Role of Procalcitonin in Evaluation of the Severity of Acute Cholecystitis

Akut Kolesistitin Şiddetini Belirlemede Prokalsitoninin Yeri

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ABSTRACT

Objective: The aim of this study is to investigate the relationship between procalcitonin (PCT) level and the severity of acute cholecystitis.

Materials and Methods: This study included 200 patients diagnosed with acute cholecystitis. To diagnose and assess the severity of acute cholecystitis; physical examination and abdominal ultrasound findings were evaluated and blood samples were taken to determine white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and levels of coagulation factors, blood gas, C-reactive protein (CRP) and PCT. Patients were classified into three stages, namely, mild, moderate, and severe, according to the severity of acute cholecystitis using the Tokyo guidelines. The role of PCT level in the assessment of severity of acute cholecystitis and the correlation between the stages and PCT level were statistically analyzed.

Results: Among patients with acute cholecystitis, 110 (55%) were classified as mild, 61 (30.5%) as moderate, and 29 (14.5%) as severe. Leukocytosis or leukopenia was positive in 48.5%, ESR elevation was found in 72.5%, CRP positivity in 55.5%, PCT elevation in 27%, and positive findings of ultrasonographic imaging in 54.5% of the patients. Serum WBC count, ESR, and CRP and PCT levels increased as the severity of disease increased ($p<0.05$). PCT could discriminate grade I from grade II–III with 95.45% sensitivity and 46.67% specificity at the best cut-off value of ≤0.52 ($p<0.001$). PCT could also discriminate grade III from grade I–II with 72.4% sensitivity and 90.06% specificity at the best cut-off value of >0.8 ($p<0.001$).

Conclusion: PCT level may be considered to be a parameter that could be added to the assessment of the severity of acute cholecystitis in the Tokyo guidelines, although further studies are needed to support our findings.

Keywords: Procalcitonin, acute cholecystitis, severity of illness index

ÖZ

Amaç: Bu çalışmanın amacı akut kolesistitin şiddeti ile prokalsitonin (PCT) seviyesi arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Bu çalışmaya akut kolesistit tanısı alan 200 hasta alındı. Tanıyı koymak ve akut kolesistitin şiddetini belirlemek için; fizik muayene ve abdominal ulltrasonografi bulguları değerlendirildi ve beyaz küre sayımı (BKS), eritrosit sedimentasyon hızı (ESH), koagülasyon faktörleri, kan gazı, C-reaktif protein (CRP) ve PCT düzeylerini belirlemek için kan örnekleri alındı. Hastalar akut kolesistitin şiddetine göre Tokyo klavuzu kullanılarak hafif, orta ve ağır olmak üzere üç evrede sınıflandırıldı. Akut kolesistitin şiddetini değerlendirmede PCT düzeylerinin yeri ve PCT düzeyi ile evreler arasındaki korelasyon istatiksel olarak analiz edildi.

Bulgular: Akut kolesistitli hastaların; 110 (%55)'u hafif, 61 (%30,5)'i orta ve 29 (14,5)'u ağır olarak sınıflandırıldı. Hastaların %48,5'inde lökositoz veya lökopeni, %72,5'inde ESH yüksekliği, %55,5'inde CRP pozitifliği, %27'sinde PCT yüksekliği ve %54,5'inde pozitif ultrasonografi bulguları saptandı. Serum BKS, ESH, CRP ve PCT düzeyleri hastalığın şiddetiyle beraber artış gösterdi ($p<0,05$). PCT evre 1'i evre 2 ve 3'den ayırmada ≤0.52 cut off değeriyle %95,45 duyarlılık ve %46,67 özgüllüğe sahipti ($p<0,001$). PCT ayrıca evre 3'ü evre1 ve 2'den ayırmada >0,8 cut off değeriyle %72,4 duyarlılık ve %90,06 özgüllüğe sahipti ($p<0,001$).

Sonuç: PCT düzeyi, Tokyo klavuzunda akut kolesistitin şiddetinin belirlenmesine eklenebilecek bir parametre olarak düşünülebilir, bununla beraber bulgularımızı destekleyecek ileri çalışmalara ihtiyac vardır.

Anahtar Kelimeler: Prokalsitonin, akut kolesistit, hastalık şiddet indeksi

Introduction

Acute cholecystitis (AC) is one of the important causes of abdominal pain on presentation to the emergency department. Early diagnosis and treatment of AC has a positive effect on morbidity and mortality [1, 2].

Acute cholecystitis is usually diagnosed based on the presence of non-characteristic local and/or systemic inflammatory findings and/or the result of ultrasonographic examination [1-3].

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Although there are no specific diagnostic criteria for AC, if it seen at an advanced stage, it may lead to mortality. The grading of AC is necessary for not only defining the severity of AC but also planning early or elective cholecystectomy [1-4].

Previously, the levels of leukocytosis and C-reactive protein (CRP) were assessed for predicting the severity of AC, but neither was found to be useful [1-5]. Moreover, CRP level is usually within the normal range in the first 6-12 h of AC. On the other hand, procalcitonin (PCT) was shown to increase in the first hours after systemic inflammation and peaked earlier than CRP did in the plasma [5].

The aim of this study is to evaluate the potential use of PCT level in defining the severity of AC apart from the standard acute-phase reactants.

Materials and Methods

Patients

This study was approved by the local ethics committee of Ankara Training and Research Hospital with a registration date of 14.10.2010 and No. 2959. This prospective study was conducted in patients who were over 17 years old and were admitted to our emergency department with a complaint of abdominal pain. A total of 200 patients who were diagnosed with AC between July 2009 and January 2011 were included in the study.

Acute cholecystitis was diagnosed based on the presence of local inflammatory findings (such as Murphy's sign, palpable mass, tenderness, and/or pain in the right upper abdominal quadrant), systemic inflammatory findings (such as fever, elevation of CRP, and/or leukocytosis), and/or findings specific for AC on ultrasonographic imaging (USI). Clinical suspicion and at least one of these signs are required for the diagnosis of AC, and the diagnosis needs to be supported by USI. Patients with AC were divided into three stages according to the Tokyo classification based on their anamnesis, physical examination, and laboratory and imaging results. Age, sex, serum white blood cell (WBC) count, CRP level, and USI results of the patients were evaluated [1].

We examined the relationship between WBC count, erythrocyte sedimentation rates (ESR), PCT level, CRP level, USI findings, and the disease stage. We also assessed the relationship between PCT and CRP levels, ESR, and WBC count.

Table 1. Comparison of WBC count, ESR, CRP and PCT levels, and USI positivity

	Stage				
	Total N:200 (%)	Mild N:110 n (%)	Moderate N:61 n (%)	Severe N:29 n (%)	p*
WBC	97 (48.5)	37 (33.6)	41 (67.2)	19 (65.5)	<0.001
ESR	145 (72.5)	76 (69.1)	46 (75.4)	23 (79.3)	0.672
CRP	111 (55.5)	49 (44.5)	37 (60.7)	25 (86.2)	<0.001
PCT	54 (27.0)	11 (10.0)	22 (36.1)	21 (72.4)	<0.001
USI (+)	109 (54.5)	36 (32.7)	54 (88.5)	19 (65.5)	<0.001

*Chi-squared test
WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PCT: procalcitonin; USI: ultrasonographic imaging

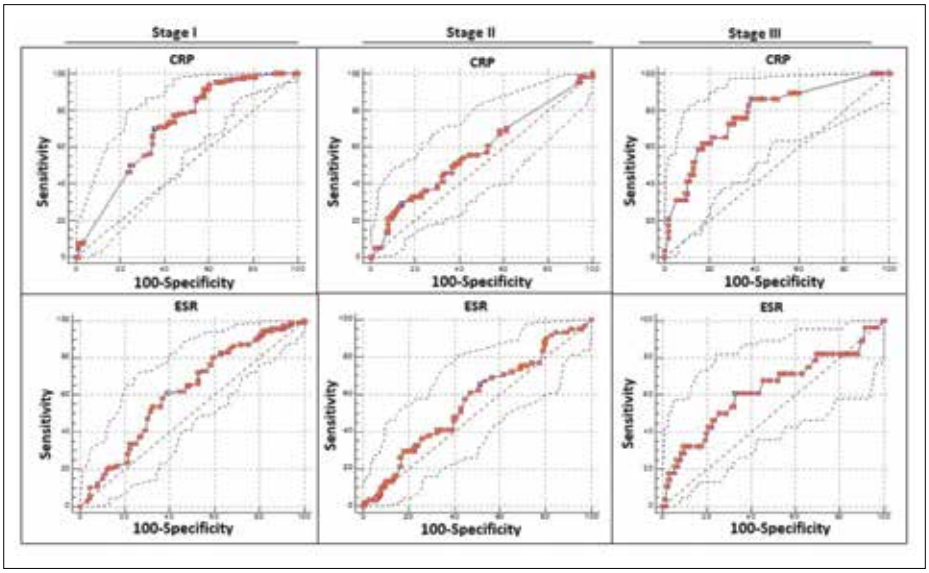

Figure 1. ROC curves for ESR and CRP levels according to stages.
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

Patients with other acute abdominal conditions and those aged under 18 years old were excluded from the study. In addition, patients with inflammatory bone diseases, malignancy, lung infections, soft tissue infections, burns, or trauma were excluded. Informed consent was taken from all of the patients.

Measurement of WBC count, ESR, and CRP and PCT levels

White blood cell count assays were performed using an automatic hemocytometer (LH-780, Beckman Coulter, USA), which was calibrated daily. Venous blood samples for WBC count assays were collected in standard tubes containing 0.072 mL 7.5% K3-ethylenediaminetetraacetic acid solution (Beckton Dickinson, USA) (reference values: 4.5-11×10^3/μL). ESR tests were performed using an automatic ESR measuring device (Test 1 THL, Alifax, Italy), which was calibrated daily. Samples of 2 mL venous blood for ESR testing were collected in tubes containing 0.072 mL 7.5% K3-ethylenediaminetetraacetic acid solution (Beckton Dickinson) (reference range: 0-20 mm/h). Blood samples collected for CRP measurements were centrifuged at 1500-2000 rpm for 10 min and serum was separated. Analyses were performed using an Afinion TM AS100 device and appropriate kits (reference range: 0-0.8 mg/dL). PCT measurements were performed using a Laisio analyzer (318101, Italy), which is an *in vitro* testing system for the quantitative determination of PCT in heparin, citrate, and ethylenediaminetetraacetic acid, in addition to human plasma (reference values: 0-0.5 ng/dL).

USI of the gallbladder was performed using an ultrasound device (Toshiba SSA-660A) and a 3.5-5 MHz convex probe.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows 15.0 (SPSS Inc.; Chicago, IL, USA) program package and the MedCalc 14 (Acacialaan 22, B-8400 Ostend, Belgium) program. Analysis of the normality of continuous variables was

Table 2. Comparison of WBC count, ESR, and CRP and PCT levels according to the disease stage

Variable	Total Median (IQR)	Stage			P*
		Mild Median (IQR)	Moderate Median (IQR)	Severe Median (IQR)	
WBC (×10⁹/L)	10.4 (5.2)	9.3 (4.1)	12.3 (6.0)	13.2 (6.5) (13.4)	<0.001
ESR (mm/h)	29 (28)	25 (22)	32 (33)	41.5 (46)	0.012
CRP (mg/dL)	1 (3.1)	0.65 (1.5)	1.80 (6)	5.6 (10.3)	<0.001
PCT (ng/mL)	0.13 (0)	0.10 (0)	0.26 (1)	3.00 (11)	<0.001

*Kruskall–Wallis test
IQR: interquartile range; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PCT: procalcitonin

Table 3. Statistical features of WBC count, ESR, and CRP and PCT levels according to stages

Stage	Variable	Cut-off	Sensitivity (%)	Specificity (%)	AUC±Se	P-value
I	CRP	≤1.1	70	64	0.707±0.037	<0.001
	ESR	≤29	60.91	60.67	0.615±0.405	0.004
	PCT	≤0.52	95.45	46.67	0.721±0.037	<0.001
	WBC	≤12200	81.82	51.11	0.658±0.041	<0.001
II	CRP	>5	29.51	85.61	0.577±0.044	0.087
	ESR	>26	65.57	48.55	0.561±0.043	0.161
	PCT	>0.14	62.3	56.83	0.575±0.043	0.085
	WBC	>10500	67.21	61.87	0.647±0.044	0.001
III	CRP	>1.1	86.2	61.4	0.782±0.046	<0.001
	ESR	>37	60.71	67.25	0.628±0.063	0.045
	PCT	>0.8	72.4	90.06	0.813±0.053	<0.001
	WBC	>16600	37.93	94.15	0.564±0.757	0.399

The ROC curve analysis used the Youden index J (Honley and McNell).
AUC: Area under the ROC curve; Se: standard error; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PCT: procalcitonin; PCT: procalcitonin

Table 4. Correlations between PCT levels and WBC count, ESR, and CRP level

	PCT	
	r	P*
WBC	0.246	<0.001
ESR	0.262	<0.001
CRP	0.357	<0.001

*Spearman correlation test
WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

performed with the Kolmogorov-Smirnov test. Descriptive statistics were given as the median, interquartile range (IQR), frequency, or percentiles. The chi-squared test was used for categorical values, and the Kruskall-Wallis test was used for numerical values. The Spearman correlation test was used for correlation analysis. P-values of <0.05 were considered to be statistically significant. The appropriate cut-off value for the validity of the test and sensitivity and specificity values were determined by receiver operating characteristic (ROC) analysis.

Results

A total of 200 patients with a mean age of 59.97±18.6 years were included in the study; 134 (67%) of the patients were females. According to the Tokyo classification, 110 (55%) of the cases were mild, 61 (30.5%) were moderate, and 29 (14.5%) were severe (Table 1).

Leukocytosis or leukopenia was positive in 97 (48.5%), ESR elevation in 145 (72.5%), CRP elevation in 111 (55.5%), PCT elevation in 54 (27%), and positive USI findings in 109 (54.5%) of the patients. We observed that the rate of elevation of WBC count and CRP and PCT levels increased as the clinical condition of the patients deteriorated (p<0.05). There was correlation between the clinical course and increase in ESR but it isn't statiscally significant (p>0.05). Positive USI findings were found to be more pronounced more frequently in the moderate group (Table 1).

In our study, the median values of the WBC count, ESR, and CRP and PCT levels were 10.4×10⁹/L (IQR: 5.2), 29 mm/h (IQR: 28), 1 mg/dL (IQR: 3.1), and 0.13 ng/mL (IQR: 0), respectively. As the disease severity increased, the WBC count, ESR, and CRP and PCT levels were found to be statistically significantly elevated (p<0.05) (Table 2).

When we determined the area under the ROC curve (AUC), cut-off value, specificity, and sensitivity according to the disease stage, PCT level showed similar findings to those of WBC count, ESR, and CRP levels at each stage (Figure 1, Figure 2, Table 3).

As shown in Table 3, PCT level could discriminate grade I from grade II-III with 95.45% sensitivity and 46.67% specificity at the best cut-off value of ≤0.52 (p<0.001). The AUC was 0.721±0.037. PCT level could also discriminate grade III from grade I-II with 72.4% sensitivity and 90.06% specificity at the best cut-off value of >0.8 (p<0.001). The AUC was 0.813±0.053.

However, PCT level could not discriminate grade II from grade I and III with statistical significance, in the same manner as that by ESR and CRP level (p-values were 0.085, 0.161, and 0.087, respectively).

We found positive correlations between PCT level and WBC count, CRP level, and ESR (p<0.05) (Table 4).

Discussion

Gallbladder disease is a common health problem and accounts for a significant proportion of patients presenting to the emergency department with abdominal pain [6].

Although the development of AC depends on hereditary and ethnic factors, its prevalence increases with age [7]. Pinto et al. [8]. and Cameron et al. [9] found that the mean age of AC patients was 54 years. In our study, the mean age of patients with AC was 59.97 years, which is consistent with that reported in the literature. We suggest that metabolic processes become catabolic and enzyme levels decrease with age and the formation of gallstones may lead to AC.

AC has been reported to develop in women three times more than in men up to the age of 50, after which the difference decreases [10]. Gurer et al. [11] found that the incidence was four times higher in women than in men who underwent laparoscopic cholecystectomy. In our study, the ratio of female patients was higher, which is consistent with that reported in the literature.

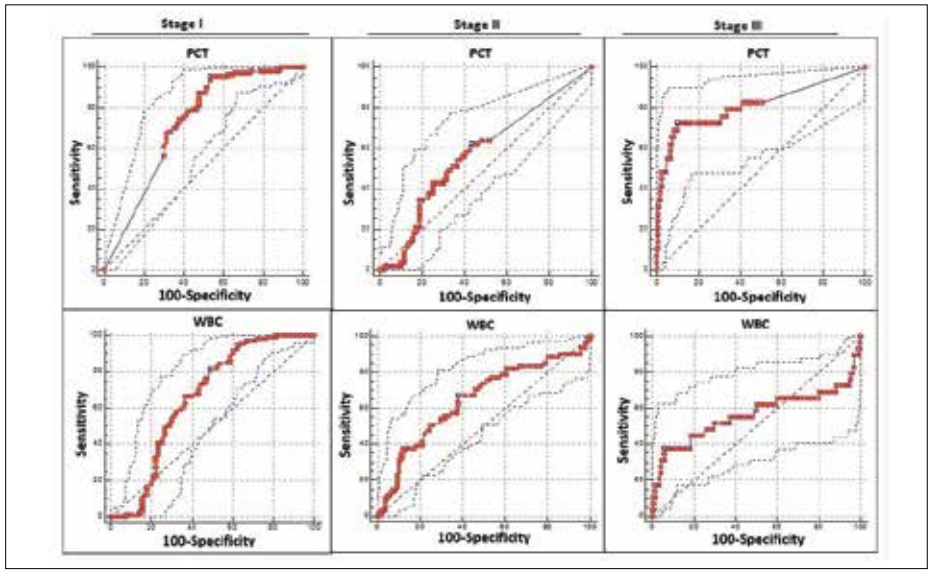

Figure 2. ROC curves for PCT level and WBC count according to stages.
PCT: procalcitonin; WBC: white blood cell

Ultrasonographic imaging examination determines the diagnosis of cholelithiasis with almost 98% sensitivity. Its diagnostic value for AC patients was reported as 54%-90% in the literature [12, 13]. Moreover, no correlation has been reported between USI findings and histopathological results for AC [7]. We observed that only 109 (54.5%) of the AC patients had positive USI findings that confirmed the diagnosis. In the present study, we did not limit the criteria of positivity for AC to the presence of a gallbladder stone, but an increase in the wall diameter of the gallbladder and pericholecystitic fluid were also included in the criteria.

White blood cell count increases in AC but is not specific for differential diagnosis. In various publications, it has been reported that an increase in WBC count supports the diagnosis of AC and complications associated with increased WBC count should be considered. In the literature, an increase in WBC count and the disease stage have been found to be positively correlated [1-5, 7-10].

CRP, which increases in 12-18 hours as a result of tissue damage owing to bacterial and viral infections, is a low-specificity marker. It can be used to support the diagnosis of AC [1, 14-16]. Beliaev et al. [14] showed that CRP level has better discriminative power than WBC count in most forms of AC and is a useful diagnostic marker of AC. CRP level increased in direct proportion with the severity of AC.

In the literature, we found no studies that show a relationship between ESR and the clinical severity of cholecystitis. However, ESR is a marker with low sensitivity and specificity, which increases in several clinical conditions such as infections, autoimmune events, neoplasia, and pregnancy [14, 17].

In our study, in agreement with the literature, we observed that ESR, as well as WBC count and CRP level, increased with the disease stage. We suggest that the main reason for this increase is the increased burden of inflammation.

We have not found any studies that investigated the effect of PCT level in determining the severity of AC. However, PCT level increase in proportion to the severity of systemic inflammation. A continual increase in PCT level indicates that infection has not been controlled and that treatment is insufficient [18]. Al-Bahrami et al. [19] and Reinhart and Meisner reported that PCT level is highly effective for showing the severity of inflammation in acute pancreatitis [16, 20]. In our study, the rate of increases in PCT level in patients with AC was 27%; this increase was correlated with the clinical status and increases in WBC count, CRP level, and ESR. It is suggested that PCT level is more sensitive and specific than other acute-phase response indicators such as CRP, interleukin-6, and tumor necrosis factor-α in defining bacterial infections [21, 22]. It has been shown that in cases of bacterial invasion, PCT level increases and then returns to normal levels faster than CRP level [20, 23]. Considering that CRP level, ESR, and WBC count may increase for several reasons, PCT level may be more meaningful in supporting the diagnosis of AC and in defining the clinical severity of the disease and adequacy of the treatment.

There are some limitations of our study. Firstly, there was no standardization between the times of occurrence of symptoms and presentation to the emergency room. Secondly, we measured serum PCT level only once. In addition, USI was not performed by one radiologist alone.

In conclusion, PCT level alone is not effective for the assessment of the severity of AC, but may be considered to be a parameter that could be added to the assessment of the severity of AC in the Tokyo guidelines, although additional studies are needed to confirm the findings of this study.

Ethics Committee Approval: Ethics committee approval was received for this study from local ethic committee.

Informed Consent: Informed consent was taken from all of the patients.

Peer-review: Externally peer-reviewed.

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