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Role of Serum Procalcitonin in Prediction of Severity in Patients with Acute Cholangitis

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Abstract

Background Cholangitis is one of the commonest emergencies encountered by gastroenterologists that may warrant drainage of biliary system. Serum procalcitonin (PCT) is an important biomarker of cholangitis with a potential to guide early therapeutic decision.

Materials and Methods We did a retrospective analysis of prospectively maintained data of patients admitted in the hospital from March 2018 to September 2020 with a diagnosis of acute cholangitis based on Tokyo 18 guidelines (TG-18). All the demographic parameters, biochemical and hematological parameters, and the result were recorded.

Results One-hundred two patients were admitted to our hospital with a mean age of 51.07 ± 7.99 years, among which 58.5% (59/102) were females with most common etiology being choledocholithiasis (64%). Fever, jaundice, and abdominal pain were seen in 78% (80/102), 73.3% (74/102), and 76.9% (78/102) of patients, respectively. Organ failure was seen in 29.3% (29/102) of patients with most common organ failure being acute kidney injury. Mild, moderate, and severe cholangitis as per TG-13 was seen in 43.9, 26.8, and 29.3% of patients, respectively. Elevated PCT levels were associated with severe disease (76.7 vs. 26.5%, $p < 0.05$). Forty-three percent (44/102) patients were managed with delayed biliary drainage, while the majority of remaining specifically with raised PCT levels needed early endoscopic intervention.

Conclusion In this retrospective analysis, we showed that most common etiology of cholangitis in was choledocholithiasis. Raised serum PCT levels were significantly associated with increased severity of cholangitis.

Keywords
- cholangitis
- choledocholithiasis
- procalcitonin

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Introduction

Acute cholangitis (AC) is one of the commonest, yet potentially treatable emergency encountered by gastroenterologists worldwide. The process of biliary stasis that is most commonly secondary to mechanical obstruction like choledocholithiasis, benign strictures, malignancy, and stent blockade, and increased intraductal pressure is main pathogenic event that leads to AC.[1] The rise in intraductal pressure causes bacterial translocation into the systemic circulation known as cholangial–venous reflux that is the basic pathophysiology behind suppurative AC.[2] Moreover, the biliary stasis abolishes the continuous flushing activity of bile and the bacteriostatic effect of bile salts, and ultimately both lead to severe systemic inflammatory cascade and multiorgan dysfunction. This becomes potentially lethal when sepsis sets in, and prompt triage is mandatory to define timely management strategy and achieve favorable outcome.

The severity assessment is currently guided by Tokyo Grading; however, recent data have shown serum procalcitonin (PCT) level at admission to be a useful predictor of clinical severity.[3] PCT is a 116 amino acid protein and precursor of calcitonin. Under physiological conditions, calcitonin is produced predominantly by C cells of the thyroid gland, and serum PCT is almost undetectable. The normal values of serum PCT are less than 0.1 ng/dL and values more than 0.25ng/dL are suggestive of infective process.[4] In states of systemic bacterial infection, PCT is readily produced by various tissues of the body (e.g., lung, kidney, liver, adipose cell, and muscle) immediately after disease onset (usually within 6–12 h), and its serum values rise to significantly higher levels.[5–8] There are noninfective causes of serum PCT elevation that include malignancies (medullary thyroid carcinoma, lung carcinoma, and lymphoma), drugs (steroids, rituximab), and chronic kidney disease (CKD).[9,10]

Given the importance of risk stratification in AC and appropriate management, serum PCT might be a helpful biomarker. We evaluated our database to see the correlation between serum PCT and grades of cholangitis across all etiologies and whether serum PCT at admission has any role in deciding treatment strategy.

Methods

We did a retrospective analysis of prospectively maintained data of patients admitted in a single tertiary care center from 2019 to September 2020 with a diagnosis of AC and severity grading as mild, moderate, and severe cholangitis as per Tokyo 18 guidelines (TG-18) guidelines. Clinical parameters, organ failures, and levels of PCT were measured at baseline. We measured serum PCT levels (measured by immunoluminometric assay) in patients and compared the values between different grades of severity of cholangitis. The upper limit normal of serum PCT was taken as 0.25 ng/dL. This study was approved by the institutional ethical committee, and was conducted according to the guidelines in the Helsinki Declaration. Written informed consent was obtained from all patients.

Patients

All patients aged more than 18 years of age with diagnosis of AC as per TG-18 were included as cases. Both referred (from peripheral healthcare facility) and direct admission patients were included. Other inclusion criteria were; if no serum PCT was done at the time of admission, patients with a history of known malignancy, patients on steroids and patients of CKD. Patient demographic characteristics including age, sex, body mass index, comorbidities were obtained. Symptoms at presentation along with hematological and biochemical variables including inflammatory markers like PCT and total leukocyte count (TLC) were recorded. All patients received fluid therapy and parenteral antibiotics. Inotropic agents were administered in fluid nonresponsive cases. The assessment of initial medical treatment response and timing and method of biliary decompression was done as per the discretion of the treating physician.

Statistics

All analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Continuous variables were summarized as mean and standard deviation. Categorical variables were summarized as frequency and percentage. Chi-squared test was used to analyze the relationship between two categorical variables. Two-sided *p*-valves were reported and a *p*-valve less than 0.05 was considered statistically significant.

Results

Patient characteristics The mean age of our study population ($n = 102$) was 51.1 ± 7.9 years, among which 58.5% (59/102) patients were females. The baseline characteristics of study cohort is given in ►**Table 1**. The four most common presenting symptoms were abdominal pain, jaundice, vomiting, and fever among which fever, jaundice, and abdominal pain were seen in 76.9 (78/102), 73.3 (74/102), and 78% (80/102) of patients, respectively. Charcot's triad including pain, jaundice, and fever was present in 45% (46/102) of patients, whereas two symptoms were present in 90% (92/102) of patients. The most common organ failure was renal failure, present in 60% of severe cholangitis patients followed by respiratory and hemodynamic failures

Etiology The spectrum of etiology included choledocholithiasis, post-cholecystectomy bile duct injury, hydatid cyst, common bile duct stent block, malignant obstruction, and others (►**Table 1**). The most common etiology in this study was choledocholithiasis (64%). Mild, moderate, and severe cholangitis was seen in 43.9, 26.8, and 29.3% of patients, respectively.

Blood cultures Blood culture was positive in 25% of patients among which 80% were having severe (grade-III) cholangitis. The various organisms grown on culture are shown in results (►**Fig. 1**).

Table 1 Baseline characteristics of acute cholangitis study cohort ($n = 102$)

Variable		Mean ± SD
Age (years)		51.07 ± 7.99
Weight (kg)		68 ± 12
Females		58%
BMI (kg/m^2)		26 ± 2.8
Comorbidity (%)	Metabolic syndrome	3
	Diabetes	5
	Hypertension	9
Presenting symptom (%)	Pain	90
	Jaundice	70
	Fever	82
	Vomiting	50
	Charcot's triad	45
Etiology (%)	Choledocholithiasis	64
	Post chole BDI	15
	Hydatid cyst	10
	CBD stent	5
	Benign biliary stricture	3
	Malignant obstruction	4
	Others	1
Blood pressure (%)	Normal	82
	Hypotension-fluid responsive	15
	Shock requiring Pressors	5
Mentation (%)	Normal	97
	Altered	3
SPO2 (%age)	Normal (>95)	75
	Mild hypoxemia (90–95)	20
	Severe hypoxemia (<90)—ARDS	7
TLC (x1000/μL)		8.7 (5.4–13.2)
Platelet (x1000/mL)		120 (90–180)
CRP (mg/dL)		4.9 (0.2–11.8)
PCT (ng/mL)		9.8 (0.4–38)
AST (U/L)		180(50–450)
ALT (U/L)		200(65–459)
ALP (U/L)		365(190–850)
Bilirubin (mg/dL)		3.5 (0.0–8.9)
INR		1.3 (0.98–1.9)
Creatinine (mg/dL)		1.57(0.78–3.2)
BUN (mg/dL)		19 (10–28)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; INR, international normalized ratio; PCT, procalcitonin; SD, standard deviation; TLC, total leukocyte count.

Procalcitonin and Other Inflammatory Markers for Assessment of Severity

The sensitivity and specificity of serum PCT for predicting grade of cholangitis and septic shock are plotted under receiver operating-characteristic with area under the curve of 0.65 and 0.97, respectively (►**Figs. 2** and **3**). Among TLC, C-reactive protein (CRP), and PCT, the statistically significant prediction for severe cholangitis was only seen with PCT,

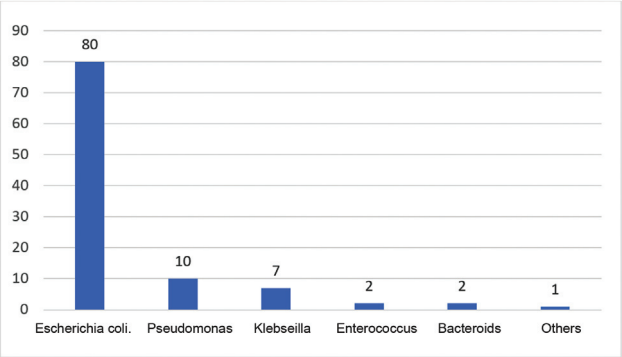

Fig. 1 Various microorganisms grown on blood cultures.

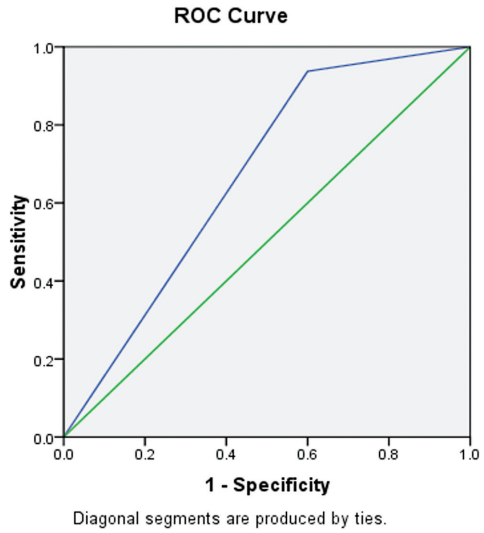

Fig. 2 Receiver operating-characteristic (ROC) curve for procalcitonin and severity of cholangitis.

with p = 0.035, $p = 0.92$, and $p = 0.052$ for PCT, TLC, and CRP, respectively (►**Table 2**).

PCT and organ failures Values of PCT vary significantly between the groups when patients were compared in terms of severity of cholangitis, cholangitis with or without organ failure, and patients with or without positive blood culture.

Correlation of PCT with severity of disease, presence or absence of organ failures and blood culture e PCT values were significantly variable in patients in terms of severity of cholangitis (mild–moderate: 0.8 [0.2–2.5] vs. severe cholangitis: 6.9 [0.6–38]) organ failure (organ failure present: 6.9 Q10 [0.6–38] vs. organ failure absent: 0.8 [0.2–2.5]) and also PCT values also differ from blood culture positive: 5.8 [0.9–38]

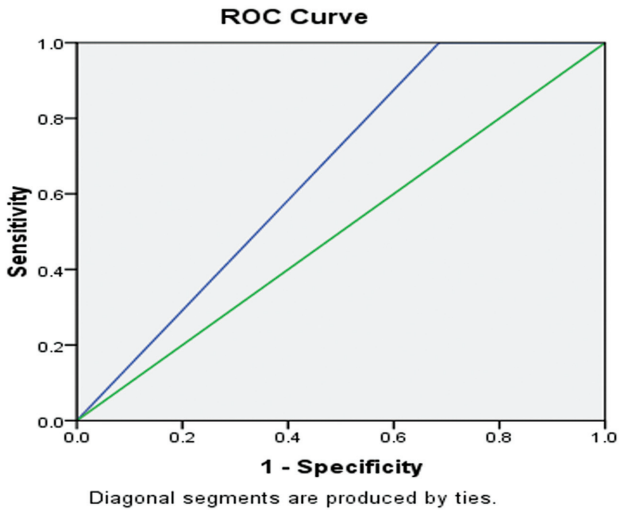

Fig. 3 Receiver operating-characteristic (ROC) curve for procalcitonin and shock.

vs. negative: 1.1 [0.4–10.5]. The mean serum PCT levels were 2.9 ± 1.2. Elevated PCT levels were significantly associated with severe disease compared to mild-to-moderate cholangitis (76.7 vs. 26.5%, $p < 0.05$), and majority of these (90%) needed early (<24 hours) endoscopic biliary drainage. Overall mortality in our studied group was 3.3%.

Discussion

AC is an emergency where endoscopic intervention in addition to aggressive medical management can be lifesaving, and the delay in same especially in severe cases results in increased mortality. According to TG-18 guidelines, severe cholangitis is characterized by sepsis-associated life-threatening organ failure, while mild-to-moderate cholangitis is not associated with organ failures. The main aim of this study was to obtain a serum biomarker, which is easily done in laboratory, and correlate its values to predict severity of disease, organ failure, response to treatment, and mortality.

There are varied etiologies of cholangitis in our study; most common etiology of AC is choledocholithiasis. The most common organ failure observed is acute kidney injury. AC results from biliary stasis due to obstruction to bile flow and subsequent infection of static bile. While the fluid therapy and antibiotics are indicated in all patients, biliary drainage becomes cornerstone treatment in AC and as per TG-18 guidelines. In patients with mild-to-moderate cholangitis, biliary drainage should be performed within 24 to 48 hours.

Table 2 Levels of different serum markers across all grades of acute cholangitis based on TG-13

Marker	Grade 1 cholangitis ($n = 43.9\%$)	Grade II cholangitis ($n = 26.8\%$)	Grade III cholangitis ($n = 29.3\%$)	*p*-Value
TLC (x1000/μL)	7.2 (4.3–12.2)	6.1(5.4–12.8)	8.5(6.5–14.2)	0.092
CRP (mg/dL)	0.8 (0.5–1.2)	3.9 (0.9–5.9)	4.6 (0.8–11.4)	0.052
PCT (ng/mL)	0.4 (0.2–1.3)	1.2 (0.5–2.5)	6.9 (0.6–38)	0.035

Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; TG-13, Tokyo Grading-13; TLC, total leukocyte count.

Patients with mild-to-moderate cholangitis that fail to respond to conservative management for 24 hours and patients with severe (suppurative) cholangitis require urgent (within 24 hours) biliary decompression. In our study, 58 (57%) patients needed emergency intervention, while 44 (43%) were subjected to delayed intervention.

Shinya et al[11] have concluded that many cases of AC with positive hemocultures or purulent bile were classified as either mild or moderate cholangitis on the basis of TG-13 grading despite the fact that these cases represent systemic septicemia and need early biliary drainage for source control to prevent imminent organ failure. This highlights the importance of serum markers to reflect impending organ failure and guide to early intervention. Serum PCT has been shown to correlate well with systemic septicemia and severity of cholangitis at the earliest and a useful serum marker to prevent delayed intervention.[6]

This study shows PCT levels at admission were significantly raised in severe AC irrespective of etiology, and the serum level was proportional to the increasing severity of AC. This finding translates into the ability of PCT to predict severe cases of AC at the earliest and be useful clinical guide to decide management. In this study, all patients with grade III with hemodynamic failure had higher elevation of serum PCT with none of them had PCT values below 3.5 ng/dL. This probably reflects the cutoff level where AC starts worsening and degenerating into septic shock. The results were similar to study conducted by Lee et al, where he recorded a cutoff 3.7ng/dL for deterioration into shock.[12] Most previous studies have reported significantly higher levels of serum procalcitonin in patients assessed as having severe AC based on the TG severity grade.[12–17]

We studied the microorganisms found in the bile and their association with grade of cholangitis. The majority of patients with positive blood culture (~95%) had hemodynamic compromise, and all patients had hypotension.[11] The low blood culture yield is probably related to containment of infection within biliary system in most patients and use of prior antibiotics before hospitalization.

Although PCT seems to be a marker for diagnosis, severity assessment, treatment response, it is important to note that PCT is not a holy grain marker for cholangitis, and its interpretation should be done in conjunction with other clinical findings and test results.

Despite small sample numbers, we showed that serum PCT levels are useful at admission when assessing the severity of AC and could prove potential guide to early intervention as backed up by some Indian studies also.[18,19]

Ethical Statement
Not applicable.

Authors' Contribution
All authors contributed equally to the article.

Data Availability Statement
There is no data associated with this work.

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Conflict of Interest
None declared.

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