ORIGINAL ARTICLE

The diagnostic value of serum urokinase-type plasminogen activator receptor in acute appendicitis

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ABSTRACT

BACKGROUND: To measure serum uPAR levels in patients operated with a preliminary diagnosis of acute appendicitis (AA) and to investigate whether these parameters can be used as a biochemical marker in the diagnosis of AA.

METHODS: Patients aged 18 or over, presenting to the emergency department between May and December 2018 and operated with a diagnosis of AA were enrolled. This study included 84 patients with surgical pathology results compatible with AA (Group A), 26 patients with surgical pathology results were not compatible with AA (Group B) and 55 healthy control groups. Serum uPAR levels were measured from venous blood samples taken at admission.

RESULTS: Mean uPAR levels were 4.53±3.47 ng/mL in the Group A, 1.13±1.63 ng/mL in the Group B and 0.80±1.21 ng/mL in the control group. Serum uPAR levels differed statistically significantly from Group A in Group B and the control group, ($p<0.05$).

CONCLUSION: uPAR was found to be significantly higher in the AA patients compared to the control group and patients with surgically determined non-AA pathologies. uPAR can be used as an aid in the diagnosis of acute appendicitis.

Keywords: Abdominal pain; acute appendicitis; adult; inflammation; urokinase-type plasminogen activator receptor.

INTRODUCTION

Acute appendicitis (AA) is the principal cause of acute abdomen in patients presenting to the emergency department due to abdominal pain.[1,2] Morbidity and mortality increase if AA is diagnosed late. Perforated appendix and associated peritonitis, intra-abdominal abscess, sepsis, and ileus can develop in the event of late diagnosis.[3] History, physical examination, an increase in blood inflammatory parameters, and clinical experience occupy an important place in diagnosis. Although radiological imaging methods, such as ultrasound (USG) and computerized tomography (CT), are used in the differential diagnosis of other pathologies causing pain in the right lower quadrant, negative surgical pathology results are encountered at a rate of 10–30% in patients operated with a preliminary diagnosis of AA.[2,4–6] Clinicians, therefore, require new research to reduce increasing malpractice suits and negative appendectomy rates. Studies have, therefore, shown a relation between AA and biochemical parameters showing acute inflammation, such as white blood cell count (WBC), C-reactive protein (CRP), and procalcitonin.[2,4]

The pathophysiology of AA is associated with mucosal impairment caused by invasive infection and inflammation.[7] Infiltration of the intestinal wall by activating neutrophils occurs following invasion by intraluminal bacteria of the appendix wall

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with an impaired mucosal barrier.[8] Degradation of the extracellular matrix is important for neutrophil invasion of tissue in the inflammatory response. One study showed immunoreactive urokinase-type plasminogen activator (uPA), involved in the conversion of plasminogen to plasma, in inflamed appendix tissue.[9] Plasmin leads to leukocytes passing the tissue barrier by reducing pericellular matrix proteins. Urokinase-type plasminogen activator receptor (uPAR, CD 87) is a glycosylphosphatidylinositol-anchored protein with high uPA receptor affinity. In addition to serving as a binding point on the cell surface, uPAR also facilitates leukocyte adhesion and migration.[10] Rijneveld et al.[11] determined that uPA and uPAR exhibit immune functions more by activating other defense cells than through fibrinolytic effects. Following an inflammatory stimulus, uPAR and proteases, such as chymotrypsin and phospholipase, facilitate leukocyte adhesion and migration, and activated neutrophils release the chemotactically active soluble form of uPAR from the cell surface into the circulation. With its direct chemotactic effect, uPAR facilitates the production of additional anti-inflammatory cells (generally neutrophils and macrophages) and the mobilization of hematopoietic stem cells in order to overcome bacterial invasion.[12]

This study was planned to measure serum uPAR levels in patients operated with a preliminary diagnosis of AA and to investigate whether these parameters can be used as a biochemical marker in the diagnosis of AA.

MATERIALS AND METHODS

This study was conducted after Ordu University Medical Faculty Clinical Research Ethical Committee approval (decision No. 2018/61). Patients aged 18 or over, presenting to the emergency department of a tertiary hospital between May and December 2018, and operated with a diagnosis of AA were enrolled. We planned to exclude patients with a non-AA focus of infection, acute coronary syndrome, hemorrhagic stroke, cerebrovascular disease, liver failure, acute pulmonary edema, cardiopulmonary arrest, acute mesenteric ischemia, or pulmonary thromboembolism, pregnant patients, subjects with acute trauma, or for whom consent to participate was not granted by the patient or relatives. We also intended to exclude patients for whom data deficiencies were determined at the end of the study period. Healthy volunteers aged over 18 with no disease and presenting to hospital for a check-up and agreeing to participate were included as the control group in this study.

The clinical and demographic characteristics, symptoms, physical examination findings, Alvarado scores, WRP and CRP values, all abdominal USG and CT imaging results, and postoperative pathology results of the patients included in this study were recorded onto study forms. We planned to measure the serum uPAR values of the patient group and the control group. Patients with surgical pathology results compatible with AA were assigned into Group A, and patients with surgical pathology results not compatible with AA were assigned into Group B.

Analysis of Biochemical Parameters

Venous blood specimens were collected at the time of presentation. Blood specimens were drawn into a serum separator tube until the vacuum was filled. Tubes with separator gel were used for serum collection, and tubes containing potassium-EDTA were used for a blood count. Plasmas were separated by centrifugation for 10 min at 3000 rpm and were stored -80 °C. Serum CRP levels were studied spectrophotometrically on a closed system with a Cobas 600 series c501 modular analyzer in our laboratory. Blood WBC levels were collected with results obtained with an XN-1000 device in our laboratory. uPAR levels in human blood serum were determined using a Cloud Clone (USCNK) (Wuhan, China) enzyme-linked immunosorbent assay (ELISA) kit in line with the manufacturer's instructions. uPAR levels in specimens were calculated as ng/mL.

Statistical Analysis

Statistical software was used for data analysis. Descriptive express was expressed as number and percentage for categorical variables and mean, standard deviation (SD), minimum (min), and maximum (max) for numerical variables. Compatibility with normal distribution was assessed using the Kolmogorov-Smirnov test. The t-test was used for two-way comparisons of normally distributed parameters, and the Mann-Whitney U test for non-normally distributed parameters. One-way analysis of variance (ANOVA) was used to compare normally distributed variables between three groups, and the Kruskal-Wallis test for non-normally distributed parameters. When significance was determined with the ANOVA test, two-group comparisons were performed using Turkey's test if the group were homogeneous, or with Tamhane's test if they were not homogeneous. The Mann-Whitney U test with Bonferroni correction was used for two-way comparisons when significance was determined using the Kruskal-Wallis test. Correlation coefficients and statistical significances were determined using Pearson's test for normally distributed variables and Spearman's test for non-normally distributed variables. The decision-determining characteristics of serum uPAR values in predicting the diagnosis of appendicitis were examined using Receiver Operating Characteristics (ROC) curve analysis. The sensitivity, specificity, positive predictive and negative predictive values were calculated for significant threshold values. At area under the curve (AUC) analysis, type 1 error levels less than 5% were interpreted as the statistically significant diagnostic value of the test. Statistical significance was set at $p<0.05$.

RESULTS

One hundred ten patients aged 18 or over, presenting to the emergency department with abdominal pain and operated

with a diagnosis of AA were included in this study. The control group consisted of 55 healthy volunteers. Twenty-five patients could not be included in this study due to insufficient data. Following examination of the postoperative surgical pathology results of the patients operated with a diagnosis of AA, although pathology compatible with AA was determined in 84 cases (Group A), non-AA histopathological results were obtained in 26 (Group B) patients. Histopathological examination of the Group B patients revealed normal appendix vermiformis tissue in 15 cases, mesenteric lymphadenitis in six, ovarian cyst hemorrhage in three, and diverticulitis in two. Distributions of the patient groups' age, sex, Alvarado score and clinical characteristics are shown in Table 1. CT was the most commonly employed diagnostic imaging modality in the emergency department among the cases enrolled in the study. CT was performed on 75 Group A patients but not on the other nine. CT imaging was reported to be compatible with AA in 18 of the patients in Group B, and four patients were operated although CT imaging was not reported to be compatible with AA (Table 1).

The patient groups' mean WBC, CRP and uPAR values were compared. Serum uPAR levels differed statistically significantly from Group A in Group B and the control group. No significant difference was observed between the serum uPAR levels of Group B and the control group (Table 2).

Table 1. The groups' demographic characteristics

Characteristics		Group A (n=84)	Group B (n=26)	Control (n=55)
Sex, n (%)	Male	60 (71.4)	11 (42.3)	35 (63.6)
	Female	24 (28.6)	15 (57.7)	20 (36.4)
Age, mean±SD (min-max)		38.8±18.9	33.2±13.7	27.7±10.8
		(18–93)	(18–62)	(18–64)
Time to onset of symptoms (hours),		14.5±13.6	9.9±9.8	–
mean±SD (min-max)		(1–72)	(2–48)	
Alvarado score mean±SD (min-max)		6.8±1.6	5.0±1.8	–
		(3–10)	(3–9)	
Right lower quadrant tenderness, n (%)	Yes	81 (96.4)	26 (100.0)	–
	No	3 (3.6)	0 (0.0)	–
Leukocytosis, n (%)	Yes	68 (81.0)	10 (38.5)	–
	No	16 (19.0)	16 (61.5)	–
Pain migration, n (%)	Yes	50 (59.5)	10 (38.5)	–
	No	34 (40.5)	16 (61.5)	–
Lack of appetite, n (%)	Yes	43 (51.2)	9 (34.6)	–
	No	41 (48.8)	17 (65.4)	–
Nausea-vomiting, n (%)	Yes	50 (59.5)	13 (50.0)	–
	No	34 (40.5)	13 (50.0)	–
Rebound, n (%)	Yes	51 (60.7)	12 (46.2)	–
	No	33 (39.3)	14 (53.8)	–
Body temperature >37.3, n (%)	Yes	17 (20.2)	2 (7.7)	–
	No	67 (79.8)	24 (92.3)	–
Left shift in neutrophils, n (%)	Yes	64 (76.2)	12 (46.2)	–
	No	20 (23.8)	14 (53.8)	–
USG imaging, n (%)	Positive	13 (15.5)	5 (19.2)	–
	Negative	7 (8.3)	1 (3.8)	–
	Not performed	64 (76.2)	20 (76.9)	–
CT imaging, n (%)	Positive	75 (89.3)	18 (69.2)	–
	Negative	0 (0.0)	4 (15.4)	–
	Not performed	9 (10.7)	4 (15.4)	–

Min: Minimum; Max: Maximum; USG: Ultrasonography; CT: Computerized tomography; SD: Standard deviation.

Table 2. Comparison of patient group blood white blood cell, C-reactive protein and uPAR levels

Characteristic	Group A[a] (n=84)	Group B[b] (n=26)	Control[c] (n=55)	p
	Mean±SD	Mean±SD	Mean±SD	
White blood cell (cells/mm^3)	14.096±3898	9953±2261	7391±1621	<0.001[α] [a,b]<0.001[γ], [a,c]<0.001[γ], [b,c]<0.001[γ]
C-reactive protein (mg/L)	3.61±4.22	1.30±1.93	0.16±0.17	<0.001[β] [a,b]=0.001[δ], [a,c]<0.001[δ], [b,c]<0.001[δ]
uPAR (ng/mL)	4.53±3.47	1.13±1.63	0.80±1.21	<0.001[β] [a,b]<0.001[δ], [a,c]<0.001[δ], [b,c]=0.439[δ]

[α]According to ANOVA test; [β]According to Kruskal Wallis test; [γ]According to Post Hoc Tamhane's testi; [δ]According to Bonferroni-corrected Mann-Whitney U test. uPAR: Urokinase-type plasminogen activator receptor; SD: Standard deviation.

Table 3. The sensitivity and specificity percent of uPAR in diagnosing acute appendicitis

uPAR (ng/mL)	Sensitivity (95% CI)	Specificity (95% CI)	+LR	-LR	PPV (%)	NPV (%)
>1.08	90.4% (82.4–95.8)	76.9% (56.4–91.0)	3.92	0.12	92.7	71.4
>1.5	82.1% (72.3–89.6)	84.6% (65.1–95.6)	5.34	0.21	94.5	59.5
>5.88	33.3% (23.4–44.5)	96.1% (80.4–99.9)	8.67	0.69	96.6	30.9

uPAR: Urokinase-type plasminogen activator receptor; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; PPV: Positive predictive value; NPV: Negative predictive value; CI: Confidence interval.

The mean uPAR value of the AA patients with Alvarado scores less than 5 (n=17) was 1.92±4.06, compared to 4.06±3.24 in the AA patients (n=93) with Alvarado scores of 5 or more serum. The difference was statistically significant (p=0.018).

The area under the curve (AUC) at ROC analysis performed to measure the diagnostic value of serum uPAR in patients was 0.88 (p<0.001, 95% confidence interval [CI] 0.80–0.97) (Fig. 1). AUC at ROC analysis performed for WBC was 0.83 (p<0.001, 95% CI 0.74–0.92), and 0.70 at ROC analysis for CRP (p<0.001, 95% CI 0.59–0.81). Analysis of correlation

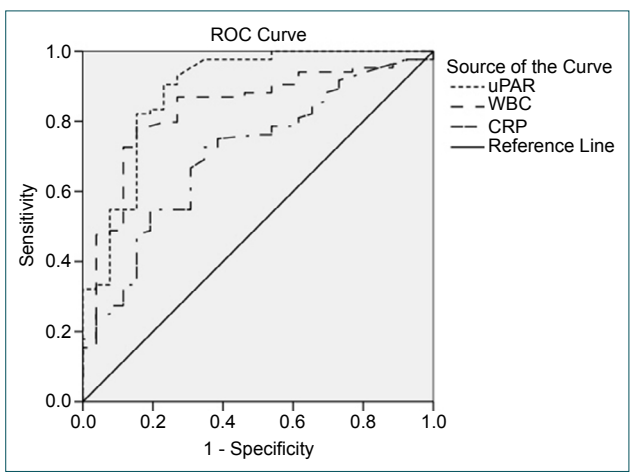

Figure 1. ROC analysis chart performed to measure the diagnostic value of WBC, CRP and uPAR in patients with acute appendicitis.

levels between uPAR values and WBC and CRP values revealed significant relations (r values 0.63 and 0.59, respectively) (p<0.001 for both). The sensitivity and specificity of uPAR in the diagnosis of appendicitis were calculated and are shown in Table 3. The specificity of uPAR in the diagnosis of appendicitis increased as uPAR values in patients' plasma increased (Table 3).

DISCUSSION

Activation of the uPA/uPAR system plays a key role in chemotaxis and inflammatory cell infiltration at the start of the inflammatory reaction.[13] In addition, the uPA system is also a key factor in cell migration, tissue remodeling, wound healing, inflammation, angiogenesis, tumor invasion, and metastasis.[14,15] uPAR (CD87) is a cellular receptor for uPA and is released from several cells, including leukocytes, and endothelial and malignant cells.[15,16] uPAR contributes to the conversion to plasmin of plasminogen, which leads to the proteolysis of matrix proteins, and the migration of leukocytes to the relevant region in the event of infection of inflammation.[15,17] Serum uPAR levels have been shown to increase in many inflammatory pathologies, such as sepsis, non-septic systemic inflammatory response (SIRS), pneumonia, pancreatitis, and intestinal inflammation.[12,18–23] Additionally, an increase in serum concentrations of the soluble form of uPAR has been shown to reflect activation of the immunological system and the severity of inflammatory diseases.[24,25] Kolber et al.[25] observed a significant increase in serum uPAR concentrations

from the first day of onset of symptoms of acute pancreatitis. That study also determined a significant correlation between uPAR and the neutrophil to lymphocyte ratio and reported that uPAR was associated with the severity of acute pancreatitis.

AA is an inflammation that frequently occurs as a result of the invasion of the appendix by micro-organisms and obstruction of the lumen. An increase in inflammatory cells as a cytokine response to inflammation and an increase in biochemical inflammation values are observed.[26] Chan et al.[27] analyzed serum soluble uPAR in the extracted intestinal segments of patients with necrotizing enterocolitis, and also in blood studied simultaneously. This revealed a close relation between impairment of the intestinal mucosa barrier and increased uPAR levels in blood. Grøndahl-Hansen et al.[9] reported negative uPA immunostaining in normal appendix tissue and positive immunostaining in acute inflamed appendix tissue. Solberg et al.[28] reported increased uPA staining in perforated and non-perforated appendix biopsies compared to normal appendix tissue biopsies. Oztan et al.[15] determined a significant increase in serum uPAR levels in perforated and non-perforated cases among pediatric appendicitis patients compared to a healthy control group. They also reported sensitivity for AA in children of 85.7%, specificity of 84.3%, and an AUC of 0.90 at a uPAR cut-off value greater than 2.2 ng/mL. We also determined a significant difference in uPAR levels between adult AA patients and healthy controls ($p<0.05$), with an increase in serum uPSR levels in patients identified as AA-positive in terms of postoperative histopathology, in agreement with the previous literature. At the same time, we determined that the uPAR levels of patients with histopathology negative in terms of AA increased less than the levels of positive patients. We, therefore, think that uPAR levels increase in appendix inflammation in a manner compatible with its role in the inflammatory response. WBC and CRP are the inflammatory markers most commonly used in the diagnosis of AA. Several studies have investigated the diagnosis of AA with these parameters. Based on the results of those studies, WBC has been reported to exhibit a sensitivity of 67–97.8% and specificity of 31.9–90.8% in the diagnosis of AA, with NPV between 77.9% and 82% and PPV between 42% and 91.8%.[2,15,29] Yu et al.[30] performed a systemic review and meta-analysis to determine the diagnostic accuracy of CRP, WBC and procalcitonin in AA patients and reported a wide range of sensitivity (39–73%) and specificity (58–97%) values for CRP. They reported large differences between CRP cut-off values in studies, and that CRP had the largest area under the ROC curve, followed by WBC and procalcitonin. Correlation analysis in our study revealed that uPAR exhibited a good level of correlation with WBC and CRP. This suggests that the diagnostic value of uPAR in AA will increase when used together with WBC and CRP.

Although AA is one of the most common surgical pathologies, difficulties continue to be experienced in diagnosis under emergency conditions. Clinical scoring systems are employed in addition to clinical findings in diagnosis. The most commonly employed scoring system in the diagnosis of AA is the Alvarado score.[26] The Alvarado scoring system relies on systemic symptoms, physical examination findings, and laboratory values. Alvarado scores of 4 or lower indicate a low probability of appendicitis, while surgery is recommended in all cases with scores ≥7.[31,32] However, prospective studies have reported that the Alvarado score alone cannot be used as a diagnostic test.[33,34] The Alvarado scores of the patients included in our study were recorded. We determined the significant difference between serum uPAR levels in patients with Alvarado scores above and below 5, suggesting a higher probability of AA in patients with high Alvarado scores and serum uPAR levels. Although history, physical examination, and Alvarado score occupy an important place in the diagnosis of AA, general surgeons currently employ imaging techniques in diagnosis due to increasing malpractice suits. Abdominal CT is a radiological methodology with high evidential value at differential diagnosis of AA and pathologies, causing right lower quadrant pain. Although the question of which radiological imaging technique should be employed is still the subject of debate, several studies have reported that CT is more reliable in the diagnosis of AA.[29] CT was also the most commonly used method in the diagnosis of AA in the present study. However, negative laparotomy results were encountered in 18 of the 93 patients with results compatible with AA at CT examination. Since atypical presentations are possible in patients presenting due to the right lower quadrant pain, we think that rather than using blood infective parameters of imaging techniques alone in the diagnosis of AA, use should be made of all findings obtained by correlating them with one another.

In conclusion, the sensitivity and specificity levels of uPAR in the diagnosis of adult AA are compatible with previous studies investigating inflammatory parameters in AA patients. uPAR was significantly higher in the AA patients compared to the control group and patients with surgically determined non-AA pathologies. We think that serum uPAR values can be used as an assistant test in the diagnosis of adult AA patients.

Limitations

The first limitation of this study is the relatively low number of patients. In addition, time to presentation to the emergency department after the onset of symptoms in AA patients is a variable and given that this leads to differences in patients' serum uPAR levels is another limitation.

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Compliance with Ethical Standards: None of the authors had any financial or personal relationships with other individuals or organizations that might inappropriately influence their work during the submission process.

Informed consent: Informed consent was obtained from all individual participants included in this study.

Conflict of interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZET*

Akut apandisitte serum ürokinaz-tipi plazminojen aktivatör reseptörünün tanısal değeri

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AMAÇ: Acil servise sağ alt kadran ağrısı ile başvuran erişkin hastalarda serum ürokinaz-tipi plazminojen aktivatör reseptörü (uPAR) düzeylerini ölçmek ve bu parametrenin akut apandisit (AA) tanısında bir biyokimyasal belirteç olup olamayacağını araştırmayı planladık.

GEREÇ VE YÖNTEM: Çalışmaya Mayıs 2018–Aralık 2018 tarihleri arasında acil servise başvuran ve AA tanısı konularak ameliyat edilen 18 yaş ve üzeri hastalar dahil edildi. Çalışmaya AA (Grup A) ile uyumlu cerrahi patoloji sonuçları olan 84 hasta, AA (Grup B) ile uyumlu olmayan cerrahi patoloji sonuçları olan 26 hasta ve 55 sağlıklı kontrol grubu dahil edildi. Hastalardan başvuru anında alınan venöz kan örneklerinden serum uPAR seviyeleri ölçüldü.

BULGULAR: Grup A'da ortalama uPAR düzeyleri 4.53±3.47 ng/mL, Grup B'de 1.13±1.63 ng/mL ve kontrol grubunda 0.80±1.21 ng/mL idi. Grup A hastaların serum uPAR düzeyinin Grup B ve kontrol grupların serum uPAR düzeyleri ile karşılaştırılmasında istatiksel olarak anlamlı fark bulundu ($p<0.05$).

TARTIŞMA: uPAR, AA hastalarında kontrol grubu ve cerrahi olarak AA dışı patoloji saptanan hastalara göre anlamlı olarak yüksek bulundu. Serum uPAR değerleri erişkin hastalarda AA tanısında yardımcı tetkik olarak kullanılabilir.

Anahtar sözcükler: Akut apandisit; erişkin; inflamasyon; karın ağrısı; ürokinaz-tipi plazminojen aktivatör reseptörü.

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