg), Cefoxitin (30 µg), Clindamycin (2 µg), Doxycycline (10 µg), Ertapenem (10 µg), Gentamicin (10 µg), Erythromycin (15 µg), Imipenem (10 µg), Levofloxacin (5 µg), Linezolid (30 µg), Meropenem (30 µg), Minocycline (30 µg), Tigecycline (15 µg), Trimethoprim-sulphamethoxazole (1.25/23.75 µg), Teicoplanin (30 µg), Piperacillin-tazobactam (100/10 µg), Vancomycin (30 µg) and Colistin (0.016–256 µg). Test strips of epsilometeric were procured from the company BioMéreux and were used using the instructions of the manufacturer. Sensitivity testing of antibiotics was performed using Kirby Bauer's disc diffusion method and Epsilometeric strip test, in compliance with the norms of the Laboratory and Clinical and Laboratory Standards Institute (CLSI).[11] Clinical and Laboratory Standards Institute guidelines were used to categorize the antibiotics as sensitive, intermediate, and resistant.[11] A record of all the diagnostic parameters was extracted from the hospital information system.

Bias

Most of the information in our study was attained from the electronic records and ward register so a possibility of data bias was strongly suspected due to the lack of necessary information maintained in records.

Study Size

The sample size was arrived at by analyzing the culture results of bile samples from the laboratory registers and electronic records of 4 years.

Quantitative Variables

Most of the quantitative information, including patient ages, was gathered through the hospital's information system. The length of intensive care unit (ICU) stays and admission were mentioned in the electronic records. The electronic records included information about the ICU admission and stay length. From the day of the patient's admittance to the day of discharge, the length of our patients' hospital stays was calculated.

Statistical Methods

The statistical data for our study was performed by observing frequencies. Quantitative variables were expressed as mean and standard deviation (SD). In the analysis of risk factors for multidrug resistance (MDR), the comparison between groups for categorical variables was estimated by using χ^2 tests. The results were presented as 95% confidence interval (CIs). Statistical analysis was performed using the software program IBM SPSS Statistics version 20.0 (SPSS Inc.), with $p < 0.05$ considered statistically significant.

Result

Participants

A total of 234 patients underwent a surgical procedure in the Department of Surgical Gastroenterology. Of the 234 patients, 118 (118/234, 50.43%) underwent intraabdominal surgeries for hepatic-pancreaticobiliary malignancies.

Descriptive Data

The mean age of 53.02 ± 13.49 years of patients with a significant number of patients below the age of 65 years underwent surgical procedures for abdominal malignancies at this center (Table 1). Although a female predominance (143/234, 61.11%) was observed in patients with biliary infections, no gender predominance was observed in patients with malignancies.

The most common causes of biliary obstruction observed in our subgroup of patients suffering from abdominal malignancies include indwelling biliary catheters (95/118, 80.51%) followed by biliary-enteric anastomosis (77/118, 65.25%) and cholecystitis (46/118, 38.98%) as described in Table 1. While all causes of biliary

Table 1: Demographic characteristics of patients and risk factors for biliary infections in patients with underlying hepatico-pancreatico-biliary malignancies who underwent surgery and those with no hepatico-pancreatico-biliary malignancies (*N* = 234)

Observational parameters	*Total bile samples (n = 234)*	*With underlying hepatobiliary malignancies who underwent surgery (n = 118)*	*Without underlying hepatobiliary malignancies (n = 116)*	*p-value*	*Confidence interval (95% CI)*
Gender					
Male	91 (38.89%)	63 (53.39%)	28 (24.14%)	<0.001*	1.21–1.40
Female	143 (61.11%)	55 (46.61%)	88 (75.86%)	<0.001*	1.53–1.69
Age					
<65 years	201 (85.89%)	89 (75.42%)	112 (96.55%)	<0.001*	1.49–1.62
≥65 years	33 (14.10%)	29 (24.58%)	4 (3.45%)	<0.001*	1.00–1.24
Causes of obstruction					
Biliovascular injury	45 (19.23%)	3 (2.54%)	42 (36.20%)	<0.001*	1.95–2.00
Benign stricture	56 (23.93%)	4 (3.39%)	52 (44.83%)	<0.001*	1.93–2.00
Indwelling biliary drainage	174 (74.36%)	95 (80.51%)	79 (68.10%)	0.03*	1.12–1.27
Cholecystitis	143 (61.11%)	46 (38.98%)	97 (83.62%)	<0.001*	1.52–1.70
Choledochal cyst	31 (13.25%)	5 (4.24%)	26 (22.41%)	<0.001*	1.92–1.99
Biliary-enteric anastomosis	136 (58.12%)	77 (65.25%)	59 (50.86%)	0.031*	1.26–1.43
Cholelithiasis	120 (51.28%)	28 (23.73%)	92 (79.31%)	<0.001*	1.68–1.84
Underlying comorbidities					
Diabetes mellitus	99 (42.31%)	53 (44.91%)	46 (39.66%)	0.415	1.46–1.64
Hypothyroidism	74 (31.62%)	34 (28.81%)	40 (34.48%)	0.351	1.63–1.79

Hypoproteinemia	97 (41.45%)	63 (53.39%)	34 (29.31%)	<0.001*	1.37–1.56
Chronic liver disease	76 (32.48%)	51 (43.22%)	25 (21.55%)	<0.001*	1.48–1.66
Immunosuppression	19 (8.12%)	14 (11.86%)	5 (4.31%)	0.034*	1.82–1.94
Chronic kidney disease	44 (18.80%)	28 (23.73%)	16 (13.79%)	0.05*	1.80–1.93
Length of hospital stay (in days)	19.33 ± 11.89	22.30 ± 14.09	16.31 ± 8.16	<0.001*	3.02–8.96
ICU stay					
Yes	33 (14.10%)	24 (20.34%)	9 (7.76%)	0.006*	1.09–1.41
No	201 (85.89%)	94 (79.66%)	107 (92.24%)	0.006*	1.46–1.60
Outcome					
Alive	209 (89.32%)	100 (84.75%)	109 (93.97%)	0.022*	1.45–1.59
Dead	25 (10.68%)	18 (15.25%)	7 (6.03%)	0.022*	1.09–1.47

*p-value ≤ 0.05 is statistically significant

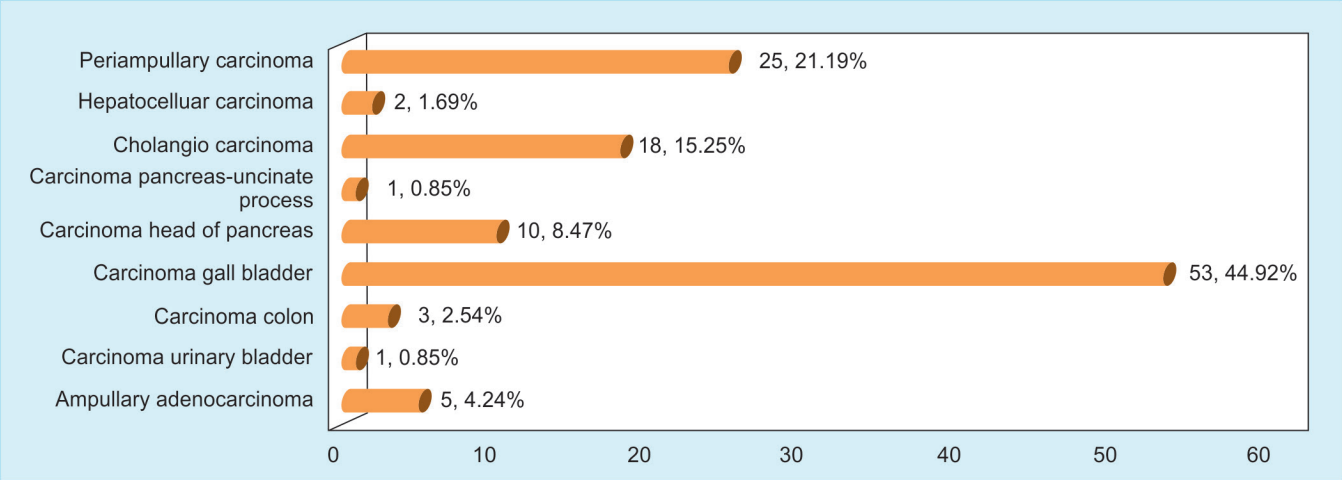


Fig. 1: The common malignances among the patients needing intra-abdominal surgeries in our study (N = 118)

obstruction which include, biliovascular injury, benign strictures, indwelling biliary catheters, cholecystitis, choledochal cysts, biliary-enteric anastomosis, and cholelithiasis (Table 1) were found statistically significant among patients with hepato-pancreatico-biliary malignancies in comparison to procedures for other intraabdominal ailments.

Main Result

The underlying risk factors in our study cohort of hepato-pancreatico-biliary and associated malignancies patients (Table 1). Among those discussed, Hypoproteinemia (63/118, 53.39%) was recognized as the most common comorbidity followed by diabetes mellitus (53/118, 44.91%) and chronic liver disease (51/118, 43.22%). We recognized hypoproteinemia, chronic liver disease, immunosuppression, and chronic kidney disease as significant risk factors in patients with hepatico-pancreatico-biliary malignancies in comparison to those without any malignancies. We identified immunosuppression in patients suffering from autoimmune diseases, undergoing prolonged steroid therapy, and those who underwent organ transplants. The length of hospital stay was significantly longer in the case of patients who underwent surgery for malignancies in comparison to those who did not undergo surgery for abdominal malignancies (Table 1).

The hepato-pancreatico-biliary and associated malignancies are represented in Figure 1. The common malignancies of the biliary system which lead to obstruction in the biliary tract leading to elevated bile levels are carcinoma gall bladder (53/118, 44.92%), periampullary carcinoma (25/118, 21.19%), cholangiocarcinoma (18, 15.25%), and ampullary adenocarcinoma (5/118, 4.24%). We observed 2 (2/118, 1.69%) cases of hepatocellular carcinoma in our study cohort. Among the malignancies associated with the pancreas, the most common site of involvement was the head of the pancreas (10/118, 8.47%). Other abdominal malignancies associated with metastatic spread of hepato- pancreaticobiliary malignancies include 3 (3/118, 2.54%) cases of carcinoma colon and one (1/118, 0.85%) case of carcinoma urinary bladder.

We compared the diagnostic parameters among patients with underlying hepatico-pancreatico-biliary malignancies who underwent surgery and those with no hepatico-pancreatico-biliary malignancies, as represented in Table 2. No significant diagnostic importance of procalcitonin assay was observed whereas CA 19.9, a marker of malignancies of pancreatic origin, was found to be significantly raised among patients with malignancies. The aspartate aminotransferase (AST), conjugated, and total bilirubin was also significantly raised in patients with abdominal malignancies in comparison to those with no malignancies.

Eighty (80/118, 67.79%) episodes of biliary infections were reported among the 118 patients who underwent surgical procedures for the removal of the tumor. Among the 80 episodes of biliary infections observed in our study, 58 (72.5%) episodes

Table 2: Comparison of diagnostic parameters among patients with underlying hepatico-pancreatico-biliary malignancies who underwent surgery and those with no hepatico-pancreatico-biliary malignancies (*N* = 234)

Diagnostic parameters	*Total bile samples (n = 234)*	*With underlying hepatobiliary malignancies who underwent surgery (n = 118)*	*Without underlying hepatobiliary malignancies (n = 116)*	*p-value*	*Confidence interval (95% CI)*
Procalcitonin (ng/mL) (mean ± SD)	2.30 ± 7.97	3.01 ± 9.43	1.57 ± 6.08	0.17	0.72–6.98
CA 19.9 (µg/mL) (Mean ± SD)	377.06 ± 1879.68	728.1 ± 2597.69	16.87 ± 79.79	0.0035*	13.04–330.31
ALT (SGPT) (mean ± SD)	65.85 ± 56.44	65.44 ± 53.41	66.27 ± 59.61	0.91	0.79–1.24
AST (SGOT) (mean ± SD)	71.37 ± 50.85	79.87 ± 47.73	62.64 ± 52.67	0.0093*	1.06–1.55
Conjugated bilirubin (mg/dL) (mean ± SD)	2.63 ± 3.93	3.64 ± 4.11	1.70 ± 3.48	<0.001*	1.44–3.54
Total bilirubin (mg/dL) (mean ± SD)	4.24 ± 5.68	5.77 ± 6.04	2.67 ± 4.83	<0.001*	4.395–8.87
Total leukocyte count (cells/cubic mm) (mean ± SD)	14496.13 ± 7986.32	14937.88 ± 6270.01	14042.86 ± 9436.29	0.39	0.92–1.24

**p*-value ≤ 0.05 is statistically significant

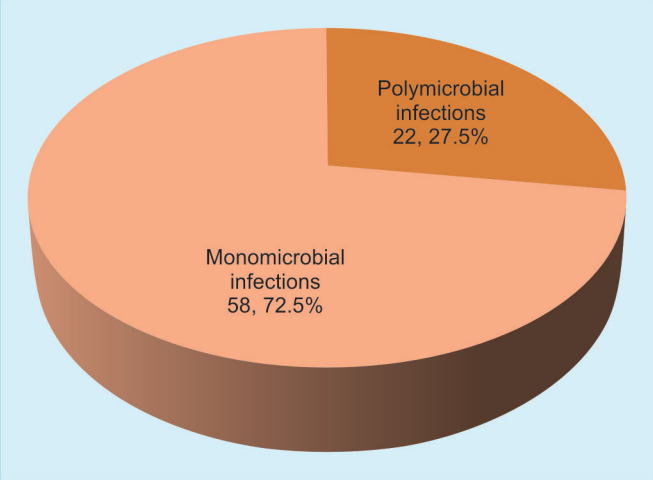


Fig. 2: Distribution of cases of infected bile cultures from patients with hepatico-pancreatico-biliary malignancies based on number of microbes isolated (*N* = 80)

were monomicrobial and 22 (27.5%) episodes were polymicrobial (Fig. 2). One hundred and two pathogenic bacteria were found responsible for these episodes of biliary infections. The most common pathogen responsible for biliary infection in patients with abdominal malignancies was *Escherichia coli* (38/102, 37.25%) followed by *Klebsiella pneumoniae* (21/102, 20.59%) and *Enterococcus* spp. (18/102, 17.65%) (Fig. 3). The most common gram-negative bacteria (GNB) responsible for biliary infection in patients with abdominal malignancies was *Escherichia coli* (38/102, 37.25%) followed by *Klebsiella pneumoniae* (21/102, 20.59%) and *Pseudomonas aeruginosa* (13/102, 12.75%).

Extended-spectrum beta-lactamase (ESBLs) resistance was predominantly recognized among the Gram-negative isolates. Seventy-eight (78/102, 76.47%) isolates were found resistant to ESBL antibiotics. *Escherichia coli* (27/78, 34.62%) were identified as the most ESBL-resistant isolate, followed by *Klebsiella pneumonia* (20/78, 25.64%) and *Pseudomonas aeruginosa* (10/78, 12.82%). Among the above-mentioned isolates, *Klebsiella pneumoniae* was found 95.24% (20/21, 95.24%) resistant, *Pseudomonas aeruginosa* was found 76.92% (10/13, 76.92%) resistant, and *Escherichia coli* was found 71.05% (27/38, 71.05%) resistant to ESBL antibiotics.

Carbapenem resistance has been identified as an emerging problem among bacterial pathogens from various sites of infection. Fifty-eight (58/102, 56.86%) bacterial pathogens isolated in this study were found to be resistant to Carbapenem antibiotics. *Escherichia coli* (22/58, 37.93%) was identified as the most ESBL-resistant isolate, followed by *Klebsiella pneumoniae* (19/58, 32.76%) and *Pseudomonas aeruginosa* (10/58, 17.24%). Among the above-mentioned isolates, *Klebsiella pneumoniae* was found 90.48% (19/21, 90.48%) resistant, *Pseudomonas aeruginosa* was found 76.92% (10/13, 76.92%) resistant, and *Escherichia coli* was found 57.89% (22/38, 57.89%) resistant to ESBL antibiotics.

Fluoroquinolone resistance was observed among 85 (85/102, 83.33%) pathogenic bacteria. *Escherichia coli* (33/85, 38.82%) was found most resistant to fluoroquinolones followed by *Klebsiella pneumoniae* (20/85, 23.53%) and *Pseudomonas aeruginosa* (11/85, 12.94%). Among the above-mentioned isolates, *Klebsiella pneumoniae* was found 95.24% (20/21, 95.24%) resistant, *Escherichia coli* was found 86.84% (33/38, 86.84%) resistant and *Pseudomonas aeruginosa* was found 84.62% (11/13, 84.62%) resistant to fluoroquinolone antibiotics.

p and *Morganella morganii* were deemed as emerging pathogens responsible for multidrug-resistant infections from various sites. Although we isolated only two (2/102, 1.96%) isolates of *A. baumannii* and three (3/102, 2.94%) isolates of *Morganella morganii* from the infected bile samples, all of them were resistant to all the first-line antibiotics used against them. Among the second-line drugs, *Acinetobacter baumannii* was established as susceptible to Colistin in 50% (1/2, 50%) of isolates and was recognized as susceptible to minocycline in 50% (1/2, 50%) isolates. Only one (1/2, 50%) isolate of *Acinetobacter baumannii* was resistant to all second-line drugs along with Ceftazidime – avibactam and aztreonam synergy which was absent.

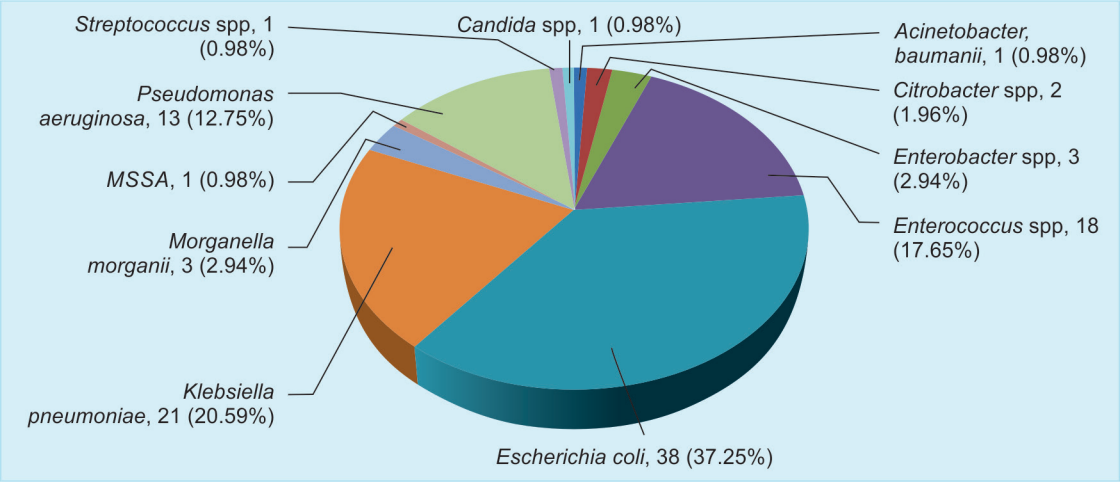


Fig. 3: Microorganisms isolated from the infected bile samples from hepatico-pancreatico-biliary malignancy patients included in this study ($N = 102$) MS*SA*, methicillin sensitive *Staphylococcus aureus*

Among Gram-positive cocci, *Enterococcus* spp. (18/102, 17.65%) was identified as the most common Gram-positive pathogen recognized among those isolated from infected bile samples. Out of the 18 *Enterococcus* spp. isolates, 14 (14/18, 77.78%) isolates were ampicillin resistant. One (1/102, 0.98%) *Staphylococcus* spp. isolate was identified but was not resistant to Cefoxitin which acts as a marker of methicillin resistance, and was identified as Methicillin-sensitive *Staphylococcus aureus*. Vancomycin and Teicoplanin were found effective in the treatment of 27 (27/35, 77.14%) isolates of *Enterococcus* spp. and all *Staphylococcus* spp. (4/4, 100%) were sensitive to it.

The demographic and risk factors responsible for the isolation of multidrug-resistant bacteria from hepato-pancreatico-biliary malignancy patients were described in Table 3. We isolated 61 (61/102, 59.80%) multidrug bacterial isolates from patients suffering from abdominal malignancies. The mean age of the patients suffering from multidrug-resistant biliary infections was 54.80 ± 11.64 years and a female (29/61, 47.54%) preponderance was observed among these patients. All underlying comorbidities like diabetes mellitus, hypothyroidism, hypoproteinemia, chronic liver disease, immunosuppression, and chronic kidney disease were significantly associated with the isolation of multidrug-resistant isolates from bile samples of patients suffering from abdominal malignancies. The increased length of hospital stays, admission to the ICU, and presence of percutaneous transhepatic biliary drain were statistically significant risk factors for the isolation of multidrug-resistant pathogenic bacteria from patients in our study cohort.

Discussion

To our best knowledge, this is one of the few studies in the literature that determines the incidence of bacterial infections and antibiotic sensitivity patterns associated with abdominal cancer patients. We identified 234 patients with suspected *bacteriobilia* in our study cohort, out of which, 118 (118/234, 50.43%) patients were suffering from hepato-pancreatico-biliary and associated malignancies. The mean age of patients was 53.02 ± 13.49 years with male predominance which agrees with a study conducted by Herzog et al.[14] As known in the literature, a healthy individual has a sterile biliary system but bacterial colonization of the biliary system can be associated with biliary pathology.[15] Biliary obstruction is a well-known cause of *bacteriobilia*.[16] A study by Negm et al.[17] supports our notion that malignant biliary strictures increase the risk of colonization.

We report positivity in bile cultures of 50.43% (118/234, 50.43%) in this study which agrees with a study conducted by Haag et al.[10] which reported a 62% incidence of *bacteriobilia* in cancer patients and low in comparison to a study conducted by Herzog et al.[14] which reported an incidence of almost 90% incidence of *bacteriobilia* in cancer patients. We isolated 102 pathogenic microorganisms from 80 episodes of bacteriobilia with a predominance of *bacteriobilia* attributable to GNB (82/102, 80.39%) with the most common microorganism isolated being *Escherichia coli* (38/102, 37.25%) followed by *Klebsiella pneumoniae* (21/102, 20.59%). The above interpretation was in agreement with a study by Herzog et al.[14] that predominantly demonstrated the isolation of GNB where the most common pathogenic microorganism isolated was *Escherichia coli* followed by *Klebsiella pneumoniae*. Whereas a study by Haag et al.[10] showed predominant gram-positive cocci *bacteriobilia* in patients that underwent endoscopic retrograde cholangiopancreatography (ERCP) in obstructive malignancies of the biliary tract. Increased isolation of *Enterococcus* spp. from bile cultures was also observed in our study which was similarly observed in studies from other institutes where the empirical therapy for *bacteriobilia* commonly covered GNB, leading to the slight increase of Gram-positive *Enterococci* spp.[10,18]

We recorded a high level of antibiotic resistance among the commonly isolated microorganisms. *Escherichia coli* was most susceptible to Amikacin and imipenem among the first-line drugs, while multidrug-resistant *Escherichia coli* tested for susceptibility to Colistin were found 100% (38/38, 100%) susceptible. Higher susceptibility of *Escherichia coli* to Amikacin was recorded in a study by Zhao et al.[18] A resistance of 89.47% to third-generation cephalosporins among *Escherichia coli* isolates from infected bile samples was recorded in our study which is very high in comparison to a study by Yun et al.[19] which record a resistance of 20–60%.

The ever-increasing use of penicillins and cephalosporins has led to reduced effectiveness in treating severe infections. Extended-spectrum β-lactamases (ESBL) character of a microorganism was found to resist the effect of penicillins and cephalosporins.[20]

Table 3: Demographic and risk factors associated with isolation of multidrug resistant bacteria from bile culture of hepatico-pancreatico-biliary malignancy patients included in this study (*N* = 102)

Observational parameters	*Multidrug resistant isolates (n = 61/102, 59.80%)*	*Drug susceptible isolates (n = 41/102, 40.20%)*	*p-value*	*Confidence interval (95% CI)*
Age (Mean ± SD)	54.80 ± 11.64	51.23 ± 13.45	0.031*	1.01–1.14
Gender				
Male	20 (32.79%)	18 (29.51%)	0.002*	1.31–1.64
Female	29 (47.54%)	12 (19.67%)	0.002*	1.15–1.44
Causes of obstruction				
Biliovascular injury	2 (3.28%)	0 (0.0%)	0.014*	1.90–2.02
Benign stricture	1 (1.64%)	0 (0.0%)	0.004*	1.94–2.02
Indwelling biliary drainage	40 (65.57%)	27 (44.26%)	0.004*	1.07–1.30
Cholecystitis	24 (39.34%)	7 (11.47%)	0.003*	1.37–1.66
Choledochal cyst	2 (3.28%)	2 (3.28%)	0.016*	1.90–2.02
Biliary-enteric anastomosis	28 (45.90%)	18 (29.50%)	0.005*	1.28–1.57
Cholelithiasis	13 (21.31%)	6 (9.84%)	0.019*	1.61–1.88
Underlying comorbidities				
Diabetes mellitus	25 (40.98%)	13 (21.31%)	0.012*	1.34–1.63
Hypothyroidism	19 (31.15%)	9 (14.75%)	<0.001*	1.47–1.75
Hypoproteinemia	25 (40.98%)	14 (22.95%)	0.010*	1.34–1.63
Chronic liver disease	22 (36.06%)	12 (19.67%)	0.021*	1.41–1.70
Immunosuppression	5 (8.20%)	5 (8.19%)	0.012*	1.81–1.99
Chronic kidney disease	16 (26.23%)	5 (8.19%)	0.003*	1.54–1.81
Length of hospital stay (in days)	25.00 ± 15.84	18.73 ± 9.89	<0.001*	1.15–1.55
Admission to ICU present	12 (19.67%)	8 (13.11%)	0.004*	1.63–1.88
Management on PTBD# after surgery	38 (62.29%)	23 (37.70%)	0.021*	1.10–1.35
Outcome				
Alive	40 (65.57%)	24 (39.34%)	0.003*	1.25–1.50
Dead	10 (16.39%)	6 (9.84%)	0.003*	1.12–1.68

*p-value ≤ 0.05 is statistically significant. #PTBD, percutaneous transhepatic biliary drain

Highest ESBL producing character among microorganisms isolated from the infected bile samples was Morganella morganii (3/3, 100%), followed by *Klebsiella pneumoniae* (20/21, 95.24%) and *Escherichia coli* (27/38, 71.05%) which corroborates with a study by Zhao et al.[18] Carbapenems were found to be resistant in more than 50% (58/102, 56.86%) of isolates which is much higher in contrast to a study by Zhao et al.[18] which could be attributed to the rampant use of carbapenems leading to the slow but steady emergence of carbapenem-resistant microorganisms.[21]

As we already know there is a trend of increasing incidence of *Enterococcus* spp. in various studies which also mirrors the finding of our study.[22,23] In agreement with previously published articles, the *Enterococcus* spp. isolates were reported to be more than 90% susceptible to linezolid, vancomycin, and teicoplanin.[18] Vancomycin was regarded as the drug of choice for the empirical treatment of *Enterococcus* spp. which was also recommended by the Tokyo Guidelines 2018.[24]

The use of newer technologies like ERCP and other ultrasonographic techniques has helped in testing the bile samples directly from the suspected site of infection. This also helps in the recognition of the antibiotic-resistant pattern of the microbes isolated from the infected bile samples.[22] Thus, the antibiotic sensitivity pattern will direct the identification of the antibiotic coverage that needs to be provided for prophylactic treatment of risk factors associated with biliary tract malignancies which need surgical procedures leading to *bacteriobilia*.[25,26]

Our research was limited by various factors; firstly, this is a retrospective observational study at a single tertiary care center. Secondly, the findings of our study only represent the spectrum of *bacteriobilia* and antibiotic resistance at a single center and are not representative of the rate of infection in other hospitals of the region.

Conclusion

This study provides insight into the annual incidence of patients undergoing surgery for hepato-pancreatico-biliary malignancies and identifies associated demographic characteristics, risk factors, and the spectrum of pathogens responsible for *bacteriobilia* along with the antibiotic resistance pattern among these isolates.

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References

1. Coss A, Byrne MF. Preoperative biliary drainage in malignant obstruction: Indications, techniques, and the debate over risk. Curr Gastroenterol Rep 2009;11(2):145–149. DOI: 10.1007/s11894-009-0022-6.
2. Sun J, Liu G, Yuan Y, et al. Operable severe obstructive jaundice: How should we use pre-operative biliary drainage? surgery. S Afr J Surg 2013;51(4):127–130. DOI: 10.7196/sajs.1597.
3. Boulay BR, Parepally M. Managing malignant biliary obstruction in pancreas cancer: Choosing the appropriate strategy. World J Gastroenterol 2014;20(28):9345–9353. DOI: 10.3748/wjg.v20.i28.9345.
4. Kruse EJ. Palliation in pancreatic cancer. Surgical Clinics 2010;90(2):355–364. DOI: https://doi.org/10.1016/j.suc.2009.12.004.
5. Moghimi M, Marashi SA, Salehian MT, et al. Obstructive jaundice in Iran: Factors affecting early outcome. Hepatobiliary Pancreat Dis Int 2008;7(5):515–519. PMID: 18842499.
6. Riaz A, Pinkard JP, Salem R, et al. Percutaneous management of malignant biliary disease. J Surg Oncol 2019;120(1):45–56. DOI: 10.1002/jso.25471.
7. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: A systematic analysis for the Global Burden of Disease Study 2017. The Lancet 2018;392(10159):1736–1788. DOI: 10.1016/S0140-6736(18)32203-7.
8. Abubakar II, Tillmann T, Banerjee A. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. The Lancet 2015;385(9963):117–171. DOI: 10.1016/S0140-6736(14)61682-2.
9. Hundal R, Shaffer EA. Gallbladder cancer: Epidemiology and outcome. Clin Epidemiol 2014;6:99–109. DOI: 10.2147/CLEP.S37357.
10. Haag GM, Herrmann T, Jaeger D, et al. Outcomes and risk factors for cancer patients undergoing endoscopic intervention of malignant biliary obstruction. BMC gastroenterology 2015;15(1):1–7. DOI: https://doi.org/10.1186/s12876-015-0399-7.
11. Gotthardt DN, Weiss KH, Rupp C, et al. Bacteriobilia and fungibilia are associated with outcome in patients with endoscopic treatment of biliary complications after liver transplantation. Endoscopy 2013;45(11):890–896. DOI: 10.1055/s-0033-1344713.
12. Kawecki D, Chmura A, Pacholczyk M, et al. Bacteria isolated from bile samples of liver recipients in the early period after transplantation: Epidemiology and susceptibility of the bacterial strains. Transplant Proc 2007;39(9):2807–2811. DOI: 10.1016/j.transproceed.2007.08. 044.
13. Bert F, Larroque B, Paugam-Burtz C, et al. Microbial epidemiology and outcome of bloodstream infections in liver transplant recipients: An analysis of 259 episodes. Liver Transpl 2010;16(3):393–401. DOI: 10.1002/lt.21991.
14. Herzog T, Belyaev O, Hessam S, et al. Bacteribilia with resistant microorganisms after preoperative biliary drainage–the influence of bacteria on postoperative outcome. Scand J Gastroenterol 2012;47(7):827–835. DOI: 10.3109/00365521.2012.679684.
15. Csendes A, Fernandez M, Uribe P. Bacteriology of the gallbladder bile in normal subjects. Am J Surg 1975;129(6):629–631. DOI: 10.1016/0002-9610(75)90334-7.
16. Kaya M, Beştaş R, Bacalan F, et al. Microbial profile and antibiotic sensitivity pattern in bile cultures from endoscopic retrograde cholangiography patients. World J Gastroenterol 2012;18(27): 3585–3589. DOI: 10.3748/wjg.v18.i27.3585.
17. Negm AA, Schott A, Vonberg RP, et al. Routine bile collection for microbiological analysis during cholangiography and its impact on the management of cholangitis. Gastrointest Endosc 2010;72(2): 284–291. DOI: 10.1016/j.gie.2010.02.043.
18. Zhao J, Wang Q, Zhang J. Changes in microbial profiles and antibiotic resistance patterns in patients with biliary tract infection over a six-year period. Surg Infect (Larchmt) 2019;20(6):480–485. DOI: 10.1089/sur.2019.041.
19. Yun SP, Seo HI. Clinical aspects of bile culture in patients undergoing laparoscopic cholecystectomy. Medicine (Baltimore) 2018;97(26):e11234. DOI: 10.1097/MD.0000000000011234.
20. Zhao C, Liu S, Bai X, et al. A retrospective study on bile culture and antibiotic susceptibility patterns of patients with biliary tract infections. Evid Based Complement Alternat Med 2022;2022(Article ID: 9255444):1–11. DOI: 10.1155/2022/9255444.
21. Kruis T, Güse-Jaschuck S, Siegmund B, et al. Use of microbiological and patient data for choice of empirical antibiotic therapy in acute cholangitis. BMC Gastroenterol 2020;20(1):65. DOI: 10.1186/s12876-020-01201-6.
22. Reiter FP, Obermeier W, Jung J, et al. Prevalence, resistance rates, and risk factors of pathogens in routine bile cultures obtained during endoscopic retrograde cholangiography. Dig Dis 2021;39(1):42–51. DOI: 10.1159/000509289.
23. Rupp C, Bode K, Weiss KH, et al. Microbiological assessment of bile and corresponding antibiotic treatment: A strobe-compliant observational study of 1401 endoscopic retrograde cholangiographies. Medicine (Baltimore) 2016;95(10):e2390. DOI: 10.1097/MD.0000000000002390.
24. Gomi H, Solomkin JS, Schlossberg D, et al. Tokyo Guidelines 2018: Antimicrobial therapy for acute cholangitis and cholecystitis. Journal of Hepato-Biliary-Pancreatic Sciences 2018;25(1):3–16. DOI: https://doi.org/10.1002/jhbp.518.
25. Maxwell DW, Jajja MR, Ferez-Pinzon A, et al. Bile cultures are poor predictors of antibiotic resistance in postoperative infections following pancreaticoduodenectomy. HPB (Oxford) 2020;22(7): 969–978. DOI: 10.1016/j.hpb.2019.10.016.
26. Okamura K, Tanaka K, Miura T, et al. Randomized controlled trial of perioperative antimicrobial therapy based on the results of preoperative bile cultures in patients undergoing biliary reconstruction. J Hepatobiliary Pancreat Sci 2017;24(7):382–393. DOI: 10.1002/jhbp.453.