

Role of change in the levels of inflammatory markers post drainage in predicting outcome in acute cholangitis

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ABSTRACT – Background – Acute cholangitis (AC) is a gastro-intestinal emergency associated with significant mortality. Role of change in the levels of inflammatory markers post drainage in predicting outcome in acute cholangitis is uncertain. **Objective** – To evaluate the predictive value of changes in C-reactive protein (CRP) and procalcitonin levels after biliary drainage in relation to outcomes (survival or mortality) at 1 month. **Methods** – A prospective observational study of consecutive adults presenting with AC was performed. At admission and at 48 hours post biliary drainage, procalcitonin and CRP were sent. **Results** – Between August 2020 till December 2020 we recruited 72 consecutive patients of AC. The median age of the patients was 55 years (range 43–62 years) and 42 (58.33%) were females. Although the delta change in serum procalcitonin (P value<0.001) and CRP (P value<0.001) was significant, it had no bearing on the outcome. Altered sensorium and INR were independently associated with mortality at 1 month. The 30-day mortality prediction of day 0 procalcitonin was measured by receiver operating characteristic analysis which resulted in an area under the curve of 0.697 with a 95% confidence interval (95%CI) of 0.545–0.849. The optimal cut-off of procalcitonin would be 0.57ng/mL with a sensitivity and specificity of 80% and 60% respectively to predict mortality. **Conclusion** – Change in serum procalcitonin and CRP levels at 48 hours post drainage although significant, had no impact on the outcome of acute cholangitis.

Keywords – Procalcitonin; CRP; acute cholangitis; biliary drainage; outcome.

INTRODUCTION

Acute cholangitis (AC), if left untreated, can have a mortality upto 20% in severe cholangitis and also increases the cost of hospitalization^(1,2) (FIGURE 1). Prompt use of antibiotics and drainage of the biliary system are essential components of management as per Tokyo Guidelines 2018⁽³⁾. Three principal drainage procedures are endoscopic biliary drainage (EBD), percutaneous trans-hepatic biliary drainage (PTBD) and surgical biliary drainage⁽³⁾. Any delay in diagnosis or initiation of antibiotics and drainage leads to life-threatening consequences.

Among the various parameters, white blood cell count (WBC) and C-reactive protein (CRP) have been used as diagnostic markers as per Tokyo Guidelines 2018 (TG-18)⁽³⁾. Serum procalcitonin, a marker of systemic bacterial infections, has been used for assessment of severity of AC⁽⁴⁻⁶⁾. Elevated procalcitonin at admission are usually associated with severe cholangitis. However, none of these parameters have been evaluated as outcome predictors in AC. Similarly, microbiology of cholangitis has not changed significantly but widespread and indiscriminate use of antibiotics over the years has led to emergence of drug resistance among these organisms. Therefore, the changing antibiotic sensitivity patterns may mandate a revision of empirical antibiotic policy in cholangitis. We hypothesized that change in inflammatory markers post

drainage might predict the outcome of AC. Hence, we planned a prospective study to evaluate the role of change in serum CRP and procalcitonin post drainage in predicting outcome of patients with AC along with observation of the microbiological spectrum in AC in order to update the local antibiogram which will ultimately help in selecting the appropriate empirical antimicrobial therapy.

METHODS

This was a prospective observational study of consecutive patients of AC who presented to a tertiary care center in North India from August, 2020 till December 2020. All adult patients who fulfilled TG18 guidelines of AC were included in the study after informed consent. All patients who did not consent were excluded. The guidelines laid by Indian council of Medical Research (ICMR) (2000) and Helsinki declaration (modified 2004) were adhered to in all patients. Approval of the Ethics Committee of the institute was taken before commencing the study (IEC no. 2020/SPL-1645). Demographic profile, detailed history and examination findings were recorded on a pre-structured proforma. Blood samples were drawn for routine investigations, procalcitonin, CRP and blood cultures. Routine investigations in the form of complete hemogram, renal and liver function tests, coagulation profile, serum electrolytes, procalcitonin, CRP, blood culture and ultrasound abdomen were sent. If a

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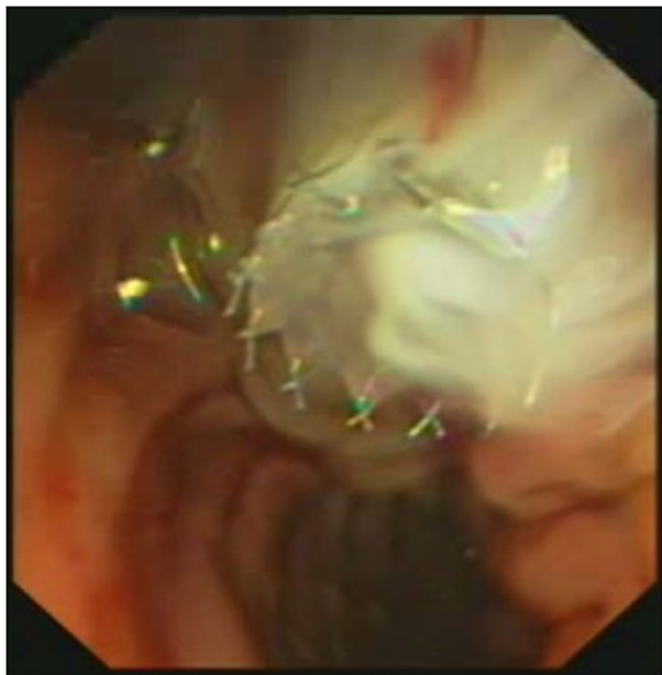


FIGURE 1. Side viewing endoscopic image showing pus gushing out of the papillary orifice in a case of severe acute cholangitis due to blocked stent.

recent computed tomography (CT) abdomen or magnetic resonance cholangio-pancreatography (MRCP) or endoscopic ultrasound (EUS) was done, the findings were noted. Initial resuscitation was done with intravenous fluids and empirical broad-spectrum antibiotics were started. The patient underwent endoscopic retrograde cholangio-pancreatography (ERCP) if the obstruction was at the level of common bile duct but below the confluence. Where the confluence was involved and not amenable for ERCP, PTBD was done. During ERCP/PTBD after taking all aseptic precautions, 5 mL of bile was aspirated in a sterile syringe and immediately sent for culture. Subsequently, biliary drainage was performed by placing a plastic biliary stent/PTBD catheter. Post biliary drainage, patients were admitted and received empirical intravenous antibiotics for 7 days. It was later modified as per the sensitivity pattern. Day 2 post ERCP/PTBD repeat procalcitonin and CRP were sent.

Follow up- all patients were followed up for 1 month through out-patient department visit/ telephonically and outcomes were assessed at the end of 1 month as complete improvement or death.

Outcomes measures

The primary outcome of the study was to evaluate the predictive value of change in CRP and procalcitonin levels post drainage in predicting complete improvement or death at 1 month. The secondary outcomes were to compare the factors associated with culture positive and culture negative cases of AC and also to study the microbiological spectrum isolated from bile and their antibiotic sensitivity pattern.

Endoscopic retrograde cholangiopancreatography (ERCP)

The ERCP was performed under conscious sedation and EVISEXERA II video duodenoscope was used for all the proce-

dures (TJFQ180V, Olympus, Japan). Standard cannulation was done by triple lumen sphincterotome (Ultratome XL, Boston Scientific, USA) that was preloaded with guidewire. Once the tip of the sphincterotome was engaged through the papillary orifice into the ductal bay, wire was advanced under fluoroscopic guidance and selective biliary cannulation was confirmed with the help of water soluble contrast cholangiogram. During the standard cannulation attempt, if it was not possible to cannulate with the Ultratome XL, we would switch over to other catheters as per our discretion.

Percutaneous transhepatic biliary drainage (PTBD)

It was performed under local anaesthesia. Under ultrasound guidance an intrahepatic duct was punctured with a fine lumbar puncture needle. Stylet was removed and needle entry into the bile duct was confirmed by aspiration of bile. Check cholangiogram with minimal contrast was obtained to confirm the biliary anatomy and level of obstruction. Then a guide wire was inserted through the needle into the biliary system and negotiated distal to the block. Needle was removed carefully and plastic dilators of various sizes were passed over the guide wire to dilate the tract appropriately. Eventually an external drain catheter with multiple side holes was advanced into the biliary system along the dilated tract and guide wire was finally withdrawn. Finally the catheter was secured at the skin insertion site with sutures.

Statistical analysis

All consecutive patients presenting within study period as mentioned above were included. The statistical analysis was carried out using IBM SPSS statistics software version 23.0. All quantitative variables were estimated using measures of central tendency (mean, median) and measures of dispersion (standard deviation). Qualitative or categorical variables were described as frequencies or proportions. Normality of data was checked by measures of skewness and Kolmogorov Smirnov tests of normality. As most of the data was skewed, median were calculated. Mann-Whitney U test was applied for comparing medians while proportions were compared using chi-square test. The significant variables identified in the above univariate analysis were then assessed using multivariate linear regression analysis. This exercise was performed to identify statistically significant factors predicting mortality and culture positivity. The mortality prediction of day 0 procalcitonin was measured by the area under the receiving operating characteristic (ROC) curve. $P < 0.05$ was considered to be statistically significant.

RESULTS

Seventy-two consecutive patients who met the inclusion criteria and gave written informed consent were enrolled in the study from August, 2020 till December, 2020 (TABLE 1). The median age was 55 years (IQR 43–62) and 42 (58.33%) patients were females. The etiology of obstruction in AC was due to benign causes in 45 (62.5%) patients and underlying malignancy was present in 27 (37.5%) patients. Choledocholithiasis was overall the most common cause of AC, observed in 33 (45.8%) patients followed by benign biliary stricture and gall bladder cancer in 8 (11.1%) patients each. The most common symptom at presentation was jaundice seen in 63 (87.5%) patients, followed by pain and fever seen in 50 (69.4%) and 47 (65.27%) patients respectively. Weight loss and anorexia was observed in 34 (47.2%) and 32 (44.4%) patients, respectively. Forty (55.5%) patients complained of cholestatic symptoms while only 2

TABLE 1. Baseline characteristics of all patients of acute cholangitis.

| Parameter | All patients (n=72) |
|---|-----------------------|
| Demography | |
| Age (years) (median, range) | 55 (43–62) |
| Females (n, %) | 42 (58.33) |
| Benign etiology (n, %) | 45 (62.5) |
| Malignant etiology (n, %) | 27 (37.5) |
| Etiology (n, %) | |
| CBD stone | 33 (45.8) |
| Benign biliary stricture | 8 (11.1) |
| Carcinoma gall bladder | 8 (11.1) |
| Hilar cholangiocarcinoma | 6 (8.3) |
| Carcinoma head of pancreas | 5 (6.9) |
| Distal cholangiocarcinoma | 4 (5.5) |
| Ampullary cancer | 3 (4.16) |
| Previous stent block | 2 (2.7) |
| Metastatic compression | 1 (3.8) |
| Portal cavernoma cholangiopathy | 1 (1.38) |
| Mirizzi syndrome | 1 (1.38) |
| Clinical parameter | |
| Jaundice (n, %) | 63 (87.5) |
| Pain (n, %) | 50 (69.4) |
| Fever (n, %) | 47 (65.27) |
| Charcot's triad (n, %) | 26 (36.11) |
| Both fever and jaundice (n, %) | 39 (54.17) |
| Weight loss (n, %) | 34 (47.2) |
| Anorexia (n, %) | 32 (44.4%) |
| Cholestatic symptoms (n, %) | 40 (55.5) |
| Altered mental status | 2 (2.8) |
| Laboratory parameter | |
| Haemoglobin (gm/dL) (mean ± SD) | 10.374±1.97 |
| WBC count (mm ³) (median and range) | 12000 (10625–15800) |
| Platelets (mm ³) (median and range) | 240.5 (173.25–321.75) |
| Serum creatinine (mg/dL) (median and range) | 0.7 (0.6–1.02) |
| AST(U/L) (median and range) | 83 (54.75–139) |
| ALT(U/L) (median and range) | 69 (42.75–115.25) |
| Total bilirubin (mg/dL) (median and range) | 9.035 (4.65–18.475) |
| Direct bilirubin (mg/dL) (median and range) | 7.75 (3.09–12.86) |
| Serum albumin (gm/dL) (median and range) | 3.0 (2.6–3.45) |
| PT-INR (median and range) | 1.20 (1.1–1.59) |
| Inflammatory markers | |
| Procalcitonin at admission (ng/mL) (median and range) | 0.55 (0.29–2.64) |
| Procalcitonin day 2 (ng/mL) (median and range) | 0.31 (0.2–1.1) |
| CRP at admission (mg/L) (median and range) | 44.1 (19.6–86.4) |
| CRP day 2 (mg/L) (median and range) | 15.8 (6.7–26.0) |

(2.8%) had altered mental status. Fourteen (19.4%) patients had a previous history of ERCP performed for biliary diseases while 13 (18.05%) patients had undergone cholecystectomy. Three patients (4.1%) had biliary-enteric anastomosis in the past. Co-morbidities in the form of diabetes mellitus and hypertension were present in 15 (20.8%) and 9 (12.5%) patients respectively. On examination 4 (5.5%) patients were found to be in shock while 2 (2.7%) had hypoxia and altered sensorium.

Median WBC count of the entire cohort was 12000 (10625–15800) mm³. The median INR of all patients was 1.20 (1.1–1.59). Similarly, median total bilirubin and direct bilirubin were 9.035 (4.65–18.475) mg/dL and 7.75 (3.09–12.86) mg/dl respectively (TABLE 1). At admission and day 2 post drainage, median procalcitonin were 0.55 (0.29–2.64) ng/mL and 0.31 (0.2–1.1) ng/mL respectively (*P* value<0.001). At admission median CRP was 44.1 (19.6–86.4) mg/L while day 2 post drainage CRP was 15.8 (6.7–26) mg/L (*P* value<0.001). (FIGURE 2 and 3).

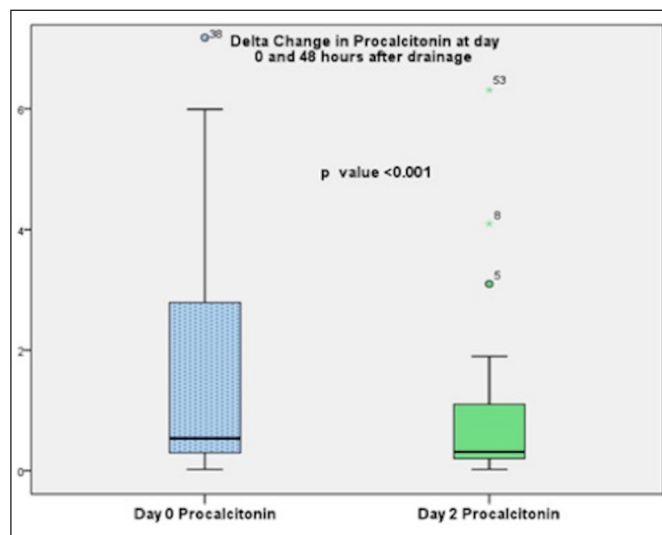


FIGURE 2. Delta change in procalcitonin between at admission (Day 0) and 48 hours post drainage (day 2) in all patients.

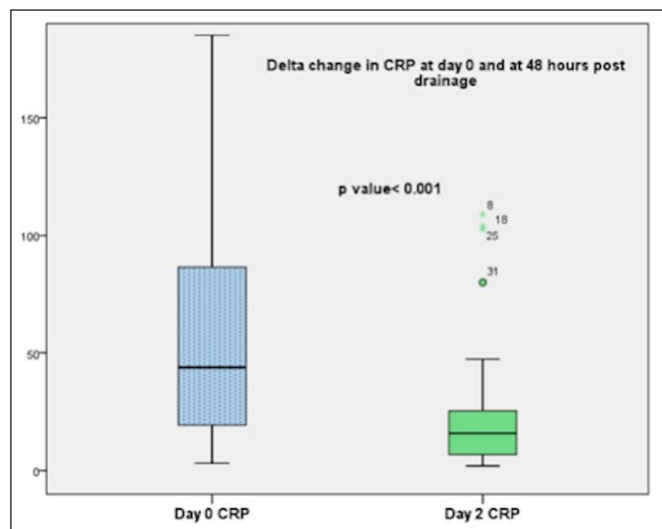


FIGURE 3. Delta change in CRP between at admission (day 0) and 48 hours post drainage (day 2) in all patients.

Out of the 72 patients, 25 (34.7%) had severe acute cholangitis, 21 (29.2%) had moderate while 26 (36.1%) had mild acute cholangitis. Among the patients with severe cholangitis (n=25), most common organ failure was found to be hepatic (INR >1.5), seen in 20 (80%) patients, followed by hematological (platelet count <1 lakh/mm³) and renal both in 7 (28%) patients. Cardiovascular collapse was found in only 4 (16%) patients.

Primary outcome

By 30 days, 57 (79.1%) patients had recovered while 15 (20.9%) patients died due to acute cholangitis. Of the 15 who died, 9 (60%) patients had underlying malignant etiology. In univariate analysis malignant etiology, absent pain abdomen, weight loss, anorexia, altered sensorium, grade of cholangitis, blood culture positivity, baseline hemoglobin, WBC count, serum albumin, INR and day 0 procalcitonin were found to be significant factors in predicting mortality. In multivariate analysis, only altered sensorium and INR were found to be independently associated with mortality (TABLE 2). Although the delta change in serum procalcitonin (*P* value<0.001) and CRP (*P* value<0.001) was significant (FIGURE 2 and 3), it had no bearing on the outcome. The 30 day mortality prediction of Day 0 procalcitonin was measured by receiver operating characteristic (ROC) analysis which resulted in an area under the curve (AUC) of 0.697 with a 95% confidence interval (95% CI) of 0.545–0.849. The optimal cut-off of procalcitonin would be 0.57ng/mL with a sensitivity and specificity of 80% and 60% respectively to predict mortality (FIGURE 4).

TABLE 2. Factors predicting 30-day mortality.

| Variables | Univariate analysis <i>P</i> -value | Multivariate analysis <i>P</i> -value |
|--------------------------|-------------------------------------|---------------------------------------|
| Malignant etiology | 0.043 | 0.882 |
| Absent pain | 0.001 | 0.772 |
| Weight loss | 0.023 | 0.995 |
| Anorexia | 0.011 | 0.524 |
| Altered sensorium | 0.005 | 0.007 |
| Grade of cholangitis | 0.001 | 0.365 |
| Blood culture positivity | 0.001 | 0.105 |
| Haemoglobin | 0.037 | 0.418 |
| WBC | 0.005 | 0.315 |
| Serum Albumin | <0.001 | 0.514 |
| PT-INR | <0.001 | 0.037 |
| Procalcitonin day 0 | 0.019 | 0.786 |

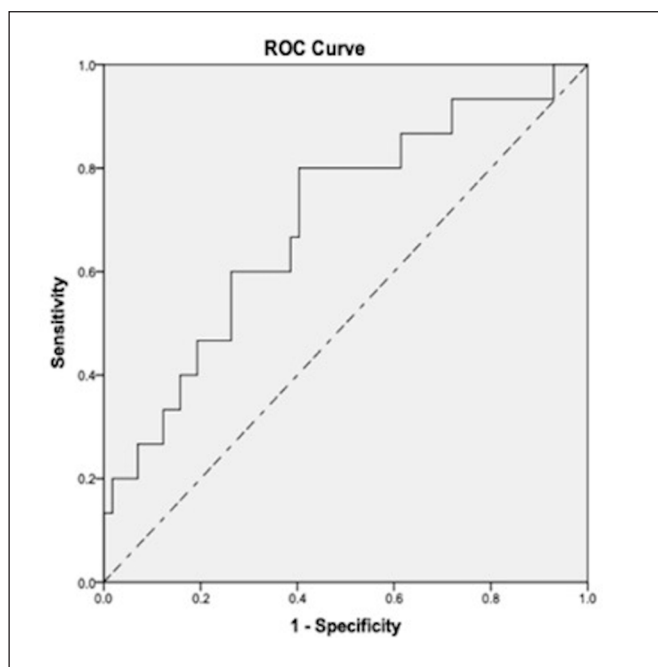


FIGURE 4. ROC curve derived for 30-day mortality prediction of day 0 procalcitonin.

Secondary outcomes

In univariate analysis it was found that history of fever, diabetes mellitus, higher grade of cholangitis, WBC count, AST, Day 0 procalcitonin, CRP and lower serum albumin were associated with culture positivity. However multivariate analysis showed that only history of fever, diabetes mellitus and WBC count were significantly associated with bile or blood culture growth. Growth in blood culture was seen in only 5 (6.9%) patients. Polymicrobial growth was noted in only 1 (20%) blood culture and the rest 4 (80%) blood samples grew a single organism. Out of the six isolates, 5 (83.3%) were gram negative and the rest 1(16.6%) was gram positive. Most common organism isolated from blood was *E. coli* (66.6%) followed by *Klebsiella pneumoniae* and *Enterococcus faecium* in 16.7% of the patients each. In blood, sensitivity of *E. coli* was 75% to amikacin, meropenem, imipenem followed by 25% to piperacillin-tazobactam, cefepime. It was found resistant to ciprofloxacin and cefoperazone-sulbactam. *Klebsiella* and *Enterococcus* were isolated in only 1 blood culture sample each where *Klebsiella* was sensitive to colistin and resistant to amikacin, gentamicin, piperacillin-tazobactam, cefepime, imipenem and meropenem. *Enterococcus* was sensitive to linezolid, teicoplanin, vancomycin and gentamicin while resistant to tetracycline, erythromycin and ampicillin.

Bile culture was collected at the beginning of drainage procedure (ERCP/PTBD). Bile culture samples showed a growth of organism in 39 (54.1%) patients out of which 5 (12.8%) samples had a growth of two organisms. A total of 44 microorganisms were isolated out of which 43 (97.6%) were gram negative and only 1 (2.3%) was gram positive organism. Most frequent microorganism isolated from bile was *E. coli* (47.7%) followed by *Pseudomonas* (22.7%) and *Klebsiella* (15.9%). *Acinetobacter* and *Enterobacter* were isolated in 4.5% of the patients each while *Enterococcus faecium* and *Aeromonas* in 2.3% each (TABLE 3). The antimicrobial sensitivity pattern of organisms in bile culture is shown in TABLE 4.

TABLE 3. Microbiological profile of included patients of acute cholangitis.

| Organism | Blood culture (n=72) | Bile culture (n=72) |
|-------------------------|----------------------|---------------------|
| Growth | 5 (6.9%) | 39 (54.1%) |
| Multiple organisms | 1/5 (20%) | 5/39 (12.8%) |
| Gram negative organisms | 5 (83.3%) | 43 (97.6%) |
| Gram positive organisms | 1 (16.6%) | 1 (2.3%) |
| <i>E. coli</i> | 4 (66.6%) | 21 (47.7%) |
| <i>Pseudomonas</i> | 0 | 10 (22.7%) |
| <i>Klebsiella</i> | 1 (16.6%) | 7 (15.9%) |
| <i>Acinetobacter</i> | 0 | 2 (4.5%) |
| <i>Enterobacter</i> | 0 | 2 (4.5%) |
| <i>Enterococcus</i> | 1 (16.6%) | 1 (2.3%) |
| <i>Aeromonas</i> | 0 | 1 (2.3%) |

DISCUSSION

In this prospective study of 72 consecutive patients of AC, we found that the delta change in serum procalcitonin and CRP although significant, had no bearing on the outcome at 1 month. History of fever, diabetes mellitus and WBC count were significantly associated with bile or blood culture growth. Altered sensorium and INR were found to be independently associated with mortality at 1 month. The 30-day mortality prediction of procalcitonin at admission, measured by ROC analysis, resulted in an area under the curve (AUC) of 0.697 (95%CI 0.545–0.849). A procalcitonin cut off of 0.57ng/mL would have a sensitivity and specificity of 80% and 60% respectively to predict mortality. Therefore, procalcitonin could be a promising option for prediction of outcome in AC.

AC is an emergency that needs prompt fluids, antibiotics and drainage. Management of AC depends on the severity. Serum procalcitonin has been used as a marker for early detection of sepsis. Higher levels have correlated with severe bloodstream infections⁽⁷⁾. Its levels are undetectable in normal conditions. The synthesis of procalcitonin is increased by bacterial endotoxins and cytokines like TNF-alpha, interleukin-6 and interleukin-1 beta⁽⁸⁾. The levels of

procalcitonin have a short time of induction (6–12 hours after start of infection) and stay in blood for a long time for early detection ($t^{1/2}$ =20–24 hours)^(9,10). Procalcitonin has a sensitivity of 77% and specificity of 79% for diagnosis of sepsis in critically sick patients⁽¹¹⁾. Procalcitonin has also been used to guide antibiotic stewardship⁽¹²⁾. Hence, procalcitonin has been not only used as a biomarker in sepsis but also for risk stratification and guide antibiotic therapy.

CRP and WBC count have been used in classification of AC in TG18 guidelines. These markers can be elevated in various non-inflammatory conditions and lack specificity for detection of bacterial infections. Shinya et al. showed higher procalcitonin levels correlated with urgent need of biliary drainage⁽⁵⁾. In a retrospective study, Lee et al. showed procalcitonin has been used as a marker for deciding the need of intervention in AC⁽¹³⁾. Umefune et al. showed a procalcitonin level of 2.2 ng/mL for prediction of severe cholangitis but the area under the curve was not significant for detection of moderate/severe cholangitis⁽⁴⁾. Similarly, IL-17 and procalcitonin have been combined for detection of severe AC⁽⁶⁾. However, none of the earlier studies used the concept of decline in procalcitonin and CRP post drainage for the prediction of outcome in AC. In our study, despite drainage and significant decline in procalcitonin and CRP, it had no significant relationship with outcomes of acute cholangitis at 1 month.

In our study, bile culture positivity was seen in 54.1% of the patients while blood culture yielded a growth in only 6.9% of the patients. Both bile and blood cultures yielded predominantly monomicrobial growth. In bile more than 95% isolates were gram negative whereas in blood cultures around 85% were gram negative. The most common organisms isolated from bile were *E. coli* (47.1%) followed by *Pseudomonas* and *Klebsiella* in 22.7% and 15.9% respectively. *Acinetobacter*, *Enterobacter*, *Aeromonas* and *Enterococcus* comprised less than 5% each. In blood, the most frequent isolate was *E. coli* (66.6%) followed by *Klebsiella* and *Enterococcus*. Studies from different geographical areas have reported positivity rates for bile culture in the range of 28% to 93% while positivity rates for blood culture ranged from 21% to 71% with gram negative organisms more common than gram positive across blood and bile cultures. Most frequent isolates in these studies were *E. coli*, *Klebsiella* and *Enterococcus*⁽¹⁴⁻²⁰⁾. Low yield of blood culture in our study could be explained by the fact that most of the patients had

TABLE 4. Antimicrobial sensitivity of organisms isolated from bile culture.

| Antibiotics | <i>E. coli</i> (%) | <i>Pseudomonas</i> (%) | <i>Klebsiella</i> (%) | <i>Acinetobacter</i> (%) | <i>Enterobacter</i> (%) |
|-------------------------|--------------------|------------------------|-----------------------|--------------------------|-------------------------|
| Amikacin | 85 | 90 | 57.1 | – | 100 |
| Gentamicin | – | 60 | – | – | – |
| Netilmicin | – | 57.1 | – | – | – |
| Tobramycin | – | 85.7 | – | – | – |
| Cefoperazone-sulbactam | 66.6 | 50 | 83.3 | 50 | 0 |
| Cefepime | 44.44 | 62.5 | 28.5 | 50 | – |
| Ceftazidime | 21.4 | 33.3 | 16.6 | – | – |
| Piperacillin-tazobactam | 61.9 | 50 | 71.4 | – | 100 |
| Imipenem | 42.8 | 50 | 42.8 | 50 | 100 |
| Meropenem | 75 | 60 | 71.4 | 50 | 100 |
| Ciprofloxacin | 10 | 66.6 | 57.1 | 50 | 0 |
| Tigecycline | 100 | – | 85.7 | – | – |

already received broad spectrum antibiotics before reaching our centre. Also, the proportion of *Pseudomonas* was higher and *Enterococcus* lesser in bile as compared to these studies. In our cohort, 41% of the patients underwent some form of biliary procedure (ERCP, cholecystectomy or biliary enteric anastomosis) before the current admission. Nosocomial pathogens can contaminate endoscopes and irrigating fluid which could explain high positivity with *Pseudomonas* in bile cultures in our study population. Overall comparison of our study with other studies have not revealed any major changes in the cultured microorganisms signifying that microbial profile has been static over the last 20 years.

In our study most of the gram-negative isolates were found to be highly sensitive to tigecycline (85–100%) and amikacin (57–90%). Good susceptibility was recorded for meropenem (60–75%), ceftazidime-sulbactam (50–83%) and piperacillin-tazobactam (50–71%). Low sensitivity was seen for imipenem (42–50%), cefepime (28–60%), ceftazidime (16–33%) and ciprofloxacin (10–60%). While the gram-positive isolates were sensitive to vancomycin, teicoplanin, linezolid and resistant to amikacin, gentamicin, tetracycline and erythromycin. A retrospective study from Germany showed gram negative bacteria with very high susceptibility to carbapenems (>95%) but low sensitivity to piperacillin-tazobactam, fluoroquinolones and cephalosporins⁽²¹⁾. A recent study showed gram negative bacilli which were sensitive to carbapenems, amikacin and piperacillin-tazobactam but were highly resistant to cephalosporins and fluoroquinolones. Gram positive cocci were more sensitive to vancomycin, teicoplanin and amoxicillin⁽²²⁾.

In our study amikacin was found to have high susceptibility against gram negative bacilli, but due to its nephrotoxic and ototoxic side effects, Surgical Infection Society/Infectious Diseases Society of America (IDSA) recommends against the empiric use of aminoglycosides when other safer and effective antibiotics are available⁽²³⁾. Thus, based on the sensitivity pattern in our study piperacillin-tazobactam, meropenem or ceftazidime-sulbactam would serve as reasonable alternatives to amikacin. This is in accordance with the TG-18 guidelines which recommend using Piperacillin/tazobactam as the empirical therapy across all the grades of acute cholangitis. Vancomycin is recommended to cover *Enterococcus spp.* for Grade III community acquired and all health-care associated AC⁽²⁴⁾.

In our study, 30-day mortality due to AC was 20.9% of which 73.3% of the patients had severe cholangitis, 20% had moderate and 6.6% had mild cholangitis. In the largest multicenter study by Gomi et al. 30-day mortality due to acute cholangitis was 2.8% and 47.7% of the patients who died had severe cholangitis, 33.1% had moderate and 19.2% had mild cholangitis⁽¹⁴⁾. In our study 63.7% of the patients had moderate or severe cholangitis which according to Tokyo Guidelines 2018 should have their biliary

system drained within 24 hours, however, patients were referred to our center with a considerable delay either due to delay in diagnosis or travel restrictions imposed in view of COVID-19. This could explain the higher mortality seen in our study. Our data showed that mortality increased with the increasing grade of cholangitis and hence validated the Tokyo Guidelines 2013/2018 severity assessment⁽³⁾.

Our study has few limitations. Firstly it was a small scale single centre study. Sample size was less due to decreased footfall in the hospital owing to the travel restrictions and lockdown imposed in view of COVID-19 pandemic. Secondly some of the patients had already received broad spectrum antibiotics before reaching our institution leading to low bile and blood culture positivity. However, the study has many strengths including the prospective consecutive enrollment of AC patients and serial monitoring for decline in inflammatory markers like procalcitonin and CRP post-drainage and assessment of their role in predicting outcomes in AC. The study also provides an updated version of organisms detected in blood and bile culture with their antibiotic sensitivity providing justification for the current choice of initial antibiotics.

To conclude, the change in serum procalcitonin and CRP levels at 48 hours post drainage although significant, had no impact on the outcome of acute cholangitis at 1 month. A procalcitonin cut off of 0.57ng/mL would have a sensitivity and specificity of 80% and 60% respectively to predict mortality in AC.

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Authors' contribution

Jain A: data collection, survey execution, writing the draft and its review, statistical analysis. Jena A: data collection, survey execution, writing the draft. Gautam V: data collection, critical review of the manuscript. Samanta J: data collection. Sharma V and Mandavdhare HS: design and concept, data collection, survey execution, statistical analysis, critical review of the manuscript. All authors: final approval of the manuscript for submission.

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Jain A, Jena A, Gautam V, Samanta J, Sharma V, Mandavdhare HS. Papel da mudança nos níveis de marcadores inflamatórios pós drenagem na previsão de resultado em colangite aguda. *Arq Gastroenterol.* 2022;59(2):212-8.

RESUMO – Contexto – A colangite aguda (CA) é uma emergência gastro-intestinal associada à significativa mortalidade. O papel da mudança nos níveis de marcadores inflamatórios pós drenagem na previsão do desfecho em CA é incerto. **Objetivo** – Avaliar o valor preditivo das alterações nos níveis de proteína reativa C (PCR) e procalcitonina após drenagem biliar em relação aos desfechos (sobrevida ou mortalidade) em um mês. **Métodos** – Realizou-se estudo observacional prospectivo de adultos consecutivos que apresentam CA. Na admissão e após 48 horas de drenagem biliar, foram analisadas a procalcitonina e a PCR. **Resultados** – Entre agosto de 2020 e dezembro de 2020, foram recrutados 72 pacientes consecutivos de CA. A idade mediana dos pacientes foi de 55 anos (faixa de 43 a 62 anos) e 42 (58,33%) do sexo feminino. Embora a variação delta no soro procalcitonina (valor $P < 0,001$) e PCR (valor $P < 0,001$) tenha sido significativa, não houve influência sobre o resultado. Sensório alterado e INR foram independentemente associados à mortalidade em 1 mês. A previsão de mortalidade de 30 dias no dia 0 da procalcitonina foi medida pela análise característica operacional receptora que resultou em uma área sob a curva de 0,697 com intervalo de confiança de 95% (IC95%) de 0,545–0,849. O corte ideal de procalcitonina seria de 0,57ng/mL com sensibilidade e especificidade de 80% e 60% respectivamente para prever a mortalidade. **Conclusão** – A mudança nos níveis de procalcitonina sérica e PCR em 48 horas após a drenagem, embora significativa, não teve impacto no resultado da colangite aguda.

Palavras-chave – Procalcitonina; proteína C reativa.

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