RESEARCH ARTICLE

Microbiology and clinical characteristics of acute cholangitis with their impact on mortality; a retrospective cross-sectional study

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Abstract

Objective: To evaluate microbiological and clinical characteristics of acute cholangitis along with their impact on mortality, and to compare the role of early versus late biliary drainage in the management of cholangitis.

Methods: The retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital Research Centre, Lahore, Pakistan, and comprised records of all patients presenting with acute cholangitis from June, 2012, to June, 2017. The risk factors, presence of bacteremia, resistance pattern of microbial pathogens and severity were assessed according to Tokyo guidelines in addition to associated mortality and recurrence at 3 months. Data was analysed using SPSS 20.

Results: Of the 230 patients, 137(59.6%) were male. The overall mean age was 56±13 years. The most common isolated organism was Escherichia coli 54(70.1%). Clinical severity (p=0.001), late biliary drainage (p=0.001) and use of multiple stents (p=0.03) were associated with increased mortality. However, in multivariable analysis, only high body mass index (p=0.01) and Tokyo severity grades II (p=0.04) and III (p=0.001) were significant factors associated with mortality.

Conclusion: Early identification of risk factors, administration of appropriate antibiotics and establishing early biliary drainage were found to be the key management steps to reduce cholangitis-related mortality.

Keywords: Cholangitis, Tokyo classification, Bacteremia. (JPMA 70: 607; 2020)
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Introduction

Cholangitis is the infectious inflammation of obstructed biliary system. Clinical manifestations of cholangitis include fever (90%), right upper quadrant (RUQ) pain (70%) and jaundice (60%); the presence of these is also known as Charcot's triad, which has a sensitivity of 70-75% in establishing the diagnosis.[1,2] In more severe cases, hypotension (30%) and altered mental status (20%) can be observed, referred to as Reynold's pentad.[3] The mean age at presentation is reported to be 60-70 years without any gender predominance.[4,5] The history of biliary disease, including cholelithiasis and benign or malignant strictures, is the major risk factor. Other risk factors include a prior history of biliary stent insertion, previous episodes of cholangitis, history of cirrhosis and liver abscess. Severity of cholangitis is based on Tokyo guidelines.[6,7] According to these guidelines, mild cholangitis responds to medical treatment alone, while in moderate cholangitis, there is a lack of response to medical treatment. Severe cholangitis is defined by the lack of response and presence of organ dysfunction. The spectrum of organ dysfunction includes hypotension, requiring ionotropic support, acute kidney injury, liver failure or multi-organ failure.[7-9] The management of cholangitis depends on three parameters: resuscitation, antimicrobials and biliary drainage. Biliary drainage, which is a cornerstone in the management, has been shown to have a significant impact on mortality from 50% to less than 10%.[9,10] In addition, early biliary drainage is recommended in moderate to severe cholangitis, according to Tokyo classification,[6,7] which obviously requires increased resources and cost. Bacteremia occurs in 20-80% of the patients with cholangitis[2,4] and is associated with a mortality of 10-20%.[4,9,10] Escherichia (E.) coli is the most common organism, followed by Klebsiella(K.) spp, Enterococcus spp, Pseudomonas (P.) aeruginosa and Enterobacter spp.[3,5] Empirical antibiotics play a pivotal role and can de-escalated once sensitivity data is known. However, widespread and indiscriminate use of antibiotics has altered the sensitivity pattern of micro-organisms which necessitates a change in the choice of empiric antibiotics. Moreover, in patients with malignant obstruction, the risk of empirical antimicrobial therapy failure is high as these patients may have resistant gram-negative organisms and Candida (C.) species.[2] Therefore, it is essential to know the native microbiology data and resistance patterns to suggest effective empirical regimen.

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The current study was planned to evaluate microbiological and clinical characteristics of acute cholangitis along with their impact on mortality, and to compare the role of early versus late biliary drainage in the management of cholangitis.

Patient and Methods

The retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital Research Centre, Lahore, Pakistan, and comprised records of all patients presenting with acute cholangitis from June, 2012, to June, 2017. After approval from the institutional review board, data of patients was selected using the keyword 'cholangitis', and all the charts were reviewed. Only data of patients with cholangitis of either gender and regardless of age was included. Diagnosis of acute cholangitis was based on any two of the three clinical characteristics; fever, jaundice (or deranged liver function test (LFT) results, and radiological evidence of biliary obstruction (biliary dilation or loss of pneumobilia in liver). Those with documented liver metastasis or having reasons of deranged LFTs other than cholangitis were excluded.

The baseline characteristics of the patients, including age, gender, body mass index (BMI),[11] primary diagnoses, and associated co-morbidities were recorded. Other factors, like the type of biliary stricture, according to Bismuth classification,[12] type of biliary stents (plastic versus metallic), yield of blood cultures, resistance pattern of microbial pathogens, the risk of developing cholangitis and clinical severity, according to the Tokyo guidelines,[13] were also recorded, and similar was the case with laboratory values of bilirubin, prothrombin time / international normalised ratio (PT/INR), white blood cell (WBC) count and creatinine levels along with blood culture results and antimicrobial susceptibility of the isolated organisms.

The effect of all these factors was analysed on recurrence of cholangitis and 3-month mortality.

Primary outcome was death in 3 months from the episode of cholangitis, and the secondary outcome was recurrence of cholangitis in 3 months.

Statistical analysis was done using SPSS 20. Continuous variables were stated as mean ± standard deviation (SD), and categorical variables were computed as frequencies and percentages. Categorical variables were compared using chi square test or fisher's exact test as deemed necessary. The continuous variables were compared using independent t-test. Statistical significance was defined as two-tailed $p<0.05$. Multivariable logistic regression (MLR) model was used to identify the independent risk factors associated with mortality.

Results

Out of 573 data sets reviewed, 230(40.35%) were included, and, of them, 137(59.6%) were male. The overall mean age of the sample was 56±13 years. Overall, 188(80.7%) patients had prior history of biliary instrumentation, 92(40%) had a history of prior cholangitis, and 164(71.3%) were diagnosed to have distal common bile duct (CBD) stricture. Other factors, like BMI, type of biliary stricture, type of biliary stents and risk of developing cholangitis and clinical severity were also assessed (Table-1). Moreover, 200(86.9%) patients had underlying cancer, the most common of which was pancreatic

Table-1: Demographic and clinical Characteristics.

Age (years) : Mean ± SD	**56 ±13**
Male	137 (59.6 %)
Female	93 (40.4 %)
BMI according to WHO criteria for diagnosis of obesity in South Asians 23.85 ± 4.92	
Under weight	33(14.3%)
Healthy Weight	78 (33.9%)
Over Weight	71 (30.9%)
Obese	48 (20.9%)
Past history of cholangitis -- 92 (40 %)	
Past history of instrumentation -- 188 (80.7 %)	
ERCP (diagnostic as well as therapeutic)	161 (70 %)
Plastic stents	110 (48 %)
Metallic stents	39 (17 %)
PTC	27 (11.7 %)
Stricture location.	
Distal	164 (71.30 %)
Proximal	41 (17.82 %)
Bismuth classification of proximal stricture	
Class I	14 (6.08 %)
Class II	11 (4.78 %)
Class IIIa	3 (1.30 %)
Class IIIb	5 (2.17 %)
Class IV	8 (3.4 %)
Multiple	4 (1.73 %)
Unknown*1	2 (0.86 %)
Clinical severity (Tokyo guidelines 2018)	
Grade I	172 (74.8 %)
Grade II	33 (14. 3%)
Grade III	25 (10.9 %)

*1Post-operative patients in which location of stricture is not known due to distorted anatomy.
BMI: Body mass index; WHO: AWorld Health Organisation; ERCP: Endoscopic retrograde cholangiopancreatography; PTC: Percutaneous transhepatic.

Table-2: Underlying diagnosis and co-morbidities.

Diagnosis	
Cancer -- 200 (86.9 %)	
Pancreatic carcinoma	66 (28.7 %)
Ampullary carcinoma	44 (19.1 %)
Others *	41 (20.5 %)
Cholangiocarcinoma	26 (11.3 %)
Gall bladder carcinoma	23 (10 %)
Non cancer -- 30 (12.17 %)	
Choledocholithiasis	18 (7.8 %)
Peri-ampullary mass	7 (3.0 %)
Post operative stricture	4 (1.7 %)
Congenital biliary atresia	1 (0.4 %)
Co-morbidities	
None	101 (43.9 %)
Multiple	56 (24.3 %)
Hypertension	27 (11.73 %)
Diabetes	25 (10.9 %)
Hepatitis C	7 (3.0 %)
Others **	7 (3.0 %)
Ischemic heart diseases	5 (2.2 %)
Breast Cancer	5 (2.2 %)
Hepatitis B	1 (0.4 %)

*Hepatocellular carcinoma: 1, Gastric Carcinoma: 7, Duodenal carcinoma: 3, Lymphoproliferative disorders: 5, Metastasis from Breast Carcinoma: 7, Metastasis from Rectal carcinoma: 1, Metastasis from prostate/ bladder Ca: 5, Metastasis from unknown primary: 6, Metastasis from colon carcinoma: 4, Metastasis from ovarian carcinoma: 2.

**Includes 1 patient each of neurofibromatosis, epilepsy, oesophageal carcinoma, chronic myeloid leukaemia (CML), chronic kidney disease (CKD), Addison's disease and nasopharyngeal carcinoma. (Cytology negative for malignancy).

carcinoma 66(28.7%), while 30(12.17%) were non-cancer, 101(43.9%) had no co-morbidities and 56(24.3%) had multiple underlying illnesses, including diabetes and hypertension (Table-2).

Of 230 patients with cholangitis, blood cultures had been drawn in 166(72.17%) cases, and bacteremia was reported in 77(46.38%) of them. The most common isolated organisms were gram-negative bacilli 65(84.4%), predominantly E. coli 54(70.12%) (Table-3).

Clinical severity (p=0.001), late biliary drainage (p=0.001) and use of multiple stents (p=0.03) were associated with increased mortality (Table-4). Univariable and multivariable analysis of different clinical characteristics and their impact on mortality were separately assessed (Table-5).

Table-4: Baseline characteristics and association with mortality.

Variables	Alive 171 (74.3%)	Death 59 (25.7%)	p-value
Age (years)			
Mean ± SD	57.44 ± 14.70	55.20 ± 10.01	0.31
Gender			
Female	64 (68.8%)	29 (31.2%)	0.11
Male	107 (78.1%)	30 (21.9%)	
BMI			
Mean ± SD	23.19 ± 5.04	24.41 ± 5.25	0.12
Duration of antibiotic			
Mean ± SD	11.84 ± 22.50	12.42 ± 28.12	0.87
Comorbidity			
No	73 (71.6%)	29 (28.4%)	0.39
Yes	98 (76.6%)	30 (23.4%)	
Stricture			
No	48 (72.7%)	18 (27.3%)	0.29
Benign	13 (92.9%)	1 (7.1%)	
Malignant	110 (73.3%)	40 (26.7%)	
Clinical severity			
Grade I	146 (84.9%)	26 (15.1%)	0.001
Grade II	21 (63.6%)	12 (36.4%)	
Grade III	4 (16.0%)	21 (84.0%)	
Time to biliary drainage			
None	22 (52.4%)	20 (47.6%)	0.001
Less than 24 hours	97 (82.9%)	20 (17.1%)	
Above 24 hours	52 (73.2%)	19 (26.8%)	
Number of stents			
None	49 (63.6%)	28 (36.4%)	0.03
Single	107 (80.5%)	26 (19.5%)	
Multiple	15 (75.0%)	5 (25.0%)	
Microbiological data			
No bacteremia	70 (78.7%)	19 (21.3%)	0.61
Bacteremia	58 (75.3%)	19 (24.7%)	

SD: Standard deviation.

Table-3: Microbiological characteristics of gram-negative organisms (Resistance Pattern).

Organism	Observations (n=77)	Ampicillin	3rd Generation Cephalosporin	Pipercillin/ tazobactam	Ciprofloxacin	Carbapenems
Escherichia coli	54 (70.1%)	52(96.3%)	46 (85.2%)	16 (29.6%)	46 (85.2%)	3 (5.6%)
Pseudomonas Aeruginosa	6 (7.8 %)	Not applicable	5 (83.3%)	1 (16.7%)	3 (50%)	1 (16.7%)
Klebsiella pneumoniae	3 (3.9 %)	3 (100%)	3 (100%)	1 (33.3%)	3 (100%)	0 (0%)
Enterobacter cloacae	1 (1.2 %)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Aermonas hydrophila	1 (1.2 %)	1 (100%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)

Table-5: Adjusted odds ratio (death).

Variables	Univariable model OR (CI), p-value	Multivariable model OR (CI), p-value
	Age (years)	
Mean ± SD	0.99 (0.97 1.01), 0.28	1.00 (0.96 1.03), 0.85
	Gender	
Female	Ref	Ref
Male	0.62 (0.34 1.12), 0.11	0.79 (0.28 2.20), 0.65
	BMI	
Mean ± SD	1.05 (0.99 1.11), 0.12	1.20 (1.07 1.34), 0.01
Duration of antibiotic		
Mean ± SD	1.00 (0.99 1.01), 0.87	1.01 (0.98 1.03), 0.58
	Comorbidity	
No	Ref	Ref
Yes	0.77 (0.43 1.39), 0.39	0.43 (0.15 1.20), 0.11
	Stricture	
No	Ref	Ref
Benign	0.21 (0.02 1.68), 0.14	-
Malignant	0.97 (0.50 1.86), 0.93	0.82 (0.27 2.44), 0.72
	Clinical severity	
Grade I	Ref	Ref
Grade II	3.21 (1.41 7.31), 0.01	3.26 (1.04 10.22), 0.04
Grade III	29.48 (9.36 92.90), 0.001	47.14 (8.87 250.61), 0.001
	Time to biliary drainage	
None	Ref	Ref
Less than 24 hours	0.23 (0.11 0.49), 0.001	0.91 (0.18 4.55), 0.91
Above 24 hours	0.40 (0.18 0.89), 0.03	1.78 (0.35 9.13), 0.49
	Number of stents	
None	Ref	Ref
Single	0.42 (0.23 0.80), 0.01	0.42 (0.11 1.56), 0.19
Multiple	0.58 (0.19 1.78), 0.34	1.42 (0.23 8.88), 0.71
	Microbiological data	
No bacteremia	Ref	Ref
Bacteremia	1.21 (0.58 2.49), 0.61	0.86 (0.32 2.27), 0.76

OR: Odds ratio; CI: Confidence interval.
REF : Reference value in multivariate regression analysis.

Discussion

Acute cholangitis is a significant cause of morbidity and mortality, especially in the elderly, and is the second commonest cause of bacteremia.[4,5] The reported risk factors for cholangitis include history of biliary stricture / obstruction, prior biliary instrumentation (Endoscopic retrograde cholangiopancreatography [ERCP] / Percutaneous transhepatic [PTC] or surgical exploration), cholelithiasis, age >70 years, history of bacteremia in the recent past and diabetes[8] also were noted in the current study. Bacteremia has been reported in 20-80% cases of acute cholangitis.[3] Bae et al. reported positive blood cultures in 31.6% cases and another study from India reported this to be 26%,[2,14,15] while in our study, blood culture yield was 46.38%, which was significantly higher. The isolated organisms were predominantly gram-negative bacilli, with E. coli as the commonest one, similar to previous studies.[2,3,5] There has been an increasing trend of bacterial resistance. A study showed increasing resistance to ampicillin (44.8%), 3rd generation cephalosporin (36.5%) and ciprofloxacin (42%),[2,4] and similar results have been shown by other studies from India and Barcelona.[5] Microbiological characteristics and resistance patterns in the current study showed increase resistance to cephalosporin and quinolones. The current practice in our institutiomnis to use quinolones as empiric antibiotics in grade-1 cholangitis, considering their excellent oral absorption and good biliary penetration, but evidence of resistance to quinolones appeared to be high. However, in moderate and severe cholangitis, empirical use of piperacillin/tazobactam is in line with the sensitivity patterns (70-80% sensitive). Bacteremia in cholangitis has mortality of 10-20%, if left untreated.[5,16] In our study, mortality was 23.37% and was highest in those with polymicrobial bacteremia 75%. However, it did not show statistical significance as a predictor of mortality.

The overall mortality in acute cholangitis is reported to be 14-40%.[17] In our study, it was 25.7%. In univariate analysis of the risk factors, renal insufficiency (increase creatinine value), increasing severity, late biliary drainage and use of multiple stents were identified as significant predictors of mortality, but in multivariate analysis, only high BMI and severity of grade II and III severity were statistically significant predictors of mortality. Though late biliary drainage appeared to have increased risk, it was not statistically significant in the current study. Among patients with advanced severity, those who had multi-organ failure were more at risk of dying.[18] These findings are in line with previous studies except the association of increased BMI with mortality, which was observed in our study. Biliary strictures of Bismuth class III and IV are associated with significant mortality,[11,19] but it was not observed in the current study. This observation might be due to limited number of cases with proximal stricture i.e. 41/230 (17.82%). The mortality in proximal strictures was 18/42 (42.8%) compared to distal strictures 36/160 (22.5%), with class-I having6/14 (42.85%), class II 7/12 (58.33%), class III 4/ 8 (50%) and class IV 2/8 (25%) deaths.

Clinical severity of cholangitis is based on Tokyo guidelines,[13] which state that early biliary drainage in addition to antibiotics is needed in patient with higher grades II or III due to higher mortality in this group. However, timeframe for this early intervention was not elucidated.[20-22] Ming Tan et al. reported association between early biliary drainage (within 24-72 hours) with improved survival in moderate to severe cholangitis (30-day mortality).[23-27] Similarly, Lee F et al. reported decreased mortality with early biliary drainage (within 48 hours).[14] Our study further suggests that the lack of early biliary drainage (within 24 hours) is associated with worse outcome, though results were not statistically significant in multivariable analysis. We suggest further research, preferably multicentre, to investigate this relationship because it will have important implications in terms of cost and outcome.

In terms of limitations, the current study was retrospective in nature, and mainly comprised cancer patients. It is, therefore, recommended to further investigate the matter in both cancer and non-cancer patients.

Conclusion

Increasing BMI, Tokyo grading of clinical severity and inability to establish biliary drainage were found to be important predictors of mortality, but biliary drainage within 24 hours of presentation needed to be further investigated. Due to emerging resistance to quinolones, institutional guidelines should be reviewed to suggest appropriate empirical antibiotics according to institutional and local antimicrobial sensitivity data.

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