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Original Contribution

Relationship between serum Pentraxin 3 and pro-adrenomedullin levels with acute cholecystitis

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ABSTRACT

Objectives: The perforation of the gallbladder (GP) is one of the most significant complications of acute cholecystitis. A biochemical marker indicating the GP has not been determined fully to date. Pentraxin 3 and pro-adrenomedullin (Pro-ADM) proteins are novel acute phase reactants. We aimed to investigate the relationship between serum Pentraxin 3 and Pro-ADM and the GP in patients with acute cholecystitis. Methods: This prospective cross-sectional study was conducted on patients with acute cholecystitis in a tertiary care emergency department during the six-month period. The acute cholecystitis patients were divided into two groups as with GP, and without GP. Additionally, patients with GP were evaluated according to pericholecystic fluid and gallbladder wall thickness. Serum levels of pro-ADM and pentraxin 3, WBC, CRP and sedimentation rate were measured in all patients.
Results: A total of 60 patients with acute cholecystitis were included in the study. Pro-ADM and pentraxin 3 levels were significantly higher in patients with GP and the with pericholecystic free fluid ($p < 0.0001$). There was no significant relationship between serum pentraxin 3 and pro-ADM with gallbladder wall thickness ($p > 0.05$) According to the ROC analysis, serum Pentraxin 3 levels of ≥4.9 ng/mL could predict GP with a sensitivity of 75% and a specificity of 85% and serum pro-ADM levels of ≥97 nmol/L with sensitivity and specificity of 100% and 95%.
Conclusion: Our study results reveal that serum Pentraxin 3 and pro-ADM may be novel biochemical parameters in the detection of GP in acute cholecystitis cases.

1. Introduction

Acute cholecystitis is a clinical condition characterized by an acute inflammation of the gallbladder, often caused primarily by gallstones, ischemia, motility disorders, collagen tissue diseases, and allergic conditions [1]. Surgery is often the treatment for acute cholecystitis accompanied by gallstones. Immediate surgery is performed in complicated cases in which perforation is detected, but in cases without perforation, laparoscopic cholecystectomy is frequently recommended within 24–72 h of onset of symptoms [2,3]. Complications, such as abscess, collection of infected fluid, and sepsis may develop in the abdomen in patients after perforation. Ultrasonography is the first imaging method in cases with acute abdominal pain and is sufficient to detect wall thickening, gallstones, and pericholecystic fluid in patients without complications, while computerized tomography (CT) is required for complex cases to identify complications, such as emphysematous cholecystitis, abscess, perforation, choledocholithiasis, and pancreatitis [1,2]. In some cases, magnetic resonance cholangiopancreatography may also be useful to evaluate the bile ducts [2].

Pentraxin 3 and pro-adrenomedullin (pro-ADM) proteins are acute phase reactants that have become increasingly important in the last few decades. Recent studies in the literature indicate that the areas of use of these two proteins will be increased in the future. Research has revealed that the serum levels of these proteins are elevated in clinical conditions that trigger systemic inflammatory responses, such as sepsis, acute myocardial infarction, acute heart failure, and pneumonia [4-7].

In cases with acute cholecystitis, the severity of inflammation, its spread within the abdomen, and presence of perforation may be predicted by certain biochemical markers. Although C-reactive protein (CRP), sedimentation, and white blood cell (WBC) count are used as markers of systemic inflammation in acute cholecystitis, they do not provide information for the detection of perforation. Timely

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identification of cases with perforation may reduce the length of stay in emergency services and accelerate the process of surgical treatment. In present study, in addition to these markers, we evaluated the relationship of the newly defined pentraxin 3 and pro-ADM markers with GP and other radiological findings in acute cholecystitis cases.

2. Materials and methods

2.1. Study design

The patients that presented to the emergency department (ED) of Adiyaman University Training and Research Hospital with right upper quadrant pain from January to June 2018 were prospectively evaluated, and those with radiologically proven acute cholecystitis and histopathologically confirmed perforation after surgical treatment were included in the study.

For the diagnosis of acute cholecystitis in the emergency department, the criteria specified in the Tokyo guidelines were used.

In accordance with these criteria, the presence of local signs (Murphy's sign, and pain and sensitivity and/or a palpable mass in the right upper quadrant) and systemic inflammation criteria (fever and elevated CRP, WBC count or sedimentation rate), in addition to significant radiological findings were determined as acute cholecystitis [1,8].

The abdominal USG and intravenous contrast-enhanced CT of the abdomen were performed on all patients. GP was detected as radiologic and surgery. Patients definitive diagnosed with acute cholecystitis were divided into two groups as the perforated group (Group 1), and non-perforated group (Group 2).

The patients that were diagnosed with acalculous cholecystitis and presented with no gallstone, those with a diagnosis of histopathologically unconfirmed acute cholecystitis, and those aged under 18 years were excluded from the study.

The local ethics committee approved the study, and written informed consent was obtained from all the patients.

2.2. Data collection

In addition to age, gender, WBC, CRP, sedimentation and routine biochemical markers, the serum levels of pro-ADM and pentraxin 3 were examined after radiological diagnosis. Furthermore, according to the data obtained from ultrasonography and abdominal CT, the presence/absence of more than a 3 mm increase in gallbladder wall thickness, pericholecystic fluid and postoperative perforation was recorded. The evaluation of the radiological findings was performed by a radiologist with six years' experience in abdominal imaging.

A Toshiba Aquilion 64 (64 section) device was used in the CT imaging with the patient in a supine position. Axial, coronal and sagittal reformatted images of 5 mm thickness were obtained from the transverse images with a slice thickness of 1.25 mm. The images were recorded in the portal venous phase following an IV injection of nonionic iodine contrast agent (0.1 mmol/kg dose and 2.5 ml/s injection rate) and 20 ml saline.

Blood samples were collected using serum separation tubes and serum samples were obtained by centrifugation at 1000 $\times g$ for 20 min for the study. After separation, serum samples were stored at −80 °C until further applications. Analysis of serum expression levels of Pro-ADM and Pentraxin 3 proteins was achieved by using ELISA kit from Sunred Biological Technology Cooperation (Shanghai, China) and suggested protocol of the manufacturer was followed. Briefly, wells for blank, standards, and samples were determined and reagents were prepared. Then, prepared samples, standards and antibodies labeled with enzyme were added and allowed to react 60 min at 37 °C. Following incubation, plates were washed for five times and Chromogen A and B solutions were added and leaved 10 min at 37 °C for incubation. Subsequently, stop solution was added and OD values were measured within 10 min at 450 nm by using EZ Read 400 spectrophotometer from Biochrom (Cambridge, UK). For the calculation of corresponding protein concentrations, a standard curve was plotted using four parameter logistic regression and concentrations were determined (Fig. 1).

Sedimentation rates were measured by *ALIFAX* (S.P.A., Padova, Italy). WBC values were measured by Cell-Dyn Ruby 3700, (Abbott, Chicago, Illinois, USA), CRP values were measured by *Immage Immunochemistry System* (Beckman Coulter, Brea, USA). The reference range for sedimentation rate, WBC and CRP levels was 2–20 mm/h, 4.3–10.3 10^3/μL and 0.0–0.8 mg/L respectively.

2.3. Statistical analysis

Statistical analysis of all variables was performed by SPSS v. 21.0 (IBM Corp., Armonk, New York, USA). Kolmogorov–Smirnov test was used to evaluate the distribution of variables, and the Levene test was used to verify homogeneity of variances. Categorical variables were expressed as number and percentage. The nonparametric numerical variables were expressed as minimum, maximum and median, and the parametric numerical variables as mean and standard deviation ($\pm$SD). The Mann-Whitney *U* test was used to evaluate the relationship between nonparametric numerical variables and the presence of perforation, pericholecystic fluid and an increase in gallbladder wall thickness. An independent-samples *t*-test was used to evaluate the parametric numerical variables. A receiver operating characteristic (ROC) analysis was performed to determine the sensitivity, specificity and predictive values of pentraxin 3 and pro-ADM for the detection of perforation.

3. Results

Eighty-eight cases with right upper quadrant pain were evaluated. Twenty-eight patients with no evidence of a gallstone, no surgical treatment or no radiologically confirmed acute cholecystitis were excluded from the study. Of the 60 cases included in the study, 15 (25%) were male and 45 (75%) were female. The mean age of these cases was 55.78 $\pm$ 19.49, ranging from 20 to 94. Perforation was detected in 20 of the cases (33.3%) and no perforation was detected in 40 (66.7%). CT revealed that the gallbladder wall thickness was >3 mm in 39 cases (65%) and below 3 mm in 21 cases (35%). Pericholecystic free fluid was present in 22 cases (36.7%). There was no significant relationship between PTX3 and pro-ADM levels with the age (for each, $p > 0.05$).

The pentraxin 3 and pro-ADM levels were significantly different between the patients with and without GP ($p < 0.0001$, for each). The pentraxin 3 and pro-ADM levels were higher in the patients with GP. However, statistically significant differences were not found between two groups in terms of CRP, WBC count, age, and sedimentation (Table 1).

When the pentraxin 3 and pro-ADM levels were considered according to gallbladder wall thickness, median pentraxin 3 value was 3.93 ng/mL (min–max: 1.5–25.82 ng/mL) in cases with a gallbladder wall thickness below 3 mm, and 3.61 ng/mL (min–max: 6.89–43.99 ng/mL) in those with a gallbladder wall thicker than 3 mm. The median pro-ADM value were 94.45 nmol/L, (61.97–911.16 nmol/L), in cases the with a gallbladder wall thickness below 3 mm and 81.33 nmol/L (51.25–755.18 nmol/L) in those with a gallbladder wall thicker than 3 mm. There was no significant relationship between increased gallbladder wall thickness and the levels of pro-ADM and pentraxin 3 ($p = 0.215$, $p = 0.152$, respectively).

When the pentraxin 3 and pro-ADM levels were considered according to pericholecystic fluid, the median pentraxin 3 value were 5.58 ng/mL (min–max: 0.39–44 ng/mL) in patients with pericholecystic fluid and 3.4 ng/mL (min–max: 1.5–8.36 ng/mL) in those without pericholecystic fluid. There was statistically significant relationship between the presence of this fluid and pentraxin 3 levels ($p < 0.0001$).

The median pro-ADM was 130.6 nmol/L, (min–max: 74.64–911.16 nmol/L) for the patients with pericholecystic fluid, and

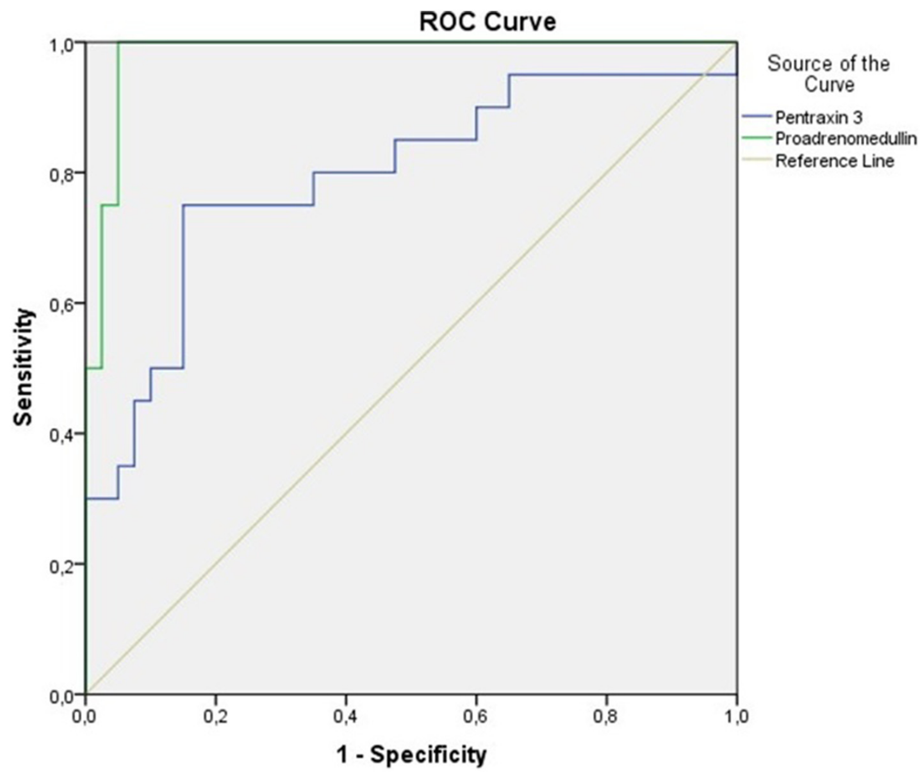

Fig. 1. ROC curve graph showing the diagnostic power of Pentraxin 3 and Pro-adrenomedullin for estimation of gallbladder perforation.

78.21 nmol/L (min–max: 51.25–137.19 nmol/L) for those without pericholecystic fluid. There was a statistically significant relationship between the presence of pericholecystic free fluid and pro-ADM levels ($p < 0.0001$).

The ROC analysis for the assessment of the diagnostic performance of pentraxin and pro-ADM in the detection of perforation in patients with acute cholecystitis revealed significant results for both markers (Table 2). Pentraxin 3 had a sensitivity of 75% and specificity of 85% at the cut-off value of 4.9 ng/mL, while pro-ADM had a sensitivity and specificity of 100% and 95%, respectively at a cut-off value of 97 nmol/L.

4. Discussion

Gallstone-related acute cholecystitis often occurs due to the obstruction of the cystic duct or the neck of the gallbladder. The incidence of complications is very high, at about 40% [9]. It is important to predict the possible development of complications in advance, since this may change the course of treatment. The most common complication is the perforation of the gallbladder, which is usually detected by radiological examination. Other indicative signs for perforation are the presence of pericholecystic fluid, loss of continuity in the wall of gallbladder, and detection of an abscess on ultrasonography and CT.

In cases of acute cholecystitis, there are parameters showing the prognosis in these cases; however, biochemical parameters indicating perforation have not been defined in the literature. For example, CRP, neutrophilic leukocyte ratio, and serum procalcitonin values have been shown to be associated with prognosis of acute cholecystitis [10-12]. Furthermore, the risk of intraoperative complications has been reported to be higher in patients with elevated CRP levels [13]. In present study, WBC, CRP and sedimentation rate values were no difference between the patients with and without GP. Additionally, those parameters were not found to be significant in detecting perforation.

Adrenomedullin is a protein from the calcitonin family of peptides and it is released at an increased level in systemic infections. It promotes immune modulation, vasodilatation, antimicrobial activity, and electrolyte balance. Pro-ADM is a precursor for adrenomedullin that is easy to measure in the serum and reflects the level of adrenomedullin. Measurement of pro-ADM levels as an acute phase reactant can provide information on clinical situations that lead to systemic inflammation [14]. Studies have shown that increased pro-ADM can be used as an indicator of poor prognosis in the clinical course of cases of sepsis and septic shock, community-acquired pneumonia, and patients that present to the emergency service with fever [6,14,15,17]. It has even been suggested that pro-ADM provides a prognostic prediction similar to APACHE II scoring in sepsis cases [16]. In previous studies, researchers used pro-ADM as a prognostic marker in pediatric patients and neonatal sepsis cases followed up in the intensive care unit [18,19]. Pro-ADM has also produced significant results in different clinical situations, such as

Table 1
Comparison of numerical data between perforated and non-perforated acute cholecystitis cases.

	Group 1 (n = 20)	Group 2 (n = 40)	p value
Age (years), mean ± SD	52.75 ± 22.33	57.3 ± 18.03	0.399
Sedimentation rate (mm/h), mean ± SD	27.7 ± 14.02	27.45 ± 8.39	0.942
CRP (mg/L), median (min–max)	2 (0.5–26)	2.6 (0.27–28.8)	0.446
WBC (10^3/μL), median (min–max)	11.58 (6.03–24.42)	11.55 (5.44–29.76)	0.661
Pentraxin 3 (ng/mL), median (min–max)	5.58 (0.39–43.99)	3.4 (1.5–8.36)	<0.0001
Pro-ADM (nmol/L), median (min–max)	144.23 (98.61–911.16)	78.21 (51.25–137.19)	<0.0001

SD: standard deviation.

Table 2
The results of ROC analysis on the detection of gallbladder perforation.

	AUC (%)	p value	Cut-off value	Sensitivity	Specificity	The Youden index
Pentraxin 3 (ng/mL)	79.4	<0.0001	4.8	75%	85%	0.6
Pro-ADM (nmol/L)	98.1	<0.0001	97	100%	95%	0.95

AUC: Area under the curve.

critical cancer cases, acute heart failure, and febrile hematologic malignancy cases [7,20,21]. Especially in cases of febrile hematologic malignancy, pro-ADM can be an important parameter in the differentiation of systemic inflammatory response syndrome and sepsis [20]. However, there are also studies reporting that pro-ADM alone is not associated with mortality in septic shock cases [22].

The relationship between pro-ADM and acute cholecystitis was reported for the first time in the present study. In present study, the level of pro-ADM was investigated in patients with acute cholecystitis due to gallstones and its relationship with radiological parameters and perforation was evaluated. There was no significant relationship between gallbladder wall thickness and pro-ADM, but a statistically significant, high-level relationship was found between the presence of pericholecystic fluid and this protein. For the detection of GP, the sensitivity and specificity of pro-ADM were 100% and 95%, respectively. The cut-off value was calculated as 97 nmol/L.

Pentraxins are a protein group that act as an inflammatory modulator. Pentraxin 3 protein is an acute phase reactant secreted from cells in the wall of vascular structures. In recent years, pentraxin-3 levels have been significantly associated with diagnosis and prognosis in various diseases with different characteristics. In sepsis, the existence of a relationship between disease prognosis and mortality has been proven [5,23]. Research has shown that pentraxin 3 can be used as an acute phase reactant in patients with rheumatoid arthritis, for the differentiation of eosinophilia and non-eosinophilic asthma, for the identification of pulmonary congestion in trauma cases, for the detection of infection in chronic obstructive pulmonary disease, and as an early marker of acute myocardial infarction [4,24-27]. In addition, in patients diagnosed with diabetes mellitus, the level of pentraxin 3 was found to be increased in the aqueous humor in the eye, which was attributed to endothelial damage secondary to microangiopathy [28]. In another study, a negative correlation was found between bone mineral density and pentraxin 3 [29].

In the present study, no significant relationship was found between gallbladder wall thickness and pentraxin 3 level in patients with acute cholecystitis; however, statistically significant results were obtained in terms of the relationship between pericholecystic fluid and the level of this protein. The cut-off value of pentraxin 3 for the detection of perforation was calculated as 4.9 ng/mL, and the specificity and sensitivity values were 75% and 85%, respectively.

4.1. Limitations

This study has certain limitations. First, the relatively low number of evaluated cases may be considered as a limitation, but the two markers provided statistically significant results even in this small population, which may indicate that they are very strong predictors. However, it is necessary to undertake a further study with a higher number of cases to obtain more reliable results. Second, the exclusion of acalculous cholecystitis cases from the study may be considered as a limitation; however, we chose to do this since the pathogenesis of this disease is different and it may have led to findings that could affect the significance of the results. To ensure homogenization of the study group, this group of patients could not be evaluated. Another issue is the lack of comparison between healthy individuals and acute cholecystitis cases. Such a comparison may provide a better understanding of the relationship between the investigated markers and acute cholecystitis with GP.

5. Conclusions

Our study showed that pentraxin 3 and pro-ADM levels were higher in the acute cholecystitis patients with GP and pericholecystic fluid. However, there was no relationship between the serum levels of these markers and the gallbladder wall thickness. Additionally, we found that pentraxin 3 and pro-ADM levels had a high sensitivity and specificity in the prediction of GP. Pentraxin 3 and pro-ADM may present as novel parameters in the detection of GP in acute cholecystitis cases.

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