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ORİJİNAL ARAŞTIRMA

Procalcitonin as a Prognostic Factor in Acute Cholangitis

Akut Kolanjitte Prognostik Bir Faktör Olarak Prokalsitonin

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ABSTRACT

Aim: In this study, we evaluated the efficacy of procalcitonin levels at admission in predicting disease severity and early biliary drainage in patients admitted to our hospital with a diagnosis of acute cholangitis.

Material and Method: The data of the patients who were treated in our clinic and whose procalcitonin level was studied within the first 24 hours were analyzed retrospectively. Tokyo criteria were used to evaluate the diagnosis of cholangitis. Within the scope of the study, 384 patients were evaluated.

Results: The median age of the patients was 69, and 215 (56%) of them were men. Biliary calculi were the most common predisposing factor. Of these, 170 (44.3%) were grade 1, 102 (26.5%) were grade 2 and 112 (29.2%) were grade 3. The median drainage time was 48 hours. At least one comorbidity was seen in 81.3% (312 patients). Procalcitonin, white blood cell and C-reactive protein median values were 2.3 ng/ml (0.01-301.9), 11.6x10^9/L (2410-55790) and 87.6 mg/L (3.4-413.2), respectively. It was determined that there was a statistically significant difference between the groups in terms of procalcitonin levels.

Conclusions: As a result of the analysis performed in our study, a strong correlation was found between procalcitonin level and disease severity and it was shown that serum procalcitonin level increased as the disease became more severe.

Keywords: Acute cholangitis, procalcitonin, severity, prognosis

ÖZ

Amaç: Bu çalışmada, hastanemize akut kolanjit tanısı ile başvuran hastalarda başvuru sırasındaki prokalsitonin düzeylerinin hastalık şiddetini ve erken biliyer drenajı öngörmedeki etkinliğini değerlendirdik.

Gereç ve Yöntem: Kliniğimizde tedavi edilen ve ilk 24 saat içinde prokalsitonin düzeyi çalışılan hastaların verileri retrospektif olarak analiz edildi. Kolanjit tanısını değerlendirmek için Tokyo kriterleri kullanıldı. Çalışma kapsamında 384 hasta değerlendirildi.

Bulgular: Hastaların ortanca yaşı 69 idi ve 215'i (%56) erkekti. Biliyer taş en sık görülen predispozan faktördü. Bunların 170'i (%44.3) grade 1, 102'si (%26.5) grade 2 ve 112'si (%29.2) grade 3 idi. Ortanca drenaj süresi 48 saatti. Hastaların %81,3'ünde (312 hasta) en az bir komorbidite görüldü. Prokalsitonin, beyaz kan hücresi ve C-reaktif protein medyan değerleri sırasıyla 2,3 ng/ml (0,01-301,9), 11,6x10^9/L (2410-55790) ve 87,6 mg/L (3,4-413,2) idi. Prokalsitonin düzeyleri açısından gruplar arasında istatistiksel olarak anlamlı bir fark olduğu tespit edilmiştir.

Sonuçlar: Çalışmamızda yapılan analiz sonucunda prokalsitonin düzeyi ile hastalık şiddeti arasında güçlü bir korelasyon bulunmuş ve hastalık şiddetlendikçe serum prokalsitonin düzeyinin arttığı gösterilmiştir.

Anahtar Kelimeler: Akut kolanjit, prokalsitonin, hastalık şiddeti, prognoz

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INTRODUCTION

Acute cholangitis is a biliary tract infection that mostly occurs due to malignant or benign obstruction in the biliary system and may have a fatal course in the absence of early biliary drainage (1). Stasis and infection develop in the biliary tract secondary to obstruction and fever, abdominal pain and jaundice are observed in the clinical picture. The most common causes of biliary obstruction in patients with acute cholangitis are biliary stones (28%-70%), benign strictures (5%-28%) and malignancy (10%-57%) (2).

Although mortality rates reported in acute cholangitis are variable, it has been shown that this rate has decreased with improved treatment methods. Nevertheless, mortality remains high in untreated or severe cases. The average mortality rate in severe cases of acute cholangitis is reported to be 20%-30% (1, 2).

In addition to clinical findings, various laboratory tests such as white blood cells, platelets, C-reactive protein, bilirubin and albumin are used to determine the severity of the disease. Procalcitonin, which has recently taken its place among the widely used laboratory tests, is a 116 amino acid propetide which is a precursor of calcitonin and mostly secreted from C cells in the thyroid gland (3). When its increase in infectious pictures was demonstrated with studies conducted in the early 1990s, it was used routinely as a serum biomarker especially in the diagnosis of sepsis and bacterial infections (4, 5).

The management of the diagnosis and treatment of acute cholangitis is determined according to the Tokyo Guidelines, which are updated and published by the Japanese Society of Hepato-Biliary-Pancreatic Surgery at approximately 5-year intervals. The value of procalcitonin in predicting severity was highlighted in the Tokyo Guide, which was last published in 2018, and was discussed within the scope of the following research questions. Referring to the limited number of studies conducted, it was stated that this situation should be evaluated and supported with further studies (2).

In this study, we aimed to examine the value and importance of serum procalcitonin levels reflecting inflammatory processes in predicting mortality and disease severity in patients with acute cholangitis.

METHODS

Our study was conducted on patients who applied to Ankara Turkey Yüksek İhtisas Training and Research Hospital Gastroenterology outpatient clinic between January 2016 and February 2018. It includes the records of patients who were diagnosed with acute cholangitis in our clinic on the specified dates according to the Tokyo 2013 guideline and whose procalcitonin level was measured in the first 24 hours.

Of the 632 patients retrospectively reviewed through their medical electronic recods, The study collected data on various factors including age, gender, presence of comorbid diseases, factors that may increase the risk of cholangitis, recent use of antibiotics within past 3 months for various infections (previous cholangitis attacks, pneumonia, urinary tract infections e.g.), history of biliary intervention within the past 6 months, recent hospitalization within the past 3 months, discharge status, duration of biliary drainage, severity of cholangitis, and laboratory test results.384 were included in the study. We excluded 144 cases in which procalcitonin was not studied within the first 24 hours, 68 cases with acute cholecystitis, 21 cases with acute pancreatitis and 15 cases with exitus due to reasons other than acute cholangitis. During the analysis of the study data, due to the publication of the new version of the Tokyo Guidelines, patients were classified as Grade-1, Grade-2 and Grade-3 in terms of disease severity by evaluating clinical and laboratory findings according to the Tokyo Guidelines 2018. In terms of disease outcome, they were grouped as discharge and exitus. It was investigated whether serum procalcitonin levels were different between severity groups and disease outcome groups.

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 25.0 (IBM Corp., Armonk, NY). Frequency and percentage for categorical variable, median, minimum and maximum for continuous variable were given as descriptive values. Kruskal Wallis H-Test was used for intergroup comparisons and Chi-Square Analysis was used for categorical variable comparisons. ROC analysis was performed for the procalcitonin value, which was thought to have a discriminative effect on disease severity and survival, and the ROC curve was drawn. The relationship between baseline procalcitonin measurements and disease severity was evaluated by Spearman's Correlation Analysis. The results were considered statistically significant when the p value was less than 0.05.

This study was complied with the ethical guidelines of the 1975 Helsinki Declaration that was then modified in 2008. The study was approved by the Ankara Türkiye Yüksek Ihtisas Training and Research Hospital Scientific Research Assessment and Ethics Committee (Date: 13.03.2018, Decision No: 35).

RESULTS

Within the scope of the study, 384 patients were evaluated. 56% (215 patients) were male and 44% (169 patients) were female. The age of the patients ranged from 26 to 98 years with a median age of 69 years. Biliary calculi were the most common predisposing factor and

were found in 259 patients (67.4%). Of these, 170 (44.3%) were grade 1, 102 (26.5%) were grade 2 and 112 (29.2%) were grade 3.

The median drainage time was 48 hours. At least one comorbidity was seen in 81.3% (312 patients). The most common comorbidities were hypertension 42.7% (164 patients), diabetes mellitus 33.9% (130 patients) and cancer 22.7% (87 patients). History of antibiotic use was 41.1% (158 patients) and history of biliary intervention was 23.7% (91 patients). The source of cholangitis was community-acquired in 63.5% (244 patients) and hospital-acquired in 36.5% (140 patients). Antibiotic treatment was initiated once in 25% (96 patients), twice in 4.9% (19 patients), three times in 2.3% (9 patients) and four times in 0.8% (3 patients). Of the patients included in the study, 6.8% (26 patients) died (**Table 1**).

Table 1. Distribution of Demographic and Clinical Findings of Patients

Descriptions (N=384)	n (%) or Median (Min-Maks)
Age	69 (26-98)
Sex	
Male	215 (56)
Female	169 (44)
Predisposing factors	
Liver transplant	7 (1.8)
Chronic pancreatitis	10 (2.6)
Choledocolitiasis	259 (67.4)
Biliary drain (PTC drain or choledochal stent)	96 (25)
Malignant stenosis	90 (23.4)
Biliary surgery	20 (5.2)
Hydatid cysts rupture into the bile ducts	4 (1)
Post ERCP	20 (5.2)
PSC (primary sclerosing cholangitis)	4 (1)
Choledochal cyst	4 (1)
Comorbidity	312 (81.3)
Chronic liver disease	21 (5.5)
Chronic lung disease	33 (8.6)
Coronary artery disease	70 (18.2)
Heart failure	20 (5.2)
Diabetes mellitus	130 (33.9)
Hypertension	164 (42.7)
Serebrovascular disease	29 (7.6)
Chronic renal failure	12 (3.1)
Cancer	87 (22.7)
Others	84 (21.9)
Antibiotic history	158 (41.1)
History of biliary intervention	91 (23.7)
Drainage time, hour	48 (1-394)
Severity of the disease	
Grade 1 (Mild)	170 (44.3)
Grade 2 (Moderate)	102 (26.6)
Grade 3 (Severe)	112 (29.2)
Latest status	
Alive	358 (93.2)
Deceased	26 (6.8)

Procalcitonin, white blood cell and C-reactive protein median values were 2.3 ng/ml (0.01-301.9), 11.6x10^9/L (2410-55790) and 87.6 mg/L (3.4-413.2), respectively. Other laboratory findings are summarized in **Table 2**.

Table 2. Distribution of Laboratory Parameters of Patients

Parameters (N=384)	Median (Min-Maks)
Procalcitonin	2.3 (0.01-301.9)
Glucose	118 (25-815)
Creatinine	0.94 (0.4-6.2)
Aspartate aminotransferase	134.5 (6.7-2537)
Alanine aminotransferase	145 (5-1496)
γ glutamyl transferase	423 (15-2415)
Alkaline phosphatase	286 (31-2084)
Albumin	3.8 (1.9-4.8)
Total Bilirubin	4.4 (0.4-31.3)
INR	1.2 (0.9-10)
White blood cell	11610 (2410-55790)
Hemoglobin	12.7 (7-17.3)
Platelets	224 (17-883)
C-reactive protein	87.6 (3.4-413.2)

Kruskal Wallis H-Test was used to evaluate whether there was a difference between the procalcitonin levels of the patients according to the severity of cholangitis and it was determined that there was a statistically significant difference between the groups in terms of procalcitonin levels and the median procalcitonin level increased as the severity of cholangitis increased (p<0.001) (**Table 3**). Spearman's correlation analysis, which evaluated the relationship between procalcitonin level and cholangitis severity, revealed a moderate positive linear relationship between procalcitonin and disease severity (**Table 4**).

Table 3. Distribution of Procalcitonin Values According to Cholangitis Severity

	Cholangitis Severity			p value
	Mild Median (Min-Maks)	Moderate Median (Min-Maks)	Severe Median (Min-Maks)	
Procalcitonin	0.58 (0.01-53.00)	3.42 (0.02-90.40)	15.62 (0.04-301.90)	<0.001

Table 4. Correlation Analysis Results Between Procalcitonin Level and Disease Severity

Spearman's Correlation		Disease Severity
Procalcitonin	r	0.596
	p	<0.001
	N	383

In the ROC analysis performed to examine the differential effect of procalcitonin value according to the severity of the disease, the area under the curve for procalcitonin was found to be 83%, the cut-off value was 2.82 and procalcitonin detected above this value was determined to have a strong (80%-90%) ability to differentiate the severity of acute cholangitis (**Figure 1** and **Table 5**). In the ROC analysis performed to examine the differential

effect of procalcitonin value according to the survival status of the patients, the area under the curve for procalcitonin was found to be 65%, the cut-off value was 1.25, and the procalcitonin level determined above this value was found to have a poor ability to discriminate disease mortality (60%-70%) (**Figure 2** and **Table 6**).

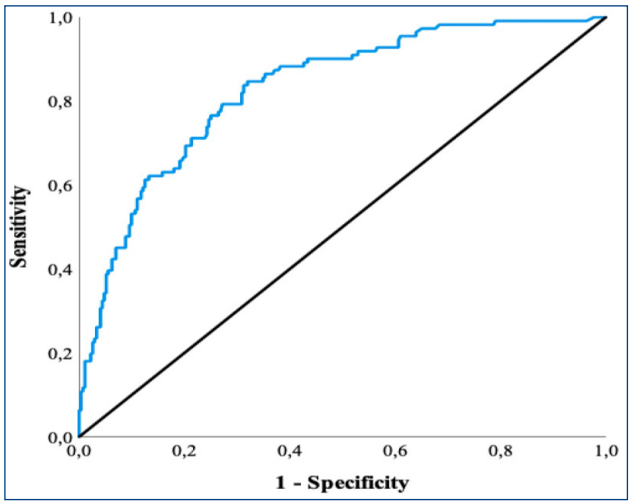

Figure 1. ROC Curve of Disease Severity on Baseline Procalcitonin Value

Table 5. ROC Analysis Result of Disease Severity on Procalcitonin Value

Risk Factor	AUC (95% CI)	Cut-Off	p	Sensitivity (%)	Specificity (%)
Procalcitonin	0.828 (0.784-0.873)	>2.82	<0.001	84.7	68.0

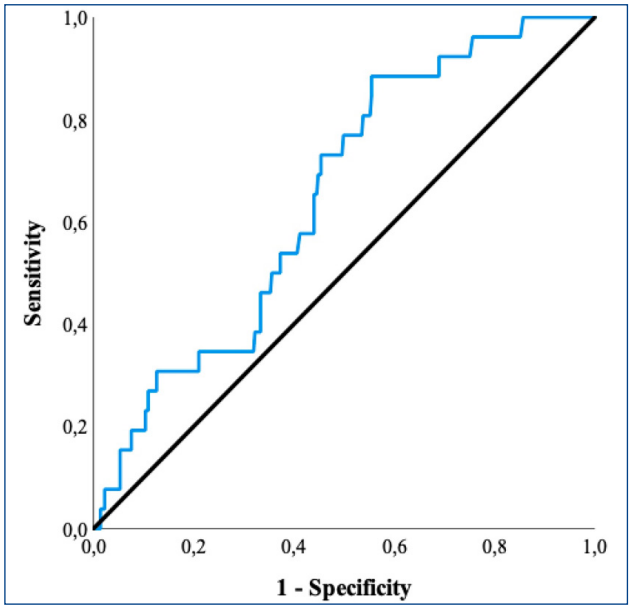

Figure 2. ROC Curve of the relationship between survival and Procalcitonin value

Table 6. ROC Analysis of the relationship between survival and Procalcitonin value

Risk Factor	AUC (95% CI)	Cut-Off	p	Sensitivite (%)	Specificity (%)
Procalcitonin	0.650 (0.555-0.744)	>1.25	0.011	88.5	44.5

DISCUSSION

Due to its high incidence and mortality, acute cholangitis continues to be important despite improved treatment approaches. Since its publication in 2007, the Tokyo Guidelines have become the primary source of standardization in the diagnosis, treatment and severity assessment of acute cholangitis.

In the Tokyo Guideline 2018, which is the most up-to-date guideline on acute cholangitis, it is recommended to use various laboratory tests such as white blood cell, platelet, C-reactive protein, bilirubin and albumin in the diagnosis and severity classification of the disease and to decide the time of biliary drainage according to the severity of the disease. In the section of the guideline related to the diagnostic process, the predictive value of procalcitonin was included within the scope of future research questions, and the importance of procalcitonin in predicting severity was emphasized. The limitations of the few number of studies cited were emphasized and it was stated that the predictive value of procalcitonin should be demonstrated with more studies (2).

In the study by Shinya et al. it was recommended that patients with high procalcitonin levels should be followed up in intensive care unit and early biliary drainage should be provided (6). In a study conducted by Humano et al. in 2013, procalcitonin was found to be associated with disease severity (7). In another study comparing procalcitonin with other biomarkers, it was found that procalcitonin predicted severe cholangitis better than traditional biomarkers and procalcitonin predicted severe cholangitis (8). When compared with the results of these studies, similar results were obtained in our study and it was shown that the median procalcitonin level increased as the disease became more severe. When the cut-off values of serum procalcitonin in predicting disease severity were examined in the studies, Shinya et al. 2.33 ng/mL (6), Umefune et al. 2.2 ng/mL (8) were reported as cut-off values. In our study, the cut-off value of procalcitonin predicting severe disease was found to be 2.82 ng/mL, which is close to those reported in the literature.

Although there is no study investigating the relationship between procalcitonin and mortality in acute cholangitis, this relationship has been investigated in sepsis and other infections. Nylen et al. reported that increased procalcitonin increased mortality in experimental sepsis (9). A study conducted in 2017 at multiple centers revealed that mortality was associated with the failure of procalcitonin to regress with treatment (10).

In a study conducted in patients followed up in the intensive care unit due to severe sepsis, a procalcitonin level above 10 ng/ml during admission to the intensive care unit predicted early mortality (11). In our study, the predictive value of procalcitonin on mortality was also

analyzed and it was found to predict mortality poorly in acute cholangitis; therefore, we think that it is not appropriate to use procalcitonin as a mortality marker in acute cholangitis.

When the literature and our study data are evaluated together, it may be useful in disease management to include serum procalcitonin levels at the time of presentation in the evidence of inflammation (Evidence of inflammatory response: WBC count (x1,000/µL) <4 or >10; CRP (mg/dL) ≥1) may be useful in disease management.

Despite the retrospective nature of our study, the absence of recorded symptom onset time, and the focus on procalcitonin levels within the initial 24 hours rather than at admission, we believe that our findings will make a valuable contribution to the existing body of literature. This is primarily due to the substantial patient sample size and the novelty of our investigation into the association between procalcitonin and mortality in cases of acute cholangitis.

CONCLUSION

As a result of the analysis performed in our study, a strong correlation was found between procalcitonin level and disease severity and it was shown that serum procalcitonin level increased as the disease became more severe. We recommend that serum procalcitonin levels should be routinely studied in patients diagnosed with acute cholangitis, early biliary drainage should be provided in patients with elevated serum procalcitonin levels, and the level of procalcitonin at presentation should be included in the inflammation findings and severity grading of the disease diagnostic criteria in the Tokyo Guidelines..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ankara Türkiye Yüksek Ihtisas Training and Research Hospital Scientific Research Assessment and Ethics Committee (Date: 13.03.2018, Decision No: 35).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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