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Original article

Soluble urokinase-type plasminogen activator receptor (suPAR) in patients with acute pancreatitis (AP) - Progress in prediction of AP severity

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ABSTRACT

Background: Soluble urokinase-type plasminogen activator receptor (suPAR) is a glycoprotein secreted during inflammation and infections. Moreover, increased levels of suPAR are observed after hypoxia and ischaemia. The aim of the study was to assess whether suPAR could represent a useful marker of acute pancreatitis (AP) severity.
Patients and methods: We have observed a cohort of 126 prospectively enrolled patients. Based on the presence of persistent organ failure (more than 48 h) and local complications (diagnosis of moderate AP [MSAP]), patients were classified into three groups: mild AP (MAP), moderate and severe AP (SAP). The blood samples were taken on admission for detecting suPAR concentrations.
Results: AP was considered severe in 33 patients (26.2%), MSAP was found in 37 patients (29.4%), and MAP was found in 56 patients (44,4%). The AUC for SAP predicted by suPAR was 0.993. The calculated cut-off point for prognosis SAP is 4.75 ng/mL. The BISAP score of $\geq$3 for detection of SAP had sensitivity and specificity of 94.6% and 63.6%, respectively. The AUC for severity predicted by BISAP amounted to 0.916. Additionally, suPAR turned out to be a good predictor of fatal AP: for the cut-off point 7.05 ng/mL, the AUC was 0.917. The AUC for death prediction in AP patients based on the BISAP score $\geq$3 was 0.894.
Conclusions: suPAR concentration is a promising new diagnostic and prognostic indicator in SAP obtainable in the early stage of disease. Larger studies are recommended to evaluate this role further.

1. Introduction

Acute pancreatitis (AP) is an inflammatory, usually self-limiting disease, although the spectrum of severity of the disease is widespread, from mild to severe and fatal cases. Severe AP (SAP) will occur in a approximately 10%–20% of patients [1,2], and in most of those cases, there was pancreatic damage leading to the development of systemic inflammatory response syndrome (SIRS) [3–5]. SIRS is considered one of the most important factors underlying the occurrence of multiple organ dysfunction syndrome (MODS) [6]. Ultimately, MODS is responsible for the majority of the morbidity and mortality in SAP [7,8].

Improvement of treatment results in SAP depends on early identification of patients with poor prognosis, early administration of enteral nutrition [9], treatment under ICU conditions [10], as well considering ERCP in patients with gallstone-induced disease.

The assessment of the severity of disease is a crucial issue in the management of AP. In the last few decades, various factors (i.e., C-reactive protein [CRP], procalcitonin, interleukins, and D-dimer) have been evaluated with respect to their value for the prediction of AP outcomes [11–14]. Our previous studies have positively assessed the exponents of hypovolemia and kidney injury neutrophil gelatinase-associated lipocalin (NGAL) and estimated glomerular

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filtration rate (eGFR) as good predictors of AP [15,16]. CRP, one of the most frequently assessed parameters, is nonspecific for AP, and its elevation is observed after 48 h [17] from the onset of symptoms, whereas the first two days of AP are critical for implementation of appropriate fluid therapy and endoscopic procedures. Thus, there is therefore a need for the detection of a new parameter of inflammation that could be applied as a rapid marker in the early prognosis of the course of AP.

The need for a new prognostic parameter is even greater because of the revision of the Atlanta classification of AP in 2012 [1], which introduced new criteria. suPAR is a glycoprotein secreted during inflammation and infections [18–20]. Moreover, increased levels of suPAR are observed after hypoxia and ischaemia [21]. Serum concentration of suPAR positively correlates with the activation stage of the immune system. suPAR plays an important role in various immunological activities, and various cell types, including lymphocytes, neutrophils, endothelial cells, macrophages, and tumor cells, have its expression [22]. It has been presumed that suPAR is implicated in the plasminogen-activating pathway of inflammation as well as the modulation of cell proliferation, adhesion, and migration [23].

High serum concentration of CRP and PTC are already known as unfavourable prognostic factors in AP [24]. However, suPAR, a parameter reflecting more accurately the level of immune system activation at an early stage of the disease, has never been evaluated as a predictor of AP severity in humans or animal models.

The aim of this study was to assess whether the serum level of suPAR could represent a useful marker of AP severity.

2. Materials and methods

We performed an observational cohort study of 126 prospectively enrolled patients (84 men and 42 women, median age: 52.3; range: 20–96 years). Informed consent was obtained from all patients before enrolment into the study. All patients were admitted to the Department of Gastroenterology of the Central Clinical Hospital of the Ministry of Interior and Administration (Poland) with a diagnosis of AP and disease onset within the last 48 h ($n = 126$). The following exclusion criteria were applied:

1. rheumatic diseases,
2. neoplastic diseases,
3. chronic kidney or liver disease,
4. time from the onset of symptoms to admission exceeding 48 h.

The diagnosis was established based on the presence of two of three following features: (i) abdominal pain typical of AP, (ii) serum lipase and/or amylase $\geq$3 times the upper normal limit, and (iii) ultrasonography (US), CT, or MRI findings suggesting AP. Based on the presence of persistent organ failure (more than 48 h) as a criterion for the diagnosis of SAP and local complications (diagnosis of MSAP), patients were classified into three groups: MAP, MSAP and SAP. MSAP was defined as AP with transient OF (less than 48 h) and/or local complication and/or systemic complication in the absence of persistent OF (more than 48 h).

Organ failure was identified using the Modified Marshall Scoring System. If failure involved more than one organ, the case was classified as multiorgan failure (MOF). All patients were treated according to the guidelines of Polish Pancreatic Club [25]. All patients with predicted SAP received enteral nutrition.

Blood samples were obtained on admission (first 5 h) for examination of suPAR concentrations. The results were available after 2 h. Concentration of suPAR was determined using a commercial, double monoclonal antibody sandwich enzyme immunoassay (suPARnostic® Standard kit; ViroGates A/S, Birkerød, Denmark) in accordance with the instructions of the manufacturer [26]. The suPARnostic® ELISA Kit was used for quantitative determination of suPAR levels in human EDTA-plasma. The kit contains suPAR standards, which can be used to create a calibration curve; plasma samples with suPAR concentrations greater than the top standard value should be diluted prior to quantitative measurements. The suPARnostic ELISA is a simplified double monoclonal antibody sandwich assay where samples and peroxidase-conjugated anti-suPAR are mixed in the mixing plate prior to incubation in pre-coated, optically transparent anti-suPAR microwells. The assay utilizes monoclonal mouse and rat antibodies against human suPAR. The suPAR standard is calibrated against an internal Golden Standard and all values are calculated backwards to ensure that samples from different labs and/or different assay lots can be compared directly when the suPARnostic kit is used. Concentrations of suPAR determined using the suPARnostic kit are expressed as ng/mL. In the assay, the suPAR standard(s), curve control and patient specimens are mixed with peroxidase-conjugated anti-suPAR in the included white microwell mixing plate. This solution is subsequently transferred from white to the optically transparent microwell plate pre-coated with anti-suPAR. During a 1-h incubation period, a sandwich consisting of solid-phase antibody, suPAR and the peroxidase-conjugated antibody is formed. Following a washing step, where unbound material is removed, a chromogenic substrate is added to the wells. Blue color of the sample intensifies with increasing amount of suPAR. After 20 min of incubation in the dark, the reaction is stopped by the addition of sulphuric acid, which changes the color in the wells to yellow. The absorbance at 450 nm is measured using a microtiter plate reader. A calibration curve is prepared from the suPAR standard, and the concentration of suPAR in the sample is interpolated [26].

The suPAR assays were performed using a standardised clinical platform (suPARnostic®). The BISAP score was determined in all patients within the first 24 h from admission.

The value of the suPAR and BISAP scores for prediction of clinical outcome was evaluated with receiver operator characteristic (ROC) curve analysis. Area under the ROC curve was computed with a 95% confidence interval as a measure of usefulness of this parameter in prediction of the outcome. For each parameter and outcome threshold was set at a value that maximized the sum of sensitivity and specificity. Sensitivity, specificity, and positive and negative predictive values of different grades and groups were computed along with their 95% confidence intervals for the threshold value. The Spearman correlation coefficient was used to evaluate the relationship between suPAR level and the duration of hospital stay. In all analyses the level of significance was set at $\alpha = 0.05$. Analyses were performed using R 3.3.1 statistical software (R Core Team (2016). R: Language and environment for statistical computing by R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

The study was approved by the Ethics Committee of the Central Clinical Hospital of The Ministry of Interior and Administration in Warsaw, Poland.

3. Results

3.1. Characteristics of patients

A total of 126 patients with AP (84 men and 42 women, median age: 52.3; range: 20–96 years) were included in the study. AP was considered severe in 33 patients (26.2%), moderately severe disease was identified in 37 patients (29.4%) and mild in 56 patients (44.4%) according to the criteria outlined in the methodology. Relatively frequently, there was a diagnosis of SAP, because the study took place at a tertiary referral centre, where the most severe forms of

AP from all over the country are referred.

The aetiology of AP was alcoholism in 55 patients (43.3%), biliary in 50 patients (39.4%), and other (post-ERCP, idiopathic, hereditary, etc.) in 22 patients (17.4%) (Table 1).

3.2. suPAR level in prediction of AP severity

The optimal cut-off point for suPAR concentration that distinguished SAP from MSAP and MAP was determined by constructing a receiver operating characteristic (ROC) curve. In ROC analysis, the AUC for suPAR was 0.993 (95% CI, 0.983–1.000) (Fig. 1).

The optimal cut-off point for discriminating between SAP and MSAP/MAP using suPAR concentration was 4.75 ng/mL, with sensitivity of 97% and specificity of 93%. PPV and NPV amounted to 84.2% and 98.9%, respectively.

The suPAR of 3.65 ng/mL was chosen as an optimal cut-off point to distinguish MSAP from MAP, and the sensitivity and specificity were 80% and 92%, respectively [AUC = 0.928 (95% CI, 0.883–0.972)]. PPV and NPV amounted to 93.3% and 78.8%, respectively.

Average values of serum suPAR concentration on admission ± SD were compared between patient groups with MAP, MSAP, and SAP, with average concentrations of suPAR (±SD) on admission of 2.6 ± 0.7 ng/mL, 3.8 ± 0.8 ng/mL, and 8.8 ± 4.9 ng/mL, respectively (Fig. 2). These differences were also statistically significant (each of them $p < 0.0001$).

3.3. Comparison to BISAP and BUN in prediction of SAP

The BISAP score ≥3 for the detection of SAP had sensitivity and specificity of 94.6% and 63.6%, respectively. The AUC for severity predicted by BISAP amounted to 0.916 (95% CI, 0.915–0.987) (Fig. 3).

BUN >16.8 mg/dL was characterized by 72.7% sensitivity and 83.9% specificity in prediction of SAP [AUC = 0.831 (95% CI, 0.742–0.918)]. Positive and negative predictive values (PPV, NPV) were 61.5% and 89.7%, respectively (Table 2).

3.4. suPAR as useful early marker for prediction of MOF and fatal AP

Using the area under the ROC curve, we determined the ability of serum suPAR levels to predict MOF. We identified the optimal cut-off point for suPAR concentration at the time of admission as 5.20 ng/mL (AUC 0.951, 95% CI 0.912–0.991), with sensitivity and specificity of 93% and 90%, respectively.

ROC curve analysis showed also that AUC for suPAR with regard to prediction of death among patients with AP was 0.917 (95% CI, 0.822–1.000). The optimal cut-off point was established at 7.05 ng/mL, with sensitivity of 83% and specificity of 90%, (Fig. 4). PPV and NPV amounted to 31.3% and 99.1%, respectively.

The accuracy of death prediction in AP patients based on a BISAP score ≥3 was 0.894 (95% CI 0.821–0.968), with sensitivity and specificity of 78.3% and 83.3%, respectively (Table 3).

Table 1
Characteristics of patients with AP included in the study.

Variable	All patients N = 126
Age (median age; range)	52.3; 20–96
Gender (male/female)	84/42
SAP 33	(26.2%)
MSAP 37	(29.4%)
MAP 56	(44.4%)
Etiology (% of total)	
Gallstones	50 (39.4%)
Alcohol	55 (43.3%)
Other causes	
(post-ERCP, idiopathic, hereditary etc.)	22 (17.4%)

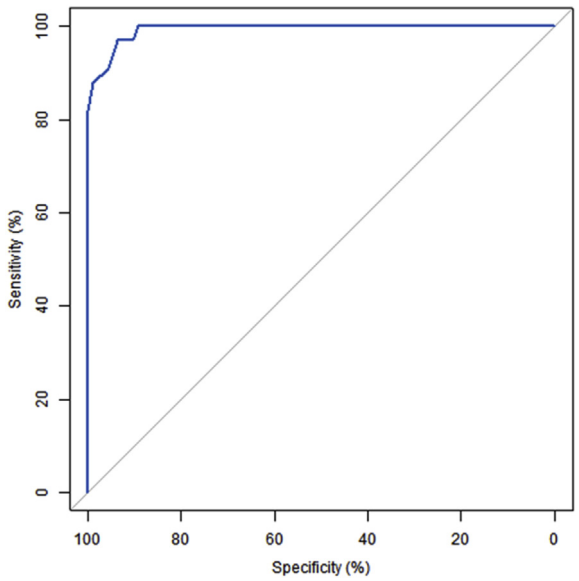

Fig. 1. suPAR level in prediction of SAP. AUC = 0.993; the cut-off value is 4.75 ng/mL.

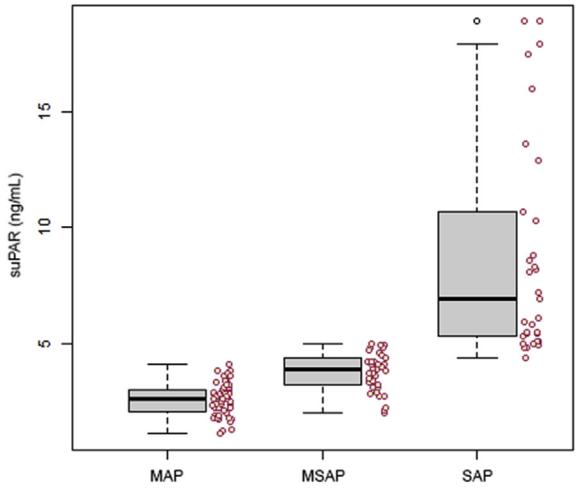

Fig. 2. Comparison of average suPAR concentration values in different types of AP.

3.5. suPAR association with the duration of hospital stay

The Spearman rank correlation analysis showed that the suPAR level was positively and significantly associated with the duration of hospital stay ($r = 0.43$, $p < 0.001$) (Fig. 5).

4. Discussion

AP is usually a self-limiting disease, but inflammatory response is not a uniform event in all cases. Inflammation could affect the surrounding tissues and other organs. Patients with early signs of organ failure are at particularly high risk of death due to AP [27–29].

Early prognosis in AP, especially during the initial hours, is still difficult and can pose a formidable challenge for clinicians. Precise, rapid determination of AP course in the early stage of disease ensures a timely and suitable therapeutic intervention.

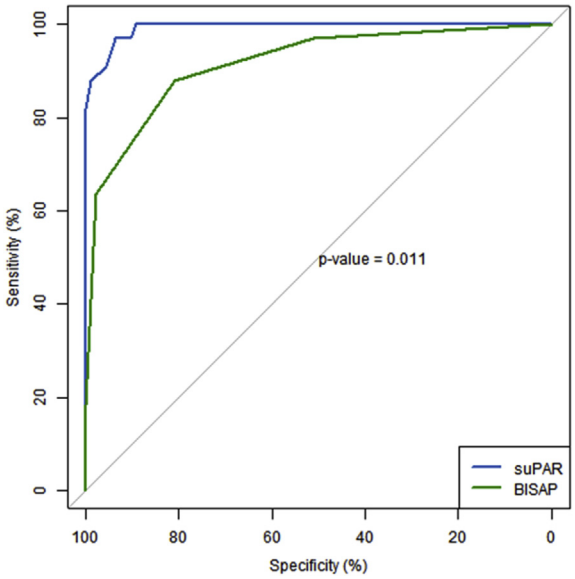

Fig. 3. Receiver-operating characteristic curves of the BISAP score and suPAR in prediction of SAP.

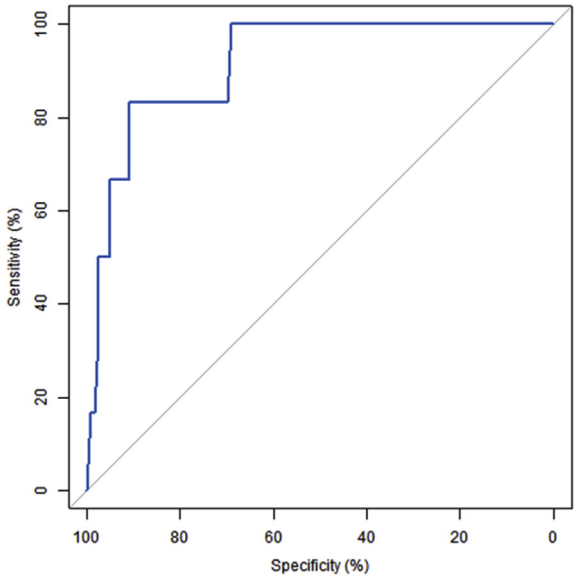

Fig. 4. suPAR in prediction of fatal AP. AUC = 0.917; the cut-off value is 7.05 ng/mL.

Table 2
Factors associated with the severity of AP.

	Mild AP	MSAP	SAP	p
n	56	37	33	
Age (years)	46.2 (15.4)	48.5 (15.5)	67.0 (17.4)	<0.001
Sex	women: 23 (41.1) men: 33 (58.9)	women: 7 (18.9) men: 30 (81.1)	women: 12 (36.4) men: 21 (63.6)	0.078
Etiology	Alcoholic: 23 (41.1) Biliary: 26 (46.4) non-A non-B: 7 (12.5)	Alcoholic: 22 (59.5) Biliary: 9 (24.3) non-A non-B: 6 (16.2)	Alcoholic: 9 (27.3) Biliary: 15 (45.5) non-A non-B: 9 (27.3)	0.060
BMI kg/m^2	26.1 ± 4.0	27.3 ± 4.6	28.3 ± 5.9	0.01
WBC (mean (SD)) 10^9/L	11.1 (3.6)	12.6 (4.7)	11.5 (4.4)	0.244
CRP 1st day of AP (mean (SD)) mg/L	32.9 (65.9)	51.8 (82.3)	80.2 (93.8)	0.002
Hematocrit (mean (sd)) %	43.0 (4.2)	43.1 (5.1)	41.4 (6.3)	0.293
BUN 1st day of AP (mean (SD)) mg/dL	12.0 (5.5)	13.5 (7.5)	26.9 (15.2)	<0.001
Volume of fluid administered during the 1st day of AP (ml)	2950 ± 850	3100 ± 1100	3250 ± 1250	0.28
Recurrence of AP (%)	First attack of AP: 32 (57.1) Recurrent AP: 24 (42.9)	First attack of AP:15 (40.5) Recurrent AP: 22 (59.5)	First attack of AP: 18 (54.5) Recurrent AP: 15 (45.5)	0.270

BMI, body mass index; WBC, white blood cells; CRP, C-reactive protein; BUN, blood urea nitrogen; non-A non-B, non-alcoholic, non-biliary; SD, standard deviation.

Thus, there is a pressing need to find a marker or simply scale, which will be in fact useful to predict the course of AP. Unfortunately, a perfect marker or score of AP course is not yet accessible [30].

Single prognostic parameters can be divided into two groups of markers: hypovolaemia (serum creatinine, haematocrit, NGAL, eGFR) and the parameters of inflammation (CRP, PCT, IL-1, IL-6).

Despite continuous progress in prognostication, the complication rates and mortality remain significant in AP. Nevertheless, there is growing evidence to support early goal-directed therapy (EGDT) in acute diseases [31] Immediate identification of patients requiring EGDT at an early stage of AP based on the most suitable markers would be of great aid in directing further management. However, since AP is characterized by specific etiology, natural history, and complications, further studies are required to provide evidence of beneficial effects of various treatments.

Although several previous studies have demonstrated greater benefit of nasoenteric tube feeding compared to oral diet, a recent trial failed to corroborate the superiority of such feeding method [32]. The same applies to indications of early ERCP in AP - it has been the subject of discussions in the previous years [33]. Limited availability of beds in an intensive care unit (ICU) for patients with predicted severe course of AP in most hospitals should also be taken into consideration. However, the symptoms of organ failure usually necessitate treatment in the ICU.

Table 3
Results from the ROC analysis of suPAR and BISAP score and optimum cut-off levels (ng/mL) for the discrimination between MSAP, SAP, and fatal AP.

	suPAR	BISAP ≥ 3
MSAP	0.928 (3.65)	
SAP	0.993 (4.75)	0.916
Fatal AP	0.917 (7.05)	0.894

Many studies have shown that serum levels of suPAR are increased with various inflammatory diseases, including arthritis [34], liver fibrosis [35,36], and paediatric inflammatory bowel disease [37]. Additionally, the serum concentration of suPAR has been shown to have prognostic value in predicting the course and outcome in patients with cancer [38,39]. Systemic levels of suPAR are moreover increased in critically ill patients [40].

The suPAR testing is not widely available in internal medicine

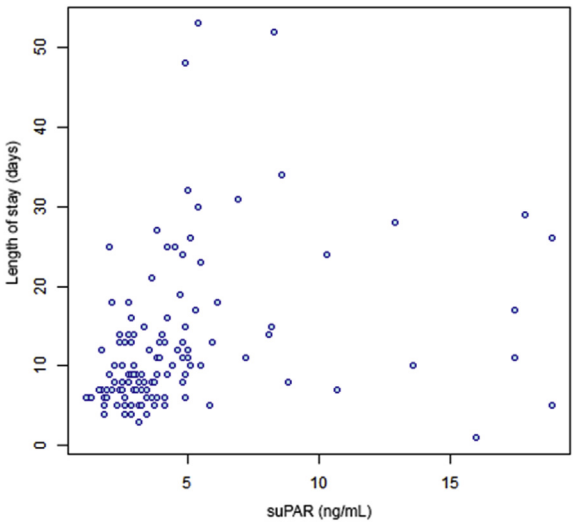

Fig. 5. Analysis of the correlation between suPAR level and the length of hospital stay.

departments. However, it might prove to be a valuable diagnostic test in prediction of AP course, which is particularly important in view of its low cost (c.a. 20 USD) and easy application.

In this study, we investigated the hypothesis that serum suPAR levels are elevated in an early stage of AP and can be used to predict the severity of AP.

Our results show that the serum concentration of suPAR was significantly elevated in patients with SAP compared to those with mild episodes. Results suggest that suPAR could be a potential predictor of AP severity. The calculated cut-off points for prognosis in SAP is 4.75 ng/mL, and the sensitivity and specificity of more than 90% in this aspect deserves special attention. It is also notable that the suPAR can predict the MSAP.

This study revealed that higher suPAR concentration was associated with a greater likelihood of MOF. Therefore, we believe that suPAR may be helpful in the early evaluation of patients with AP, available in the early phase of the disease also as a rapid triage test with respect to the necessity to secure ICU admission. Moreover, it is worth stressing that high suPAR concentration appeared to predict fatal AP with the cut-off value of 7.05 ng/mL.

It is worth noting that the demonstration of the relationship between an increased concentration of suPAR and the duration of hospital stay may be of particular importance in the case of MSAP. Specifically, in the case of MSAP, we are dealing with a longer hospital stay, without a significant increase in mortality risk.

Our results support the hypothesis that in the early phase of SAP release, suPAR is a part of pathophysiological process typical for acute systemic diseases accompanied by ischaemic and damaged organs.

Our study assessed the utility of suPAR and BISAP in prediction of disease severity and mortality among patients with AP using an accurate [41], multifactorial scoring system. The AUC of BISAP ($\geq$3) for the prediction of SAP was 0.916 and was inferior to suPAR AUC = 0.993, with sensitivity of 97% and specificity of 93%, whereas only the sensitivity of BISAP exceeded 90% with a relatively low sensitivity of 63.6%. However, it is particularly noteworthy that AUC of suPAR for predicting fatal AP amounted to 0.917 (sensitivity and specificity was 83.3% and 90.8%, respectively, for a best cut-off value of 7.05 ng/mL) and was also better than the respective results obtained using the BISAP scale (AUC. 0.894 with sensitivity and specificity of 78.3% and 83.3%, respectively, for the score $\geq$3).

Taking into account the various factors underlying the superiority of suPAR in relation to BISAP should note the fact that suPAR is not only a parameter of inflammation. The observation is noteworthy that this parameter increases in various disease states known as the worsening-prognosis AP: hypoxia, ischaemia [21], organ damage [42] and necrosis. Therefore, suPAR could be more accurate for the prognosis of AP severity.

Many studies conducted to date concerning the prediction of the course of AP have not used the new criteria of disease severity. In our study, patients were prospectively observed until discharge or death to apply the revised Atlanta criteria.

There are certain limitations to our study. Our data came from one centre and, therefore, require validation from external sources. Therefore, a prospective, multicenter study should be conducted.

In conclusion, our results indicate that the suPAR level seems to be a promising new indicator of prognosis in SAP obtainable in an early stage of the disease.

Disclosure statement

The authors have no conflicts of interest.

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