Nobel Med 2021; 17(1): 48-53

SERUM UROKINASE-TYPE PLASMINOGEN ACTIVATOR RECEPTOR IN PATIENTS WITH ACUTE PANCREATITIS

Ümmügülsüm Can[1], Salih Başer[2], Fatma Hümeyra Yerlikaya[3], Deniz Karasoy[4]

[1]*Konya Education and Research Hospital, Department of Biochemistry, Konya, Turkey*
[2]*Keçiören Education and Research Hospital, Department of Biochemistry, Ankara, Turkey*
[3]*University of Necmettin Erbakan, Meram Faculty of Medicine, Department of Biochemistry, Konya, Turkey*
[4]*Konya Education and Research Hospital, Department of İnternal Medicine, Konya, Turkey,*

ABSTRACT

Objective: *Acute pancreatitis (AP) is an inflammatory disease in which digestive enzymes produced by pancreas destroy the gland via protease pancreatic autodigestion. Soluble urokinase-type plasminogen activator receptor (suPAR), an inflammatory biomarker, is responsible for various immunological functions, including inflammation, cell adhesion, migration and proteolysis. The main goal of our study was to evaluate serum suPAR level in patients with mild AP, compared with controls.*

Material and Method: *The study was performed on 40 patients with mild AP and 50 healthy controls. Controls were matched with patients as to age and body mass index (BMI). The diagnosis of AP was established under the Ranson criteria. Serum suPAR levels were measured through ELISA method.*

Results: *Serum suPAR levels of patients were significantly higher than those of control subjects (4.81±3.30; 1.98±1.78 ng/ml, respectively) ($p<0.001$). No significant correlation was found between suPAR levels, amylase, lipase, CRP, hs-CRP and fibrinogen levels ($p>0.05$ for all parameters).*

Conclusion: *Our study indicated that serum suPAR may play an important role in the inflammatory process in AP, and suPAR could be used as a clinically beneficial marker in the diagnosis of AP.*

Keywords: *Acute pancreatitis, soluble urokinase-type plasminogen activator receptor, inflammation.*

CORRESPONDING AUTHOR: Ümmügülsüm Can Konya Eğitim Araştırma Hastanesi, Hacışaban Mahallesi, Yeni Meram Caddesi, No:74 Karatay, Konya, Turkey cangulsum@yahoo.com

UC https://orcid.org/0000-0002-8967-2924 **SB** https://orcid.org/0000-0002-3448-6454 **FHY** https://orcid.org/0000-0002-4107-5389

DK https://orcid.org/0000-0002-2981-5399

DELIVERING DATE: 18 / 02 / 2020 • **ACCEPTED DATE:** 15 / 10 / 2020

AKUT PANKREATİT HASTALARINDA SERUM UROKİNAZ-TIP PLASMİNOJEN AKTİVATOR RESEPTÖR

ÖZET

Amaç: Akut pankreatit kendi proteazları ile sindirimi sonucu ortaya çıkan inflamatuvar bir hastalıktır. Solubl urokinaz-tip plasminojen aktivatör reseptör (suPAR) inflamasyonda salgılanan ve plazminojen aktivasyonu, hücre adezyonu, migrasyon, proliferasyon, kemotaksi, proteolizis, immun sistem aktivasyonu ve invazyonda yer alan bir serin proteinazdır. Amacımız akut pankreatit hastalarında kontrol grubu ile karşılaştırıldığında suPAR düzeylerinin nasıl değiştiğini incelemekti.

Materyal ve Metot: Hasta grubu 40 kişi ve kontrol grubu 50 kişi olup yaş ve cinsiyet yönünden benzerdi. Akut pankreatit teşhisi Ranson kriterlerine göre konuldu. Serum SuPAR düzeyleri ELİSA yöntemi ile çalışıldı.

Bulgular: Akut pankreatit hastalarında kontrollere göre serum suPAR düzeyleri anlamlı şekilde yüksekti (4,81±3,30; 1,98±1,78 ng/ml sırası ile) (p<0,001). SuPAR düzeyleri ile amilaz, lipaz, CRP, hs-CRP ve fibrinojen düzeyleri arasında anlamlı bir ilişki bulunmadı (tüm parametreler için p>0,05)

Sonuç: Bulgularımıza göre AP vakalarında suPAR düzeyleri yüksek olup, AP tanısında faydalı bir göstergedir.

Anahtar kelimeler: Akut pankreatit, solubl urokinaz-tip plasminojen aktivator reseptör, inflamasyon.

INTRODUCTION

Acute pancreatitis (AP) is known as a reversible inflammatory disorder with various clinical features ranging from mild to severe and a necrotizing disease with high morbidity and mortality without specific treatment. The pathogenesis of the condition still remains unknown.[1,2] As well as its effects on pancreas, AP also causes pulmonary, renal, cardiovascular, central nervous and coagulation system injuries potentially resulting in a multiorgan dysfunction syndrome with high mortality.[3] AP, an inflammatory disease, is led by the autodigestion of pancreas by its own activated digestive proteases. The premature activation of digestive proteases such as trypsin, elastase and lipase within the pancreatic acinar cells is of an early and critical importance in the pathogenesis of AP. As a result, acinar cells show more propensity to the deteriorating effects of activated zymogens subsequently by bringing about vacuole accumulation, recruitment of inflammatory cells such as neutrophils and macrophages, local and systemic inflammation, and death of acinar cells through both necrosis and apoptosis.[4,5] Another significant event encountered in AP at initial is the increased acinar cell expression of inflammatory regulators. These regulators consist of such cytokines as tumour necrosis factor α (TNF-α), interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8 and IL-18; the chemokines including IL-8, monocyte chemoattractant protein-1(MCP-1) and macrophage inflammatory protein-1 (MIP-1); and, the adhesion molecules, platelet activating factor and reactive-oxygen and reactive-nitrogen species.[3,5] Adhesion molecules such as selectins and integrins are of a crucial role in the accumulation and activation of leukocytes during an inflammation.[6,7]

Amylase and lipase released into the circulation by acinar cells are the most significant clinical markers of pancreatic injury used to diagnose AP.1 Strategies to be developed to treat AP should target both trypsin and other proteases in order to reduce protease activities in acinar cells and achieve maximal and effective results.[8]

Urokinase-type plasminogen activator receptor (uPAR, CD87) is a highly glycosylated, glycosylphosphatidylinositol (GPI)-anchored cell membrane protein. uPAR exists on the surfaces of many cell types, including monocytes and macrophages, polymorphonuclear neutrophils, vascular endothelial, smooth muscle (SMCs) and epithelial cells, and has also contributions to the inflammatory process through such different mechanisms as chemotaxis, cell migration and cell adhesion.[9,10] The function of active uPAR-bound uPA, a serine protease, is proteolytic conversion of plasminogen into plasmin, another serine protease, which in turn, commences a proteolytic cascade, including matrix metalloproteinases (MMP). Hence, this function gives uPAR-expressing cells a high potential for pericellular proteolysis, extracellular matrix (ECM) processing and cell motility. uPAR takes part in cell adherence and migration through other routes such as ECM adhesive protein vitronectin and various integrins.[9] Cell-surface-bound uPAR is broken down between the D1-D2 linker sequence, resulting in the release of suPAR after the exposure to pro¬teases, MMP, cathepsin G and elastases released from acti¬vated monocytes and macrophages.[9,10]

Plasma suPAR levels definitely elevate during the inflammation process and most systemic inflammatory diseases, such as bacterial and viral infections, sepsis, rheumatoid arthritis, atherosclerosis and cancer,

Table 1. Demographic and laboratory findings of patient and control groups

	Patients (n=40)	Controls (n=50)	*p*
Age (yrs)	50.23±15.45	46.06±4.26	0.162
Female/Male	18/22	20/30	0.112
Leukocytes (10000/mm3)	9847.33 (4970-17600)	5528.71 (2034-9420)	< 0.001
ESR (mm/h)	25.73 (8-50)	6.19 (1-22)	< 0.001
Albumin (g/dL)	3.53 (2.5-4.7)	4.36 (3.8-4.7)	< 0.001
AST (U/L)	158 (12-460)	16.8 (11-32)	< 0.001
ALT (U/L)	177 (7-666)	19.9 (1-51)	< 0.001
Amylase (U/L)	1829 (131-5325)	58 (34-84)	< 0.001
Lipase (U/L)	4805 (328-12000)	21.9 (9-54)	< 0.001
CRP (mg/L)	39.43 (3-204)	3.98 (3-11)	< 0.001
hs-CRP (mg/L)	18.68 (3-93)	1.41 (0.3-7)	<0.001
Fibrinogen (g/L)	590.15 (283-1367)	307.77 (172-428)	< 0.001
suPAR (ng/mL)	4.81 (1-13)	1.98 (0.3-6)	< 0.001
Hemoglobin (g/dL)	12.83(9-16)	14.98 (11-17)	< 0.001
Glucose (mg/dL)	117.00 (75-176)	90.87 (71-111)	<0.001
Blood urea (mg/dL)	37.47 (16-89)	25.90 (17-42)	0.002
Serum creatinine (mg/dL)	0.96 (0.5-2.6)	0.81 (0.5-1)	0.080
Serum Ca (mg/dL)	8.60 (6.9-10.10)	9.17 (8.2-9.6)	< 0.001

ESR: Erythrocyte sedimentation rate, **AST:** aspartate aminotransferase, **ALT:** alanine aminotransferase, **CRP:** C-reactive protein, **Ca:** calcium, **hs-CRP:** high-sensitivity C-reactive protein, **suPAR:** soluble urokinase plasminogen activator receptor.

Table 2. Correlations of laboratory findings of patient and control groups

		Patients (n=40)	Controls (n=50)
	Amylase	**Fibrinogen**	**suPAR**
WBC	r=0.6	r=0.1	r=0.2
hs-CRP	r=0.5	r=0.3	r=0.1
CRP	r=0.1	r=0.6	r=0.1
Fibrinogen	r=0.1	--	r=0.2
Sedimentation	r=0.1	r=0.3	r=0.1

p>0.05

CRP: C-reactive protein, **hs-CRP:** high-sensitivity C-reactive protein, **suPAR:** soluble urokinase-type plasminogen activator receptor, **WBC:** leukocytes.

reflecting the activation of the immune system. Cytokines influence the release of suPAR from neutrophils, endothelial cells, monocytes and SMCs.[9-11] The relationship between proteolytic activation and inflammation in AP remains complex and have yet to be understood well. To the best of our knowledge, our study is the first to investigate the effect of suPAR on AP. We consider that suPAR has a diagnostic value for and related to the pathogenesis of AP. Serum suPAR may play an important role in the inflammatory process in AP, and suPAR could be used as a clinically beneficial marker in the inflammation process of AP. Therefore, we measured suPAR levels in the sera obtained from patients with AP and compared them with those of healthy controls.

MATERIAL AND METHOD

The present study was performed on 40 patients (22 men and 18 women) with mild AP aged between 25-70 years (mean 50.23±15.45 yrs) and 50 healthy controls (30 men and 20 women) aged between 25 and 70 years (mean 46.06±4.26 yrs). Control subjects were matched with patients in terms of their age and sex. We select randomly select two similar age group and gender. AP subjects were recruited from the outpatient clinic of Internal Medicine Department in Konya Education and Research Hospital. The control group recruited from the hospital staff. Period of the study was from november 2013 to may 2014.

The study protocol was approved by the Ethics Committee of Meram Medical School, Necmettin Erbakan University, Konya, Turkey (Decision No: 2013/26 (23.10.2013). All patients were informed on study design, and written consents were obtained from all participants.

Based on acute onset of epigastric pain with at least threefold increase in levels of serum amylase or lipase and ultrasonographic evidence of pancreatitis, the diagnosis criteria of AP was defined. Computerized tomography was utilized only for severe or necrotising cases of pancreatitis. The Ranson criteria and Glasgow scales of patients were calculated. The patients who were at the first stage of AP constituted the participants in our study. Exclusion criteria for the study included the existence of a malignant disease, diabetes mellitus, chronic liver, chronic kidney, thyroid and infectious diseases, hypertension, chronic pancreatitis and a history of cardiovascular disease.

Biochemical Analyses

Blood samples were drawn after overnight fasting in empty vacuum tubes and in tubes containing EDTA. Plasma and serum samples were obtained after suitable centrifugation, and samples were kept frozen at -80oC until the day of serum suPAR analysis. Arterial blood gas analyses and several blood tests including glucose, calcium, urea, creatinine, albumin, blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), high-sensitivity CRP (hs-CRP), fibrinogen, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, amylase and lipase were performed on admission. These tests were repeated if required. Biochemical parameters were measured through commercially available kits with routine methods on Architect C 8000 System (Abbott Laboratories, Abbott Park, Illinois, USA). Fibrinogen levels were measured with colorimetric method (BCS XP autoanalyser, SIEMENS Diagnostic Systems), and CRP and hs-CRP levels were measured with nephelometric method (BN2 autoanalyser, SIEMENS Diagnostic Systems).

Measurements of suPAR

Analyses of suPAR were detected in serum samples using the AssayMax Human Urokinase Receptor (uPAR) ELISA Kit (Assaypro, St Charles, MO) in accordance with the manufacturer's guidelines. All of the samples were diluted as 1:4 in the supplied buffer and measured in duplicate. Absorbance was measured at 450 nm on an ELx800 Absorbance Microplate Reader (Biotek, Winooski, VT). This assay is used as a quantitative sandwich enzyme immunoassay technique to measure suPAR. Mean value of the duplicate readings for each standard and sample was calculated and then multiplied by the dilution factor. Unknown sample concentration was determined from the standard curve. Concentration values were reported as ng/mL.

Statistical Analysis

All values were expressed as mean±standard deviation (SD) for normally distributed variables, and median and range (min-max) for non-normally distributed variables. Statistical analyses were performed using Statistical Package for the Social Sciences for Windows 20.0 (SPSS Inc, IL. USA). To compare the ratio of categorical variables, we used the chi-square test [sex (female/male)]. The normality of the variables was evaluated using the one-sample Kolmogorov-Smirnov test. The comparisons between groups were performed via the independent samples t test for parametric variables, and the Mann-Whitney U test for non-parametric variables.

Correlations between variables were determined using the Pearson's correlation test. Differences were considered significant at a probability level of $p<0.05$.

RESULTS

Demographic and laboratory findings of the subjects are presented in Table 1. As seen from the table, no statistically significant differences were present between age and gender of patients and controls. Leukocytes (WBC), ESR, albumin, AST, ALT, amylase, lipase, CRP, hs-CRP and fibrinogen levels of patients were significantly higher ($p<0.001$) than those of controls. In addition, suPAR levels of patients were significantly higher ($p<0.001$) than those of controls. The Ranson criteria of all patients were found as ≤ 3. suPAR, CRP, WBC, ESR and fibrinogen variables were visualized in a bar graph and standardized to adjust the scale in Figure.

A positive correlation was observed between amylase levels, and WBC and hs-CRP levels (r=0.571, $p<0.01$ and r=0.504, $p<0.01$, respectively). In addition, a positive correlation was observed between fibrinogen and CRP levels (r=0.587, $p<0.01$). No significant correlation was found between suPAR levels, and WBC, ESR, albumin, AST, ALT, amylase, lipase, CRP, hs-CRP and fibrinogen levels ($p>0.05$ for all parameters) (Table 2).

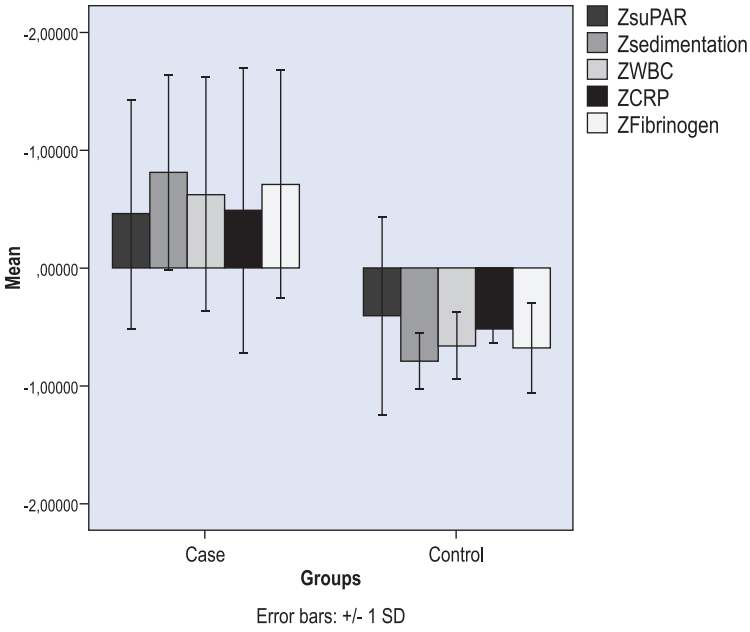

Figure. Bar graph with ± SD of some important variables.

DISCUSSION

Although autodigestion of pancreas by proteases such as trypsin is considered the main mechanism of pathogenesis of AP, the molecular basis still remains unclear, and no specific treatment has yet to be developed for AP.[12] In our study, serum suPAR, CRP, hsCRP, WBC, ESR and plasma fibrinogen levels were found to be significantly higher in patients, compared to those in the control group, and we consider that suPAR may be a useful therapeutic target in AP.

In the pathogenesis of AP, multiple pathologic cellular events such as autophagy, endoplasmic reticulum (ER) and oxidative stress, and lysosomal and mitochondrial dysfuncion are seen.[12] The premature activation of proteases by cathepsin-L and B within acinar cells causes the acini to be disrupted. Furthermore, some of the proinflammatory mediators, such as cytokines and chemokines, are initially released by pancreatic acinar cells, resulting in the recruitment of neutrophils and monocytes.[5,13] Additionally, neutrophils and monocytes in circulation become activated and express the adhesion molecules called intercellular adhesion molecule-1 (ICAM-1).[5] After the upregulation of its expression, ICAM-1 interacts with integrin on the surfaces of cells and increases leukocyte-endothelial cell adhesion. As a result, the migration of leukocytes is facilitated to inflammatory regions, and so excessive inflammatory reactions are induced.[14]

In the liver, the synthesis of acute phase proteins, such as CRP and procalcitonin is stimulated by IL-6.[5,13] In a study performed by Mayer *et al.*, it was found the main value of CRP is to define the severity of the inflammation in AP, and CRP concentrations have better diagnostic value than WBC, ESR and temperature.[15]

suPAR is involved in the plasminogen-activating pathway, inflammation, the modulation of cell adhesion, migration and proliferation. Both membrane-bound and soluble uPARs are asserted to be responsible for cell adhesion by binding ECM adhesive protein vitronectin and various integrins, the regulation of chemotaxis and the cell proliferation.[16,17] Also, the soluble form of uPAR is known to have a direct effect on chemotactic properties, which may increase the recruitment of inflammatory cells such as neutrophils and monocytes.[18,19]

As consistent with the findings determined in previous studies, we found that serum suPAR levels were significantly higher in patients, compared to those of controls. These studies reported that systemic levels of suPAR were increased in different infectious and inflammatory illnesses.[20] In addition, suPAR was shown to be of a prognostic role in the course of critically ill patients.[19,20] Ostrowski *et al.* found that plasma concentrations of suPAR were higher in patients with malaria, while the highest concentrations were in those who died and with complicated malaria.[18] In another study performed by Eugen-Olsen *et al.*, suPAR levels were detected to be elevated in patients with tuberculosis and associated with high mortality.[21] Upon admission to the intensive care unit, Koch *et al.* found that suPAR serum concentrations were increased in sepsis and non-sepsis patients, and likely to reflect the activation state of the immune system and to remain stably elevated at the initial phase of treatment.[22] In another study, Donadello *et al.* also showed that higher level of serum suPAR concentrations predicted mortality in patients with active tuberculosis and other diseases associated with an inflammatory response.[23]

A correlation between an elevated plasma level of suPAR and higher mortality among individuals with various infectious diseases, including pneumococcal pneumonia, HIV-1 and sepsis, was asserted.[24-26] In the study by Wittenhagen *et al.* where suPAR levels were compared in survivors with pneumococcal bacteraemia and those who died from the infecion, it was found that the increase in suPAR levels may demonsrate the increased expression by vascular or inflammatory cells in the cases of pneumococcal sepsis.[24] In a study, pulmonary levels of suPAR were found to be elevated in burn patients with inhalation trauma and to be correlated with pulmonary inflammation and coagulation. In the same study, suPAR was suggested as a biologic marker of fibrinolysis and inflammation.[27] In another study, Edsfeldt *et al.* discovered that suPAR is correlated with several main proinflammatory cytokines and chemokines in plaque tissue responsible for atherosclerotic process, including IL-6, MCP-1, MIP-1β, IL-1β and TNF-α.[10] In addition to abovementioned findings, in the study performed by Sorio *et al.*, suPAR urinary levels were shown to be increased in a large subgroup of patients with pancreatic ductal adenocarcinoma, and such an increase is rarely seen among patients with chronic pancreatitis.[28] Unlike other markers, suPAR plasma cyclic changes in their levels are very few. Sampling time does not matter, which makes suPAR a clinical routine makes it advantageous in use.[29]

However, our study also includes several limitations, such as small sample size of participants and the inclusion of only patients with mild AP, so suPAR levels could not be investigated in patients with severe AP. Finally, these measurements were not repeated after AP treatment.

CONCLUSION

Consequently, a specific treatment for patients with AP still remains unknown. The management of AP is restricted to supportive care as a result of incomplete understanding of pathophysiology of AP as in literature. It is suggested that the soluble form of suPAR is a new biological marker in the immunologic activation. Thus, suPAR might be involved in the pathogenesis of AP. We also consider that suPAR is associated with the pathophysiology of mild AP, and that serum suPAR may be used together with CRP, WBC, ESR, hsCRP, plasma fibrinogen, amylase and lipase in the diagnosis of AP. Future studies investigating the association of suPAR with pancreatic enzymes will be beneficial to enlighten the entity.

Contributorship Statement:

All patients were examined by Salih Başer and Deniz Karasoy.

Data analysis was performed by Ümmügülsüm Can and Fatma Hümeyra Yerlikaya in Department of Biochemistry in University of Necmettin Erbakan, Meram Faculty of Medicine.

Study design, data interpretation, literature search, generation of figures, writing of the manuscript was performed by Ümmügülsüm Can.

*The authors declare that there are no conflicts of interest.

REFERENCES

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis, 2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013; 62: 102-111.
2. Gukovsky I, Pandol SJ, Mareninova OA, et al. Impaired autophagy and organellar dysfunction in pancreatitis. J Gastroenterol Hepatol 2012; 27 (Suppl 2): 27-32.
3. Matej R, Housa D, Olejár T. Acute pancreatitis: proteinase-activated receptor-2 as Dr. Jekyll and Mr. Hyde. Physiol Res 2006; 55: 467-474.
4. Otsuki M, Takeda K, Matsuno S, et al. Criteria for the diagnosis and severity stratification of acute pancreatitis. World J Gastroenterol 2013; 19: 5798-5805.
5. Kylänpää L, Rakonczay Z Jr, O'Reilly DA. The clinical course of acute pancreatitis and the inflammatory mediators that drive it. Int J Inflam 2012; 2012: 360685.
6. Von Dobschuetz E, Hoffmann T, Messmer K. Inhibition of neutrophil proteinases by recombinant serpin Lex032 reduces capillary no-reflow in ischemia/reperfusion-induced acute pancreatitis. J Pharmacol Exp Ther 1999; 290: 782-788.
7. Dios ID. Inflammatory role of the acinar cells during acute pancreatitis. World J Gastrointest Pharmacol Ther 2010; 1: 15-20.
8. Gorelick FS, Thrower E. The acinar cell and early pancreatitis responses. Clin Gastroenterol Hepatol 2009; 7(11 Suppl): 10-14.
9. Beaufort N, Leduc D, Eguchi H, et al. The human airway trypsin-like protease modulates the urokinase receptor (uPAR, CD87) structure and functions. Am J Physiol Lung Cell Mol Physiol 2007; 292: L1263-1272.
10. Edsfeldt A, Nitulescu M, Grufman H, et al. Soluble urokinase plasminogen activator receptor is associated with inflammation in the vulnerable human atherosclerotic plaque. Stroke 2012; 43: 3305-3312.
11. Jo M, Thomas KS, Wu L, et al. Soluble urokinase-type plasminogen activator receptor inhibits cancer cell growth and invasion by direct urokinase-independent effects on cell signaling. J Biol Chem 2003; 278: 46692-46698.
12. Sah RP, Dawra RK, Saluja AK. New insights into the pathogenesis of pancreatitis. Curr Opin Gastroenterol 2013; 29: 523-530.
13. Ohmuraya M, Yamamura K. Autophagy and acute pancreatitis: a novel autophagy theory for trypsinogen activation. Autophagy 2008; 4: 1060-1062.
14. Zhang XP, Li ZJ, Zhang J. Inflammatory mediators and microcirculatory disturbance in acute pancreatitis. Hepatobiliary Pancreat Dis Int 2009; 8: 351-357.
15. Mayer AD, McMahon MJ, Bowen M, et al. C reactive protein: an aid to assessment and monitoring of acute pancreatitis. J Clin Pathol 1984; 37: 207-211.
16. Rabna P, Andersen A, Wejse C, et al. High mortality risk among individuals assumed to be TB-negative can be predicted using a simple test. Trop Med Int Health 2009; 14: 986-994.
17. Can U. Soluble urokinase-type plasminogen activator receptor (suPAR) in multiple respiratory diseases. Receptors Clin Investig 2015; 2: e473.
18. Ostrowski SR, Ullum H, Goka BQ, et al. Plasma concentrations of soluble urokinase-type plasminogen activator receptor are increased in patients with malaria and are associated with a poor clinical or a fatal outcome. J Infect Dis 2005; 191: 1331-1341.
19. Backes Y, van der Sluijs KF, Mackie DP, et al. Usefulness of suPAR as a biological marker in patients with systemic inflammation or infection: a systematic review. Intensive Care Med 2012; 38: 1418-1428.
20. Donadello K, Scolletta S, Covajes C, et al. suPAR as a prognostic biomarker in sepsis. BMC Med 2012; 10:1-9.
21. Eugen-Olsen J, Gustafson P, Sidenius N, et al. The serum level of soluble urokinase receptor is elevated in tuberculosis patients and predicts mortality during treatment: a community study from Guinea-Bissau. Int J Tuberc Lung Dis 2002; 6: 686-692.
22. Koch A, Voigt S, Kruschinski C, et al. Circulating soluble urokinase plasminogen activator receptor is stably elevated during the first week of treatment in the intensive care unit and predicts mortality in critically ill patients. Crit Care 2011; 15: R63.
23. Donadello K, Scolletta S, Taccone FS, et al. Soluble urokinase-type plasminogen activator receptor as a prognostic biomarker in critically ill patients. J Crit Care 2014; 29: 144-149.
24. Wittenhagen P, Kronborg G, Weis N, et al. The plasma level of soluble urokinase receptor is elevated in patients with Streptococcus pneumoniae bacteraemia and predicts mortality. Clin Microbiol Infect 2004; 10: 409-415.
25. Sidenius N, Sier CF, Ullum H, et al. Serum level of soluble urokinase-type plasminogen activator receptor is a strong and independent predictor of survival in human immunodeficiency virus infection. Blood 2000; 96: 4091-4095.
26. Kofoed K, Eugen-Olsen J, Petersen J, et al. Predicting mortality in patients with systemic inflammatory response syndrome: an evaluation of two prognostic models, two soluble receptors, and a macrophage migration inhibitory factor. Eur J Clin Microbiol Infect Dis 2008; 27: 375-383.
27. Backes Y, van der Sluijs KF, Tuip de Boer AM, et al. Soluble urokinase-type plasminogen activator receptor levels in patients with burn injuries and inhalation trauma requiring mechanical ventilation: an observational cohort study. Crit Care 2011; 15: R270.
28. Sorio C, Mafficini A, Furlan F, et al. Elevated urinary levels of urokinase-type plasminogen activator receptor (uPAR) in pancreatic ductal adenocarcinoma identify a clinically high-risk group. BMC Cancer 2011; 11: 1-9.
29. Bilgili B, Cinel İ. Yoğun bakım hastalarında 'soluble urokinase plasminogen activator receptor (supar)'ın önemi. J Turk Soc Intens Care 2013; 11: 33-39.