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The role of soluble urokinase plasminogen activator receptor (SuPAR) as an indicator of the severity of acute pancreatitis

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Background/aim: Soluble urokinase plasminogen activator receptor (suPAR) has been reported to have a positive correlation with the activation degree of the immune system. This study's aim is to investigate the efficiency of SuPAR serum levels in acute pancreatitis (AP) patients in determining the severity of disease.

Materials and methods: This prospective research involves patients who arrived at the emergency service, were over 18 years old, had nontraumatic abdominal pain and diagnosis of AP, and agreed to join the study. Demographic characteristics, contact information, laboratory and imaging test parameters, Ranson's criteria, the Balthazar Severity Index, the Rapid Acute Physiologic Score (RAPS), and the modified Glasgow (Imrie) score of all patients were recorded. Two study groups were created as score of <3 (mild, Group I) and ≥3 (severe, Group II) for pancreatitis according to Ranson's criteria.

Results: During the study period, 59 sequential patients with AP were included in the study. It was seen that 79.7% of the study group (n = 47) were in Group I. Etiologically 67.8% (n = 40) cases were biliary and 32.3% (n = 19) were nonbiliary diseases. According to the results, suPAR level was effective in distinguishing the severity of AP (AUC = 0.902, P < 0.001 (95% CI: 0.821–0.984)). With regard to determining severe disease, suPAR had an optimum cutoff value of 6.815 ng/mL, sensitivity of 91.66%, specificity of 82.97%, and negative predictive value of 97.5%.

Conclusion: Our study was performed the determine the efficiency of suPAR level in predicting severe disease in AP patients. We found it significant in indicating the severity of disease according to the study results.

Key words: Acute pancreatitis, biomarker, abdominal pain, suPAR

1. Introduction

Acute pancreatitis (AP) is a situation in which inactive pancreas enzymes are activated and cause inflammation by digesting pancreatic tissue and the surrounding structures. Increased morbidity and prolonged length of stay in the hospital is an important problem for patients with AP. Thus, indicators that can predict the prognosis, severity, length of hospital stay, and treatment requirements in the intensive care unit are needed for patients with AP. However, classifying severity and prognosis is difficult since severity progresses with clinical findings in a wide range. Predicting the severity of disease is important in determining the systemic antibiotic treatment and treatment requirements in the intensive care unit. Numerous scoring systems were developed for this purpose. The best known of those are Ranson's criteria, the modified Imrie criteria, and the Balthazar criteria (1–5).

Soluble urokinase plasminogen activator receptor (suPAR) (6) is a receptor expressed on immune system cells, including endothelial and malignant cells, neutrophils, active T lymphocytes, and macrophages. It is reported that the level of suPAR has a positive correlation with the activation level of the immune system. It is also reported that, though it has a low diagnostic value in sepsis groups, it is valuable as a prognosis indicator. It is claimed to be better than C-reactive protein and procalcitonin for indicating mortality in the hospital for sepsis (6–8).

This study aims to investigate the efficiency of suPAR serum levels in patients with AP in determining the severity of the disease.

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2. Materials and methods

This study was approved by the decision, dated 21.02.2014 and numbered 2014/595, of the Noninvasive Clinical Studies Ethics Committee Directorate at the Meram Faculty of Medicine of Necmettin Erbakan University (Konya, Turkey).

2.1. Study population

This prospective observational study involves patients who arrived at the emergency service, were over 18 years old, had nontraumatic abdominal pain, had at least two of the AP diagnostic criteria, and agreed to join the study (Table 1). Researchers had no influence on the clinical decisions of the emergency physicians for the involved patients during the period of the emergency service visit.

While the study group was being determined, patients with at least two of the following diagnostic criteria were identified as having acute pancreatitis:

1) Having abdominal pain, which is characteristic for AP;
2) Serum amylase and/or lipase values being 3 times above normal or more;
3) Characteristic findings for AP in computed tomography (CT).

2.2. Sampling and biochemical analysis

Blood samples were taken from the involved patients for tests that were chosen as a result of an emergency service evaluation and the remaining samples were used in our study. Blood samples were centrifuged for 10 min at a speed of 1500–2000 × *g*. Blood samples for suPAR parameters were kept at –25 °C until the biochemical analyses were made. All samples were studied using an ELISA kit (suPARnostic, lot 204LK1-1, ViroGates, Denmark)

2.3. Parameters analyzed in the study

Demographic characteristics, contact information, laboratory and imaging test results for tests planned at the emergency service, Ranson's criteria, the Balthazar Severity Index, the Rapid Acute Physiologic Score (RAPS), and the modified Glasgow (Imrie) criteria of all patients were calculated and recorded. The study group was divided into two groups according to Ranson's criteria as 'mild pancreatitis' (Group I) if the score was <3 and 'severe pancreatitis' (Group II) if the score was ≥3.

2.4. Statistical analysis

The analyses were performed with SPSS (IBM Corp., Armonk, IL, USA). Descriptive statistics of the variables were presented as frequency and percentages in categorical situations and as mean ± standard deviation (median, min, max) for continuous data. Continuous variables were analyzed by the Kolmogorov–Smirnov test for normal distributions. In comparison of the groups, the Student t-test and Mann–Whitney U test were used as necessary. The exact Monte Carlo chi-square test was used for determining the correlation between categorical variables. Pearson correlation analysis was used for determining the direction and size of the correlation between the continuous variables and Spearman rho correlation analysis was done for variables that did not correlate with normal distribution. Results for which the variation or correlation was found to be significant were illustrated with related graphics. ROC analysis was done in order to determine the diagnostic characteristics of suPAR for severe AP. Logistic regression analysis was done in order to determine the effects of the parameters considered significant on severe AP disease and odds ratios were studied by coefficients. Diagnostic methodological decision-making values (specificity, sensitivity, accuracy, false positive rate, false negative rate, positive predictive value, negative predictive value, positive likelihood) were obtained for the factors related to the severity of disease. Type I error performance was accepted as 5% in the whole study and $P < 0.05$ was accepted as statistically significant. Power analysis was performed with GPower software. For an allocation ratio of 1, the sample size was found to be 18 for each group using suPAR values with power of 90%, type I error of 5%, and effect size of 0.20. For an allocation

Table 1. Criteria for being included in or excluded from the study.

A. Criteria for being included in the study
1. Being over 18 years old 2. Applying to the emergency service with nontraumatic abdominal pain 3. Meeting at least two of the acute pancreatitis diagnostic criteria
B. Criteria for being excluded from the study
1. Being under 18 years old 2. Applying to the emergency service with traumatic abdominal pain 3. Patient requiring immediate treatment and cardiopulmonary resuscitation 4. Not giving consent to be involved in the study

Table 2. Results of parameters according to the study groups in patients with acute pancreatitis.

		Group I	Group II	P
Sex	Male	21 (44.68%)	5 (41.67%)	0.852
	Female	26 (55.31%)	7 (58.33%)	
Age		55.74 ± 13.94	74.92 ± 13.18	0.002
Etiology	Biliary	32 (68.08%)	8 (66.67%)	0.926
	Nonbiliary	15 (31.9%)	4 (33.33%)	
Scores	Glasgow (Imrie)	1.81 ± 1.32 (2, 0, 5)**	4.08 ± 0.16 (2, 0, 7)**	<0.001
	RAPS*	1.17 ± 1.59 (0, 0, 7)**	2.25 ± 2.05 (2.5, 0, 6)**	0.059
	Balthazar	2.94 ± 3.36 (1.5, 0, 10)**	1.33 ± 0.57 (1, 1, 2)**	0.634
Length of stay in hospital (days)		(7, 2, 32)**	(7, 5, 10)**	0.041
Hospital outcome	Nonsurvivors	1 (2.12%)	1 (8.33%)	0.293
	Survivors	46 (97.88%)	11 (91.67%)	
suPAR		5.22 ± 3.02	12.33 ± 9.22	
Blood gas	Lactate	1.35 ± 0.78	2.37 ± 1.83	0.167
Complete blood	Hemoglobin	13.74 ± 1.83	13.88 ± 1.81	0.813
	White blood cells	(2587, 219, 37,778)**	(3836, 326, 21,540)**	0.016
	Platelets	255.23 ± 74.29	232.75 ± 90.33	0.374
	Neutrophils	9.00 ± 5.23	14.38 ± 6.21	0.006
	Eosinophils	0.079 ± 0.09	0.025 ± 0.04	0.083
	RDW*	14.15 ± 1.70	13.97 ± 0.94	0.713
Biochemistry	Glucose	149.06 ± 81.85	185.25 ± 89.71	0.048
	Albumin	3.84 ± 0.39	3.73 ± 0.53	0.408
	Urea	2.80 ± 3.31	3.11 ± 1.69	0.011
	Creatinine	2.28 ± 9.80	2.02 ± 2.49	0.022
	LDH*	441.43 ± 265.12	657.42 ± 336.48	0.004
	AST*	160.15 ± 156.52	484.08 ± 417.92	<0.001
	ALT*	167.19 ± 161.11	394.67 ± 379.43	0.027
	Total bilirubin	2.80 ± 3.31	3.11 ± 1.69	0.150
	Direct bilirubin	1.51 ± 2.35	1.89 ± 1.25	0.039
	GGT*	346.04 ± 503.01	345.58 ± 144.26	0.060
	ALP*	180.43 ± 157.93	283.75 ± 246.91	0.155
	CRP*	31.67 ± 44.49	34.87 ± 37.66	0.259
	Amylase	1463.04 ± 1667.07	1506.92 ± 934.04	0.309
	Lipase	4711.87 ± 6438.03	4952.0 ± 5636.02	0.624
	Calcium	8.89 ± 0.54	9.25 ± 0.78	0.062
	pO_2*	74.55 ± 12.81	70.50 ± 13.08	0.335

*ALP: Alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; pO_2: partial pressure (tension) of oxygen; RAPS: Rapid Acute Physiology Score; RDW: red cell distribution width; SuPAR: soluble urokinase plasminogen activator receptor.
**Denotes (median, min, max) values for discrete and nonnormally distributed variables.

ratio of 3, the sample sizes were determined as 9 and 27 with power of 90%, type I error of 5%, and effect size of 0.20. We chose the latter results as AP is a rare disease.

3. Results

Fifty-nine patients were involved in the study within the determined study period (Table 2) and 79.7% of the whole patient group was included in Group I. While there was no statistically significant difference between the study groups regarding sex distribution, there was a statistically significant difference regarding age distribution (P = 0.852 and P = 0.002, respectively). When the distribution was evaluated etiologically, there was no statistically significant difference between groups (P = 0.956) (Table 2).

The Glasgow (Imrie), RAPS, and Balthazar scores, which evaluate the severity of disease between study groups, were higher in Group II, but only the difference in the Glasgow (Imrie) scoring system was statistically significant (P < 0.,001, P = 0.059, and P = 0.634, respectively) (Table 2).

While a statistically significant difference in the length of stay in the hospital was present between the study groups, there was no statistically significant difference regarding mortality (P = 0.04 and P = 0.293, respectively) (Table 2).

When laboratory results were evaluated, there was a statistically significant difference between the study groups regarding white blood cell count, neutrophil count, levels of glucose, urea, creatinine, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and direct bilirubin, which were all higher in Group II except the level of creatinine (P = 0.016, P = 0.006, P = 0.048, P = 0.011, P = 0.022, P = 0.004, P < 0.001, P = 0.027, and P = 0.039, respectively) (Table 2).

suPAR levels were statistically significantly higher in Group II than in Group I (P < 0.001) (Table 2; Figure 1). ROC analysis was conducted for determining if the suPAR level was sufficient or not in order to distinguish the severity of the disease. According to the results, suPAR level was seen to be effective in distinguishing the severity of AP (AUC = 0.902, P < 0.001 (95% CI: 0.821–0.984)) (Figure 2). The optimum cut-off value for suPAR, which was calculated for determining severe disease, was 6.815 ng/mL. Then suPAR values were determined for diagnosis of severe AP for this cut-off value: sensitivity 91.66%, specificity 82.97%, negative predictive value 97.5%, positive predictive value 57.89%, and accuracy 84.74%.

Optimum cut-off values were calculated for leukocyte and neutrophil counts, level of glucose, urea, creatinine, LDH, AST, ALT, and direct bilirubin, which had statistically significant differences between the study groups, by conducting ROC analysis and methodological diagnostic

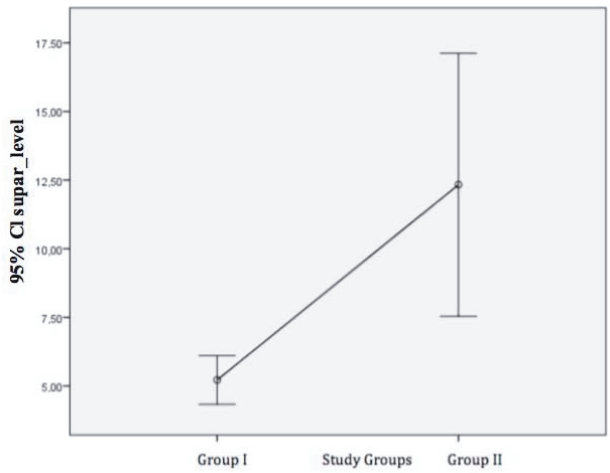

Figure 1. Distribution of suPAR levels among study groups.

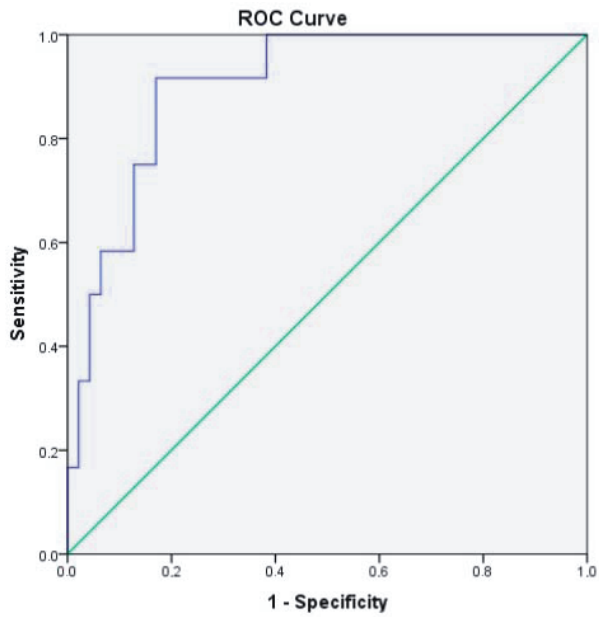

Figure 2. ROC curve for suPAR levels.

rates were found (Table 3). The logistic regression model that was developed regarding severe AP risk factors was not found significant (Hosmer–Lemeshow test = 0.106, P = 0.993).

4. Discussion

AP is an important problem due to increased morbidity and prolonged length of stay in the hospital. While mortality ranges between 2% and 10%, this rate increases

Table 3. Methodological diagnostic rates according to optimum cut-off values determined for full blood, biochemistry, and score parameters for severe acute pancreatitis diagnosis.

Biomarkers*	AUC	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy	Positive likelihood ratio
Leukocytes (13.05)	0.727	75%	75%	43%	92%	75%	294%
Neutrophils (13.00)	0.757	75%	83%	53%	93%	81%	441%
Glucose (158.4)	0.686	75%	77%	45%	92%	76%	320%
Urea (54.4)	0.739	50%	85%	46%	86%	77%	336%
Creatinine (0.78)	0.715	75%	62%	33%	90%	64%	196%
LDH (465.5)	0.722	75%	74%	42%	92%	75%	294%
AST (247.50)	0.842	83%	83%	56%	95%	83%	490%
ALT (114)	0.708	92%	45%	30%	95%	54%	166%
D. Bil. (0.955)	0.842	83%	62%	36%	94%	66%	218%

*Optimum cut-off levels are expressed within parentheses. ALT: Alanine transferase; AST: aspartate transferase; LDH: lactate dehydrogenase; D. Bil: direct bilirubin.

to 25% in the severe form (9,10). Thus, determining the severity of the disease contributes to the treatment strategy. The biggest disadvantage of many scoring systems that are used for this purpose is their complexity and difficulty of use. Using a biochemical indicator as an indicator for severity may be clinically advantageous.

Systemic inflammatory situations (SIRSs) occur in the course of AP. It is stated that free oxygen radicals play a significant role in SIRS pathogenesis associated with AP (11,12). It was found in the study of Yilmaz et al. (13) that suPAR levels increased in patients with SIRSs. Increased suPAR levels in various clinical pictures, especially in infectious situations, may depend on an increase in suPAR expression and dissociation or an increase in the number of cells that express suPAR such as monocytes and macrophages. The most possible source of in vivo suPAR seems to be dissociation of suPAR by uPA or other proteases in monocytes and endothelial cells (14,15).

Various scoring systems are used in order to determine the severity of the clinical picture and prognosis in the earlier stage of AP. Ranson's criteria are reliable indicators for showing the prognosis and clinical severity of AP (16,17). The Atlanta criteria, which were identified in 1992, are used to determine the clinical severity of AP. If the Ranson score is ≥3 and the APACHE II score is ≥8, this situation is called severe pancreatitis according to the Atlanta criteria (18).

It has been reported in various studies that leukocyte, albumin, and ALT levels can be used in determining the severity of the AP clinical picture (19–21). On the other hand, it has been found that amylase and lipase levels, which are often used to diagnose AP, are not determinant in determining the severity of disease (22). It has been ascertained in our study that leukocyte and neutrophil count, together with glucose, urea, creatinine, LDH, AST, ALT, and direct bilirubin serum levels can be used in discriminating severe AP with different methodological rates (Tables 2 and 3).

suPAR reflects pathophysiological mechanisms that are active at the cell level. Increased suPAR levels are regarded as an indicator for activation of immune and inflammatory systems. suPAR plays a significant role in the prediction of diagnosis, prognosis, and survival rate for inflammatory cases. It has been shown in studies that it can be used in diagnosing infectious diseases such as Crimean–Congo hemorrhagic fever and pneumonia, and also in determining sepsis, SIRSs, and bacteremic diseases (23–28). suPAR levels of cerebrospinal fluid from patients with proven central nervous system infections have been found to be significantly higher than those of patients with no infection, and there was positive correlation with the Glasgow Coma Scale and mechanical ventilator requirement (27).

It was determined that suPAR levels were statistically significantly higher in the severe AP group among our study groups (Table 2; Figure 1). It was understood that suPAR has the highest accuracy and negative predictive values in distinguishing the severity of AP disease among other biochemical parameters (Table 3).

In the literature there are many publications that show the relation of suPAR with pneumonia related to ventilators and mortality related to tuberculosis and malaria (29–31). It was shown in another study that suPAR was a successful indicator in predicting mortality in patients with a

suspicion of infection who applied to emergency services and suPAR was found to be far superior to procalcitonin (32). It was reported in another study (24) that suPAR was an independent indicator that could predict intensive care requirements and long-term mortality in critical patients. In our study the suPAR levels of two nonsurviving patients were 30.46 and 19.75 ng/mL. This gives rise to thought that suPAR levels may be related to mortality. However, no precise conclusion can be reached due to the limited number of patients.

Nikkola et al. conducted a study involving 104 patients in order to determine the prognostic value of suPAR in the first acute alcoholic pancreatitis attack. It was indicated, in analogy to our study, that suPAR concentration had a correlation with the severity of the disease and may serve as a novel potential marker for AP severity on admission to the hospital (33). Similarly, it was emphasized in the study of Lipinski et al. that suPAR concentration is a novel diagnostic and prognostic marker for AP severity in the early stage of the disease (34).

Our study results show that suPAR serum levels are more effective in determining the severity of AP disease compared to other biomarkers. Taking the limitations of our study into consideration, wider prospective studies are needed regarding the relation between suPAR and AP diagnosis and prognosis. Our study has limitations due to being a single-center study and the size of the study groups.

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