Research article

Soluble urokinase-type plasminogen activator receptor (suPAR) – a possible biomarker for bacteremia in sepsis

Forma solubilă a receptorului pentru activatorul de plasminogen de tip urokinază (suPAR) – un biomarker posibil pentru bacteriemie în sepsis

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Abstract

*Background. Validating new sepsis biomarkers can contribute to early diagnosis and initiation of therapy. The aim of this study is to evaluate the sepsis predictive capacity of soluble urokinase plasminogen receptor (suPAR) and its role in evaluating the prognosis of bloodstream infections. **Material and method**. We conducted a prospective pilot study on 49 systemic inflammatory response syndrome (SIRS) patients admitted to the intensive care unit (ICU), that were divided, on the basis of bacteremia in group A (SIRS with bacteremia, n=14) and group B (SIRS without bacteremia, n=35). Hemoculture and blood samples were drawn on the first day to determine suPAR, C-reactive protein (CRP) and procalcitonin (PCT). We set to identify significant cut-off values in estimating bacteremia and mortality in septic patients. **Results**. In group A, suPAR values were 14.3 ng/mL (range 10-45.5 ng/mL) and in group B, 9.85 ng/mL (range 3.4-48 ng/mL) p=0.008. Area under the curve (AUC) for suPAR was 0.745 (95% CI: 0.600-0.859), for CRP 0.613 (95% CI: 0.522-0.799) and for PCT 0.718 (95% CI: 0.477-0.769). Cut-off value for suPAR in bacteremia prediction was 9.885 ng/mL, with 100% sensibility and 51.43% specificity. Mortality in group A was 85.7% (12/14) and in group B 74.3% (26/39), p>0.05. Area under the curve (AUC) for suPAR was 0.750 (95% CI: 0.455-0.936), for CRP 0.613 (95% CI: 0.413-0.913) and for PCT 0.618 (95% CI: 0.373-0.888). Cut-off value of suPAR in predicting mortality was 11.5 ng/mL, with 66.67% sensibility and 100% specificity. **Conclusions**. In our study suPAR had a predictive capacity for bacteremia and seems to be an independent factor for mortality prognosis in septic patients.*

Keywords: Sepsis, suPAR, biomarkers, bacteremia, mortality

Rezumat

Introducere. Validarea unor noi biomarkeri în sepsis poate contribui la diagnosticul mai precoce al acestuia şi la iniţierea mai rapidă a terapiei. Scopul acestui studiu este acela de a evalua capacitatea formei solubile a

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receptorului pentru activatorul de plasminogen tip urokinaza (suPAR) în predicţia bacteriemiei din sepsis şi a rolului său în evaluarea prognosticului. **Material şi metodă**. *Am realizat un studiu pilot, prospectiv pe 49 de pacienţi cu sindrom de răspuns inflamator sistemic (SIRS) internaţi în Clinica de Terapie Intensivă, care au fost împărţiţi, în funcţie de existenţa bacteriemiei, în lotul A (SIRS cu bacteriemie, n=14) şi lotul B (SIRS fără bacteriemie, n=35). S-au recoltat în prima zi probe sanguine pentru determinarea suPAR, proteina C reactivă (CRP), procalcitonina (PCT) şi hemocultura. Am urmărit identificarea unor valori de cut-off cu semnificaţie statistică în estimarea bacteriemiei şi a mortalităţii la pacienţii septici.* **Rezultate**. *În lotul A valorile suPAR au fost de 14,3 ng/mL (interval 10-45,5 ng/mL) iar în lotul B, de 9,85 ng/mL (interval 3,4-48 ng/mL), p=0,008. Aria de sub curbă (AUC) pentru suPAR a fost de 0,745 (95% CI: 0,600-0,859); pentru CRP, AUC a fost de 0,613 (95% CI: 0,522-0,799); pentru PCT, AUC a fost de 0,718 (95% CI: 0,477-0,769). Valoarea de cut-off a suPAR în predicţia bacteriemiei a fost de 9,885 ng/mL, cu sensibilitate de 100% şi specificitate de 51,43%. Mortalitatea în lotul A a fost de 85,7% (12/14), iar în lotul B de 74,3% (26/39), p>0,05. AUC pentru suPAR a fost de 0,750 (95% CI: 0,455-0,936); pentru CRP, AUC a fost de 0,613 (95% CI: 0,413-0,913); pentru PCT, AUC a fost de 0,618 (95% CI: 0,373-0,888). Valoarea de cut-off a suPAR în predicţia mortalităţii a fost de 11,5 ng/mL, cu sensibilitate de 66,67% şi specificitate de 100%.*

Concluzii. *In studiul nostru suPAR a prezentat capacitate de predicţie a bacteriemiei şi pare un factor independent de prognostic al mortalităţii la pacienţii septici cu bacteriemie.*

Cuvinte cheie: *Sepsis, suPAR, biomarkeri, bacteriemie, mortalitate*

Introduction

Sepsis continues to represent an important mortality and morbidity cause in intensive care units, multiple lines of evidence proving that early diagnosis and treatment can improve the outcome of such patients. The Surviving Sepsis Campaign recommends the initiation of antibiotherapy as soon as possible, preferably in the first hour after recognizing sepsis (1) .

Sepsis is defined as a systemic, deleterious host response secondary to documented or suspected infection, leading to acute organ dysfunction and septic shock. (1) Sepsis diagnosis implies identifying the systemic inflammatory response syndrome (SIRS), which is a non-specific reaction to aggression (2). The immune system reacts to danger associated molecular patterns (DAMPs), inflammatory response occurring as a result of the release in circulation of mitochondrial DNA fragments capable of inducing noninfectious SIRS (3). On the other hand, microbial agents have a specific pattern (pathogen-associated molecular pattern - PAMPs) which activates nonspecific immunocytes, but the acute-phase response is similar for both DAMPs and PAMPs (4). The differentiation of those two causes of SIRS is extremely important in therapeutic decision.

A significant proportion of patients with SIRS have bacteremia; conversely patients with bloodstream infections (BSI) frequently display SIRS signs and symptoms (2, 5). Although blood cultures remain the golden-standard in sepsis diagnosis, only 20-30% of patients with sepsis have positive blood cultures, and even then if positive, the result is obtained tardily (6, 7). New techniques of culture-independent microbial nucleic acid amplification have significantly reduced the delay but they have the disadvantage of needing an elaborate technique that involves qualification and increased costs (8).

The use of biomarkers (BM) was proposed as a means to improve the promptitude of diagnosis in sepsis and provide prognostic tools for BSI; until 2010 over 175 distinct molecules were studied from 3370 references, although fewer were subject to rigorous testing. Out of those, only 20% showed some degree of specificity, mostly by associating them with the presence of BSI (9, 10). The most studied and used, characterized by highly elevated levels in sepsis, were

C-reactive protein (CRP), an acute-phase protein released from the hepatocytes immediately after the occurrence of an inflammatory response, proportional to its intensity, used especially for infection monitoring and procalcitonin (PCT) - calcitonin prehormone - which proved its utility in discriminating between bacterial infections and other causes of inflammatory response (11-16). Furthermore, PCT has prognostic value in critical patients but the determination of one value is insufficient for assessing the prognostic (17-19).

However, given the lack of an ideal BM, none of the existing markers has the capacity of individually differentiating between SIRS and sepsis. Available meta-analyses demonstrate both low sensitivity and specificity for CPR and PCT and obvious limits of their prognostic value in critical patients (10, 11, 19, 20).

The soluble form of urokinase plasminogen activator receptor (suPAR) is one of the recently studied BM and is regarded as having a possible predictive role in bacteremia patients (21). Pathogenic implications of suPAR in septic inflammatory process are consequent to activation of immune cells that express urokinase plasminogen activator receptor (uPAR) (granulocytes, activated lymphocytes and macrophages) and its release through a proteolytic cleavage at cellular level (22).

SuPAR's significance as a stable marker for inflammation is supported by a good positive correlation with other inflammation markers (C-reactive protein), inflammatory cytokines (TNF-alpha tumor necrosis factor) and white blood cells count (23, 24). According to recent research it has some value as a risk marker in general population, due to its increase in low-grade inflammation, which explains its lack of diagnostic specificity (24, 25). Serum increase of suPAR level was reported in severe inflammatory, infectious diseases (tuberculosis, HIV infection), degenerative and neoplastic diseases (26).

The diagnostic contribution of suPAR in systemic infections is controversial: the gradual increase in critical patients without SIRS towards patients with SIRS and respectively sepsis is sustained but its diagnostic value in identifying infection in critical patients appears to be limited (27). The capacity of suPAR to discriminate between bacterial infection and other causes of sepsis seems to be also limited (27-29). Several studies support its superior value as a prognostic BM in sepsis (28, 30, 31).

The objective of this study was to evaluate the capacity of suPAR to predict bacteremia in sepsis and its role in evaluating the prognostic of BSI. We set to identify significant cut-off values for estimating septic bacteremia and fatality in BSI. The predictive and prognostic value of suPAR was compared to commonly used BM (CRP, PCT).

Material and method

We conducted a prospective study between January and November 2014 in the Anesthesiology and Intensive Care Clinic of the Tîrgu Mureș Emergency Hospital, Romania. The study protocol was approved by the Ethics Commission of the University of Medicine and Pharmacy Tîrgu Mureș. Prior to inclusion in the study, all patients or their next-of-kin signed the informed consent form.

Criteria for inclusion in the study were: age over 18, existence of at least 2 SIRS criteria as previously described (fever or hypothermia, tachycardia, tachypnea and leukocytosis or leucopenia) together with the presence or clinical suspicion of an infectious process (1, 12).

Exclusion criteria were: a surgical intervention in the last 72 hours and the administration of antibiotherapy in the 5 days prior to inclusion.

The group consisted of 49 patients, the reason for Intensive Care Unit admission (ICU) being a medical condition for 35 patients and a surgical pathology for 14 patients.

In the first day after being admitted to the ICU, whole blood and serum samples were collected to determine suPAR and other BM (CRP, PCT), as well as hematological counts (white blood and neutrophil count), biochemical parameters (creatinine, urea, transaminases) and INR together with drawing hemocultures.

Recording the results and clinical data (admission condition, source of infection, days of mechanical ventilation, duration of hospitalization, mortality) was done using a standardized template.

For blood cultures, 7-10 mL of blood was drawn in two sets of determinations, each of those containing one aerobic and one anaerobic vial. Three sets of hemocultures were drawn only in patients with fever. In all cases blood was drawn prior the antibiotic therapy. In some cases the severe evolution did not allow for full sampling protocol prior to treatment onset. Hemoculture was performed regardless of fever if at least two SIRS criteria were met. Blood was collected through different peripheral punctures, in aseptic conditions (antisepsis performed with chlorhexidine). Samples were processed using the automated blood culture system BacT/Alert 3D (Biomerieux, France). The existence of bacteria was confirmed when minimum one blood culture was positive. We excluded two patients with a single positive blood culture with coagulase-negative staphylococci due to possible contamination. Three cases with similar strains were included due to bacteremic growth in both sets of hemocultures.

Serum aliquots were stored until processing at -80 degrees Celsius. ELISA assays (Bio-Medica Group) were performed for quantitative determination of PCT (PromoKine) and suPAR (Virogates). For PCT, analytical sensitivity was 30 pg/mL and the intra-assay and inter-assay coefficient of variability (CV) were <10% and <12% respectively. For suPAR analytical sensitivity was 0.1 ng/mL and the intra-assay and inter-assay CV were 4.7% and 3.5% respectively. Expected serum levels for apparently healthy volunteers were: for PCT <0.15 ng/mL and for suPAR 1.1-1.4 ng/mL.

For hsCRP determination we used a particle enhanced immunoturbidimetric technique (Cobas6000, Roche). Measuring range for CRP was 1.00-250 mg/L, normal value for adults: <5 mg/L; intra-assay CV was 0.9% and inter-assay CV - 1.3%.

Statistical analysis was performed using MedCalc Software, Version 12.5.0.0. Data were considered as nominal or quantitative variables. Nominal variables were characterized using frequencies. Quantitative variables were tested for normality of distribution using Kolmogorov-Smirnov test and were characterized by median and percentiles (25-75%) or by mean and standard deviation (SD), when appropriate. A chi-square test using Yates' correction or Fisher's exact test, when appropriate was used in order to compare the frequencies of nominal variables. Quantitative variables were compared using t test, Mann-Whitney test, when appropriate. To compare the predictive value of the BM and severity scores, receiver-operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was determined. Optimal cutoff points were calculated considering the suPAR, CRP, and PCT levels that maximized the weighted combination of sensitivity (Se) and specificity (Sp) (i.e. that maximized the Youden index) for a ratio false-negatives, false-positives and for the prevalence of in-hospital mortality in the sample. Based on these cut-off points, the main parameters of diagnostic validity were estimated: Se, Sp, positive predictive value (PV+), negative predictive value (PV-) and likelihood ratios. The 95 % confidence intervals (95 % CI) were calculated. To estimate the strength of associations, the scores and BM were divided into dichotomous variables according to these optimal cut-off points, and adjusted odds ratios (OR)

with their 95 % CI for in-hospital mortality were calculated using unconditional logistic regression. The level of statistical significance was set at 0.05 and all tests were two-tailed.

Results

A number of 49 patients were included in the study. Out of those, 16 patients (32.65%) presented at least one positive blood culture.

Excluding contaminants, the study group with SIRS and bacteremia (named group A) was composed of 14 patients (28.6%). Group B was represented by 35 patients with SIRS and infection but without bacteremia (71.4%). The most important baseline demographic, clinical and biological characteristics of the studied patients and respectively from the two groups are presented in Table I.

Table I. The baseline demographic, clinical and biological characteristics of the studied patients.

Variables	Patients with SIRS infections (n=49)	Patients with bacteremia (n=14)	Patients without bacteremia (n=35)	p value
Age (years), mean±SD	71±15	69±11	72±16	0.500*
Male, no	24	8	16	0.400**
BMI (Kg/m2), median (IQR)	25.7 (18.4-66.6)	25.5 (19.5-66.6)	25.7 (18.4-46.9)	0.400***
Primary site of infection (n):				
pulmonary	29	11	18	0.150*
cutaneous	7	3	4	0.650*
digestive	7	0	7	0.170*
urinary	5	0	5	0.330*
articular	1	0	1	0.620*
suPAR (ng∕mL), median (IQR)	11.5 (3.4-48)	14.3 (10-45.5)	9.85 (3.4-48)	0.008***
PCT (ng/mL), median (IQR)	0.87 (0.001-13.2)	1.53 (0.1-11.1)	0.52 (0.001-13.2)	0.035***
CRP (mg∕L), median (IQR)	128 (2-545)	104 (22-403)	157 (11-545)	0.063***
ICU stay (days), median (IQR)	3 (1-24)	3.5 (1-10)	3 (1-24)	0.400***
Mechanical ventilation (days), median (IQR)	2 (0-23)	2 (0-10)	2 (0-23)	0.200***
Vasoactive use (days), median (IQR)	2 (0-7)	2 (0-6)	2 (0-7)	0.700***
Hospital mortality, n (%)	38 (77.6)	12 (85.7)	26 (74.3)	0.380**
Hemoglobin (g/dL), mean±SD	10.58±2.96	9.86±2.64	10.87±3.07	0.280*
Hematocrit (%), mean±SD	32.78±9.63	31.07±7.72	33.46±10.31	0.430*
MCV (%) mean±SD	88.16±10.82	91.12±7.61	86.98±11.75	0.230*
MCH (%) mean±SD	29.24±2.68	29.67±2.60	29.07±2.73	0.480*
MCHC (%) mean±SD	32.75±1.15	32.51±1.10	32.85±1.18	0.360*
White blood cells (n x 103/mm3) median (IQR)	20.65 (2.8-57.6)	15.8 (6.0-35.49)	19.90 (2.8-57.6)	0.100***
NS+S (%) median (IQR)	83.42 (54-96)	92 (60-93)	86 (54-96)	0.400***
Lymphocytes (%) median (IQR)	7.92 (2-32)	6.0 (3-32)	6 (2-19)	0.900***
Creatinine (mg/dL), median (IQR)	8.2 (0.37-14.55)	3.6 (0.48-14.55)	1.6 (0.37-10.16)	0.200***
Urea (mg/dL), median (IQR)	124.3 (14.9-452)	99.5 (19.9-452)	106.2 (14.9-358.20)	0.400***
GOT (U/L), median (IQR)	69.5 (10-407)	43.5 (11-407)	37 (10-43)	0.400***
GPT (U/L), median (IQR)	66.5 (6-390)	32.5 (7-390)	29 (6-372)	0.900***
GGT (U/L), median (IQR)	101.4 (7-446)	68 (12-334)	79 (7-446)	0.700***
INR (n) mean±SD	1.54±0.65	1.46±0.36	1.57±0.73	0.590*

The values are presented as medians and interquartile ranges (IQR) or medians with standard deviation (SD). Results with statistical significance are highlighted in bold. The following tests were used: *: Student test, **: chi squared test, ***: Mann Whitney test.

In group A, 9 patients (out of 14) presented Gram positive germs and 5 patients presented Gram negative germs (Table II).

Comparative analysis of CRP and PCT levels evidenced statistically significant differences in the case of PCT (p=0.035) and small differences, without statistical significance, in the case of CRP (p=0.063) (Table 1).

Comparatively between the two groups, suPAR level was significantly higher in septic bacteremia patients than in the group without bacteremia: 14.3 ng/mL vs. 9.85 ng/mL, p=0.008.

Multivariable regressive analysis, on the entire group of 49 patients, regarding bacteremia influence on the three studied BMs showed that suPAR (p=0.05) was the only one significantly influenced by bacteremia.

We did not find different suPAR levels in Gram-negative bacteremia patients versus Gram-positive patients: median 13.10 ng/mL, IQR 5.02-26.87 ng/mL vs median 14.57 ng/mL, IQR 5.66-45.46 ng/mL.

Eleven patients from group A (11/14) had a pulmonary sepsis point origin and for 3 of them (3/14) the origin was cutaneous. Thirteen patients were admitted to the ICU for a medical condition, only one patient being admitted for a surgical pathology (profound thigh abscess).

A median of 11.5 ng/mL was identified in the study group (n=49) for suPAR values taken in the first day of admission, concomitantly with blood culture collection. The optimal cut-off value for suPAR concentration for predicting bacteremia in septic patients was estimated using the Youden index. The suPAR value at a cut-off of 9.885 ng/mL showed an excellent sensitivity (100%) but a modest specificity (51.43%). Similarly, optimal cut-off value for bacteremia prediction in sepsis were calculated for PCT and CRP (Table III).

Table II. Blood culture germs distribution based on the sepsis point of origin in bacteremic patients

Germ type	No	%	Sepsis point of origin
Gram positive	9	18.2	
Enterococcus faecium	3	6.1	Pulmonary
Methicillin-resistant Staphylococcus aureus (MRSA)	3	6.1	Pulmonary
Coagulase-negative staphylococcus (CoNS)	2	4.1	Cutaneous (1) + pulmonary (1)
Streptococcus pneumoniae	1	2.0	Pulmonary
Gram negative	5	10.1	
Escherichia coli ESBL	2	4.1	Cutaneous (1) + pulmonary (1)
Klebsiella pneumoniae ESBL	1	2.0	Pulmonary
Pseudomonas aeruginosa	1	2.0	Pulmonary
Stenotrophomonas maltophilia	1	2.0	Cutaneous/soft tissue
Contamination (group CoNS)	2	4.1	
Negative	33	67.3	
Total	49		

ESBL: extended-spectrum beta-lactamase

Table III. Optimal cut-off values for suPAR, CRP and PCT in bacteremia prediction for SIRS and septic patients

	AUC	95% CI	Cut-off	Se%	95% CI	Sp%	95% CI
suPAR	0.745	0.600-0.859	>9.885 ng/mL	100	76.8-100	51.4	34.0-68.6
PCT	0.718	0.477-0.769	>523.42 ng/mL	64.3	35.1-87.2	51.4	34.0-68.6
CRP	0.613	0.522-0.799	<77.38 mg/L	50	23.0-77	88.6	73.3-96.8

AUC: area under the curve; 95% CI: 95% confidence interval; Se: sensitivity; Sp: specificity.

ROC curves analysis showed that suPAR had the highest area under the curve (AUC) for predicting bacteremia in septic patients: 0.745 (95% CI: 0.600-0.859). AUC values for the other BMs are shown in Table III. The ROC curves are illustrated in figure 1.

Pairwise comparison analysis of ROC curves between suPAR - CRP, suPAR-PCT and CRP-PCT showed that the registered differences were statistically insignificant for all associations.

Patients from group A had a series of comorbidities: cardiac diseases (8/14 patients), diabetes (4/14 patients), chronic obstructive pulmonary disease COPD (4/14 patients) and chronic renal insufficiency (4/14 patients). To eliminate the influence of other comorbidities on suPAR values, we performed a multivariable logistic regression on all 49 patients, which included the above-mentioned pathologies. Chronic renal insufficiency present in 9 patients (4 from group A and 5 from group B) seems to influence suPAR values (p=0.01). By eliminating the values for those patients, suPAR remains uninfluenced by other factors.

Overall mortality in the first 30 days from admission to the ICU was 77.5% (38 deaths out of 49 patients). In the bacteremia group the mortality was insignificantly higher: 85.7% (12 out of 14 patients), comparatively with the mortality in the group B: 74.3% (26/35 patients).

In bacteremia patients, suPAR and PCT values are significantly higher in the deceased than in the survivors: for suPAR - 14.96 ng/mL vs. 10.98 ng/mL, p=0.01; for PCT: 1.53 ng/mL vs. 0.38 ng/mL, p=0.02. For CRP the values were lower: 73.5 mg/L vs. 274 mg/L, p=0.02) (Table IV).

By comparing deceased patients that had bacteremia with deceased that did not have bacteremia we found that suPAR values were sig-
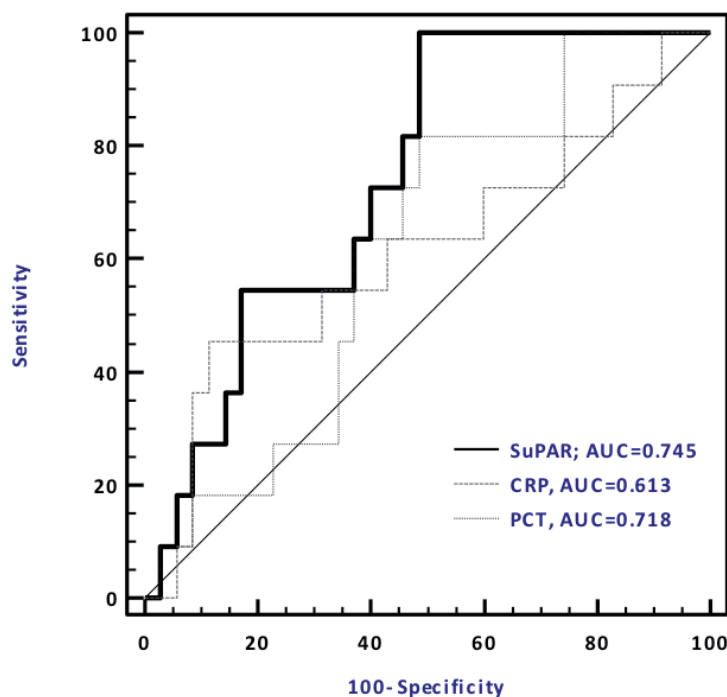

Figure 1. Receiver operating characteristic (ROC) curve for the levels of suPAR, PCT and CRP detected in relation to bacteremia in septic patients

Table IV. suPAR, PCT and CRP serum concentrations in deceased vs. survivors

	suPAR (ng/mL)		PCT (ng/mL)		CRP (mg/L)	
Bacteremia	Yes	No	Yes	No	Yes	No
Deceased median (IQR)	14.96 (5 - 45.5)	10.34 (3.4 - 48)	1.53 (0.005 - 11.07)	1.24 (0.001 - 13.24)	73.5 (2 - 403)	186 (11 - 545)
p value	0.04		0.96		0.008	
Survivors median (IQR)	10.98 (10.4 - 11.5)	9.4 (5.5 - 27.3)	0.38 (0.14 - 0.6)	0.34 (0.012 - 2.68)	274 (250 - 298)	127 (39 - 260)
p value	0.74		0.65		0.04	

IQR: interquartile range

nificantly increased in bacteremia patients (median: 14.96 ng/mL vs. 10.34 ng/mL, p=0.04); CRP values were significantly increased in non-bacteremia patients (median: 73.5 mg/L vs. 186 mg/L, p=0.008). For PCT, the differences were not statistically significant: median - 1.53 ng/mL vs. 1.24 ng/mL.

In the case of survivors (n=11) differences were statistically significant only for CRP (274 mg/L in bacteremia, vs. 127 mg/L for non-bacteremia patients, p=0.04). In this group, suPAR and PCT values did not show statistically significant values relating to the presence/absence of bacteremia: suPAR: 10.98 ng/mL vs. 9.40 ng/mL; PCT: 0.38 ng/mL vs. 0.34 ng/mL.

In 5 patients out of the 12 deceased from group A, the death occurred within 48 hours from admission in ICU. In those, suPAR levels were very high compared to those who died after this interval (n=7), yet the difference was not statistically significant (median 23.4 ng/mL, IQR 10.7-45.5 ng/mL vs. 14.2 ng/mL, IQR 10.0-26.9 ng/mL). The most tardive death took place on day 10 after ICU admission.

In bacteremia patients, the optimal cut-off value of suPAR for mortality prediction in sepsis patients was 11.5 ng/mL, being determined by ROC curves and Youden index; similarly, the cut-off serum concentrations were determined for the other studied BM. Receiver operating characteristics curves of the three BM for mortality prediction in bacteremic patients with SIRS showed the highest area under the curve (AUC) for suPAR: 0.75, 95% CI: 0.455-0.936. CRP and PCT resulted in an AUC of 0.613 and 0.618, respectively (Table V).

Analyzing pairwise comparison of ROC curves (figure 2) between suPAR – CRP, suPAR-PCT and CRP-PCT, the differences registered are not statistically significant.

Using logical regression calculations we observed that the suPAR level was not influenced by underlying chronic conditions of bacteremia patients (cardiac insufficiency, diabetes, obesity of COPD). SuPAR levels over 11.5 ng/mL in the bacteremia group seem to be associated with an increased mortality: 9 deaths (9/14) versus 5 deaths (5/14) but the small number of the stud-

Table V. Optimal cut-off values for suPAR, CRP and PCT in mortality prediction for SIRS and bacteremia patients

	AUC	95% CI	Cut-off	Se%	95% CI	Sp%	95% CI
suPAR	0.750	0.455-0.936	>11.51	66.67	34.9-90.1	100	15.8-100
CRP	0.613	0.413-0.913	≤77.38	58.33	27.7-84.8	100	15.8-100
PCT	0.618	0.373-0.888	>0.84	66.67	34.9-90.1	100	15.8-100

AUC: area under the curve; 95% CI: 95% confidence interval; Se: sensitivity; Sp: specificity
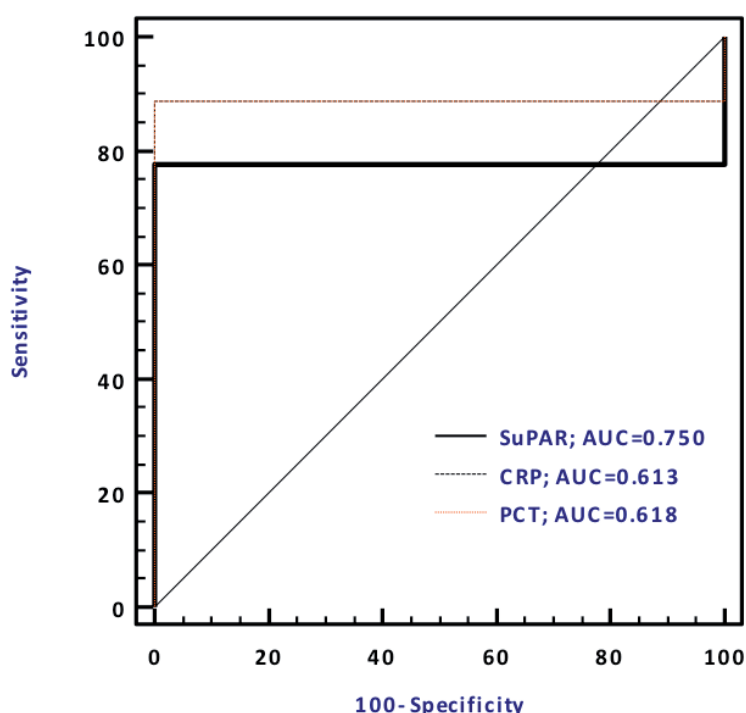
Figure 2. Receiver operating characteristic (ROC) curve for the level of suPAR, PCT and CRP detected simultaneously with blood culture result in relation to mortality prediction in septic patients.

ied patients is a limit in establishing of statistical significance.

Discussions

Sepsis represents the main cause of death in infected patients (32). Still, less than 50% of patients that have signs or symptoms of sepsis have positive blood cultures or other microbiologic proof of infection (33). Complementary to blood cultures and, more recently, molecular assays for whole blood analysis, the usage of serum BMs is gaining grounds in diagnosing septic patients and identifying BSI. Despite their lack of performance in characterizing the immune and inflammatory response in sepsis, and implicitly the limited capacity to stratify patients in homogeneous risk groups, there is an increasing preoccupation to use BMs in current clinical practice for prognostic evaluation and estimating

the course of disease in septic patients (34, 35).

Firstly, median suPAR serum concentrations (11.5 ng/mL) in this study group of septic patients was markedly higher when compared to previously communicated levels from studies on healthy patients; in Denmark, on 6000 healthy adults, the reported suPAR level, evaluated using the same diagnostic kit as the one used in the present study was 3.38 ng/mL (IQR 2.75-4.30 ng/mL), while Haggard reported higher values of 4.2±1.35 ng/mL determined on an extended group of 40 adults with ages between 40 and 70 (36, 37); in elders, the normal reported values were similar, slightly elevated in women compared to men (4.5 ng/mL vs 4.3 ng/mL) (38). To confirm, suPAR values were determined on a group of 13 healthy adults (members of our medical staff), the median on this lot being 1.67 ng/mL (IQR 0.42-5.05 ng/mL), those being

similar to the one identified by Donadello on a similar control group (2.5 ng/mL, IQR 2.1-3 ng/mL) (30). Although overall the diagnosing value of suPAR in sepsis is admittedly low, AUC to discriminate between septic and non-septic ICU patients being poor, this study confirms elevated levels of this BM in septic patients (26-28).

From the septic patients group, only 32.65% presented at least one positive blood culture (16/49 patients). After excluding possible contaminants (species of coagulase-negative staphylococcus found in one blood culture - two strains) 28.6% of blood cultures were positive (14/49 patients). Similar percentages of positive blood cultures were reported in other studies: Loonen identified in an emergency department a total percentage of 21.6% positive blood cultures and 16% were considered relevant from a group of 140 patients, using the BacT/Alert system also used in the present study, and Lodes reported 20% positive blood cultures (8, 39). Larger percentages (41%) were identified by Hoenigl in an emergency department for SIRS patients after eliminating 8/132 strains considered contaminated, 37% was reported by Donatello for 94 patients diagnosed with sepsis on admission to ICU and 51.76% by Yilmaz. (30, 40, 41). In our group, Gram-positive germs were predominant (9/14 strains, 64.2%), other authors also reporting Gram-negative germs as prevalent, constituting the majority (8, 40).

In the study group we noted significant differences in suPAR levels (p=0.008) and PCT levels (p=0.035) between the patient groups with and without bacteremia; CRP serum values did not differ significantly. The results support the conclusion of previous studies confirming the capacity of suPAR and PCT to discriminate SIRS patients on the basis of bacteremia. Loonen reported on a group with similar admission criteria, statistically significant differences in the two BMs, reporting an AUC of 0.793 (95% CI 0.660-0.926) for suPAR in predicting bacte-

remia, comparable to the one identified in this study but inferior to the one for PCT evaluated at 0.806 (95% CI 0.669-0.913) (8). In another study in which the presence of SIRS and not infection was the inclusion criteria, AUC values for suPAR and PCT were very close and superior for the latter: 0.726 (95% CI 0.638-0.814) and respectively, 0.744 (95% CI 0.650-0.838), these two BMs continuing to be predictive bacteremia factors in SIRS patients, including after multivariable logistic regression analysis (40). Recently, Donatello confirmed the predictive capacity of suPAR for bacteremia in a group of patients admitted for surgical sepsis or a medical cause in an ICU and Wittenhagen reported that serum levels of suPAR were greatly increased in pneumococcal bacteremia (5.5 ng/mL IQR 2.4-4.0 ng/mL vs 2.6 ng/mL IQR 1.5-4 ng/mL) (30, 42). Differences of suPAR values in Gram-positive germs versus Gram-negative germs bacteremia were not recorded, result that is different from the conclusion of a larger study done on 132 patients with SIRS in which the values were significantly higher in Gram-negative bacteremia but the result is concordant with the results reported by Huttunen (21, 40). Optimal cut-off value for suPAR in predicting sepsis bacteremia in our study was 9.885 ng/mL at which the specificity is modest but the sensitivity is excellent, owed to the small group of patients. Few authors established cut-off values for predicting sepsis bacteremia, Loonen proposed a value of 7.5 ng/mL at which specificity is better but the sensitivity is more modest (80% and 70% respectively) (8). Given the paucity of studies that investigate suPAR values in predicting bacteremia we consider that further studies to evaluate the ability of suPAR to differentiate BSI among patients with SIRS and infections differentiated on types of germs are necessary.

Evaluating the impact of an underlying conditions on the suPAR levels, patients with chronic renal failure in the bacteremia group displayed

elevated values. (p=0.01) (43). Despite this, after adjusting for preexisting renal failure, suPAR levels that exceed the cut-off value maintained their independent value in predicting sepsis bacteremia. Significantly higher values of suPAR in patients with impaired renal function were recorded as results in the previously cited study of Hoenigl, that took place on a group of septic patients (p=0.0017) but in this group the significant difference was not maintained in the bacteremia subgroup (30, 40). Previously, other authors reported that the serum levels of this BM are related to renal failure, independent on the presence or absence of sepsis in critical patients admitted to the ICU (27, 30). The lack of specificity of this BM for a certain pathology is the reason its diagnostic value in sepsis is limited, evaluated as inferior to the one of CRP; this modest diagnosing contribution being the conclusion of multiple studies and meta-analyses previously performed (25-27, 30).

However, the same authors that reported in 2007 a weak diagnostic value of suPAR levels in predicting sepsis bacteremia, subsequently reported its excellent prognostic value for mortality in SIRS patients; in the investigated group (n=151), 63.6% of patients were septic and 15% were bacteremia patients (AUC for predicting mortality 0.80; CI 0.69-0.92) (44, 45).

In the present study we investigated the prognostic value of suPAR serum levels in evaluating mortality in a group of bacteremia patients. Serum suPAR levels were statistically significant higher in deceased compared to survivors, a significant difference being also recorded in PCT levels. Of the three investigated BMs, suPAR had the highest AUC in the prediction of case fatality. The established suPAR cut-off value of 11 ng/mL, has an excellent specificity but only a moderated sensitivity in predicting mortality and is very close to the value reported by Huttunen on a larger group of 132 patients with BSI (11.5 ng/mL, Se 83%, Sp 76%); the study identified

suPAR as an independent risk factor for fatality (the other two BMs were not evaluated) and had the advantage of a heterogeneous study population, given the severity of diseases and implicitly, the varied outcomes, aspect which was obvious in the different mortality percentages from our group (13.63% vs. 85.7%). (21) Hoenigl confirms statistically significant differences of initial suPAR levels between the deceased and survivors group after 28 days (10.72 ng/mL vs 6.80 ng/mL, p=0.028) associated with a lack of significance for CRP and PCT, but the results are not directly comparable with our study, given the fact that only 41% of the patients had bacteremia, and the patient group was not homogenous in terms of the severity of diseases (the mortality in the bacteremia group - 36.36%) (40). In Raggam's study on 902 sepsis patients (the prevalence of bacteremia in the entire group was 32.81%) the predictive mortality value at 30 days was very close to the one reported by us (AUC 0.739; CI: 0.693-0.785), suPAR being an independent predictor for mortality after 48 hours, 30 and 90 days, and PCT and CRP had lower AUC values, not maintaining their value as mortality predictors after multivariable regressions (46).

In Staphylococcus aureus bacteremia (SAB), Molkanen identified the predictive capacity of suPAR for mortality, AUC being comparable to the one reported by us (0.754) but the optimal cut-off value for 30-days mortality was inferior (9.25 ng/mL) similar to the ones reported on other two SAB groups; the study reconfirms the prognostic incapacity of CRP and brings edifying data regarding the persistence of elevated suPAR levels for at least 10 days, which could represent an advantage when used clinically (42, 47, 48). Wittenhagen found that suPAR is an independent and potent predictor for mortality in pneumococcal bacteremia when levels were superior to the cut-off value of 10 ng/mL (42).

Through the studies' results, suPAR seems to confirm the ability to early diagnose septic bac-

teremia patients with an increased risk of death. Most of the above-mentioned studies have not evaluated the prognostic value of this BM on homogenous groups of BSI in septic patients with ICU admission criteria, results being obtained on groups of septic patients that included patients with positive blood cultures, often conducted in the emergency departments. Cut-off values of suPAR in predicting mortality in our group of patients are slightly higher than those found by many other authors, one of the reasons being the homogeneity of the group regarding the SIRS criteria and the severity of the clinical condition that prompted the admission to the ICU evidenced by the very high mortality in this group. The study confirms the prognostic superiority of this BM compared to PCT and CRP. The great limitation of this research is the small group of bacteremia patients included, which does not allow for statistical significance of the results.

It could be argued that the test might be of lesser value in pathogenic conditions with white blood cell depletion. Interestingly, it was shown that this is not the case, at least in (some) neutropenia: Kaya et al. (49) have actually shown that there still is an increase in suPAR levels in neutropenic patients with hematological malignancies and this is thought to be correlated with infections developing during the course of febrile neutropenia.

To conclude, the results obtained suggest a potential diagnostic contribution of suPAR in identifying bloodstream infections in SIRS + infection patients or in the preselecting of those that could benefit from molecular diagnostic methods.

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List of abbreviations

AUC = area under the curve
BMs = biomarker(-s)
BMI = body mass index
CI = confidence interval
CoNS = coagulase-negative staphylococci
COPD = chronic obstructive pulmonary disease
CRP = C-reactive protein
CV = coefficient of variability
DAMPs = danger associated molecular patterns
ESBL = extended-spectrum beta-lactamase
ELISA = enzyme-linked immunosorbent assay
GGT = gamma-glutamyl transpeptidase
GOT = glutamic-oxalacetic transaminase
GPT = glutamic-pyruvic transaminase
hsCRP = highly sensitiv CRP
ICU = intensive care unit
INR = international normalized ratio
IQR = interquartile ranges
MCH = mean corpuscular hemoglobin
MCHC = mean corpuscular hemoglobin concentration
MCV = mean corpuscular volume
MRSA = Methicillin-resistant Staphylococcus aureus
NS = Not significant
NS+S = non-segmented and segmented leucocytes
PAMPs = pathogen-associated molecular pattern
PCT = procalcitonin
PV = predictive value

ROC = receiver-operating characteristic curves

SAB = Staphylococcus aureus bacteremia

SD = standard deviation

Se = sensitivity

SIRS = systemic inflammatory response syndrome

Sp = specificity

suPAR = soluble form of urokinase plasminogen activator receptor

TNF = tumor necrosis factor

References

1. Dellinger RH, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Sur-viving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013. Feb;41(2):580-637.
2. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knauss WA, et al. Defini-tions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992 Jun;101(6):1644–55. DOI: 10.1378/chest.101.6.1644
3. Matzinger P. The danger model: a renewed sense of self. Science. 2002 Apr 12;296(5566):301-5. DOI: 10.1126/science.1071059
4. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mito-chondrial DAMPs cause inflammatory responses to injury. Nature. 2010 Mar 4;464(7285):104-7. DOI: 10.1038/nature08780
5. Jones GR, Lowes JA. The systemic inflammatory response syndrome as a predic-tor of bacteremia and outcome from sepsis. QJM.1996 Jul;89(7):515-22. DOI: 10.1093/qjmed/89.7.515
6. Bates DW, Sands K, E. Miller E, Lanken PN, Hibberd PL, Graman PS, et al. Pre-dicting bacteremia in patients with sepsis syndrome. Academic Medical Center Consortium Sepsis Project Working Group. J Infect Dis. 1997 Dec;176(6):1538-51. DOI: 10.1086/514153
7. Bauer M, Reinhart K. Molecular diagnostics of sepsis--where are we today? Int J Med Microbiol. 2010 Aug;300(6):411-3. DOI: 10.1016/j.ijmm.2010.04.006
8. Loonen AJM, de Jager CPC, Tosserams J, Kusters R, Hilbink M, Wever PC, et al. Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit. PLoS ONE 2014. Jan; 9(1):e87135. DOI: 10.1371/journal.pone.0087315
9. Reinhart K, Bauer M, Riedermann NC, Hartog CS. New approaches to sepsis: molecular diagnostics and biomarkers. Clin Microbiol Rev. 2012 Oct;25(4):609-

34 DOI: 10.1128/CMR.00016-12
10. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. Crit. Care. 2010;14(1):R15. DOI: 10.1186/cc8872
11. Riisbro R, Christensen IJ, Hogdall C, Brunner N, Hogdall E. Soluble urokinase plasminogen activator receptor measurements: influence of sample handling. Int J Biol Markers. 2001 Oct-Dec;16(4):233–9.
12. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003 Apr;31(4):1250-6. DOI: 10.1097/01.CCM.0000050454.01978.3B
13. Hatzistilianou M. Diagnostic and prognostic role of procalcitonin in infections. ScientificWorldJournal. 2010 Oct;10:1941–6. DOI: 10.1100/tsw.2010.181
14. Uzzan B, Cohen R, Nicolas P, Cucherat P, Perret GY. Procalcitonin as a diagnos-tic test for sepsis in critically ill adults and after surgery or trauma: a systematic re-view and meta-analysis. Crit Care Med. 2006 Jul;34(7):1996-2003. DOI: 10.1097/01.CCM.0000226413.54364.36
15. Bloos F. Clinical diagnosis of sepsis and the combined use of biomarkers and culture and non-culture-based assays. Methods Mol Biol. 2015;1237:247-60. DOI: 10.1007/978-1-4939-1776-1_19
16. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993 Feb 27;341(8844):515-8. DOI: 10.1016/0140-6736(93)90277-N
17. Bopp C, Hofer S, Bouchon A, Zimmermann JB, Martin E, Weigand MA. Soluble TREM-1 is not suitable for distinguishing between systemic inflammatory re-sponse syndrome and sepsis survivors and nonsurvivors in the early stage of acute inflammation. Eur J Anaesthesiol. 2009 Jun;26(6):504-7. DOI: 10.1097/EJA.0b013e328329afca
18. Povoa P, Teixeira-Pinto AM, Carneiro AH, Portuguese Community-Acquired Sepsis Study Group SACiUCI. C-reactive protein, an early marker of community-acquired sepsis resolution: a multi-centre prospective observational study. Crit Care. 2011 Jul;15(4):R169. DOI: 10.1186/cc10313
19. Suberviola B, Castellanos-Ortega A, Ruiz Ruiz A, Lopez-Hoyos M, Santibanez M. Hospital mortality prognostication in sepsis using the new biomarkers suPAR and proADM in a single determination on ICU admission. Intensive Care Med. 2013 Sep; 39(9):1945-52. DOI: 10.1007/s00134-013-3056-z
20. Schuetz P, Christ-Crain M, Muller B. Procalcitonin and other biomarkers to improve assessment and antibiotic stewardship in infections - hope for hype? Swiss Med Wkly. 2009 Jun;139(23-24):318–26.
21. Huttunen R, Syrjanen J, Vuento R, Hurme M, Huhtala H, Laine J, et al. Plasma level of soluble uroki-

nase-type plasminogen activator receptor as a predictor of disease severity and case fatality in patients with bacteremia: a prospective cohort study. J Intern Med. 2011 Jul;270(1):32-40. DOI: 10.1111/j.1365-2796.2011.02363.x

22. Georgescu AM, Azamfirei L. Cell receptors as biomarkers in sepsis pathology. J Rom Anest Terap Int. 2014 April;21(1):45-52.

23. Andersen O, Eugen-Olsen J, Kofoed K, Iversen J, Haugaard SB. Soluble urokinase plasminogen activator receptor is a marker of dysmetabolism in HIV-infected pa-tients receiving highly active antiretroviral therapy. J Med Virol. 2008 Feb; 80(2):209-16. DOI: 10.1002/jmv.21114

24. Eugen-Olsen J, Andersen O, Linneberg A, Ladelund S, Hansen TW, Langkilde A, et al. Circulating soluble urokinase plasminogen activator receptor predicts cancer, car-diovascular disease, diabetes and mortality in the general population. J Intern Med. 2010 Sep; 268(3):296-308. DOI: 10.1111/j.1365-2796.2010.02252.x

25. Eugen-Olsen J. suPAR – a future risk marker in bacteremia. J Intern Med. 2011 Jul; 270(1):29-31. DOI: 10.1111/j.1365-2796.2011.02372.x

26. Backes Y, van der Sluijs KF, Mackie DP, Tacke F, Koch A, Tenhunen JJ. et al. Use-fulness of suPAR as a biological marker in patients with systemic inflammation or in-fection: a systematic review. Intensive Care Med. 2012 Sep; 38(9):1418-28. DOI: 10.1007/s00134-012-2613-1

27. Koch A, Voigt S, Kruschinski C, Sanson E, Dückers H, Horn A, 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 pa-tients. Crit Care. 2011; 15(1):R63. DOI: 10.1186/cc10037

28. Donadello K, Scolletta S, Covajes C, Vincent JL. suPAR as a prognostic biomarker in sepsis. BMC Med. 2012 Jan;5:10:2. DOI: 10.1186/1741-7015-10-2

29. Siahanidou T, Margeli A, Tsirogianni C, Charoni S, Giannaki M, Vavourakis E, et al. Clinical value of plasma soluble urokinase-type plasminogen activator receptor levels in term neonates with infection or sepsis: a prospective study. Mediators Inflamm. 2014 May;2014:375702.

30. Donadello K, Scolletta S, Taccone FS, Covajes C, Santonocito C Cortes DO, et al. Soluble urokinase-type plasminogen activator receptor as a prognostic biomarker in critically ill patients. J Crit Care. 2014 Feb; 29(1):144-9. DOI: 10.1016/j.jcrc.2013.08.005

31. Koch A, Tacke F. Why high suPAR is not super-diagnostic prognostic and potential pathogenic properties of a novel biomarker in the ICU. Crit Care. 2011 Dec;15(6):1020. DOI: 10.1186/cc10577

32. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003 Apr;348(16):1546–54 DOI: 10.1056/NEJMoa022139

33. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006 Feb;34(2):344-53. DOI: 10.1097/01.CCM.0000194725.48928.3A

34. Samra RS, Zingarelli B, Wong HR. Role of biomarkers in sepsis care. Shock. 2013 Nov;40(5):358-65. DOI: 10.1097/SHK.0b013e3182a66bd6

35. Marshall JC, Reinhart K. International Sepsis Forum. Biomarkers of sepsis. Crit Care Med. 2009 Jul;37(7):2290–8. DOI: 10.1097/CCM.0b013e3181a02afc

36. Pisinger C, Ladelund S, Eugen-Olsen J. Influence of Lifestyle on suPAR Levels. The Inter99 Study; 2012 [http://suparnostic.com/images/stories/3rd_supar_symposium_2012_abstracts_program.pdf:11-11]

37. Haugaard SB, Andersen O, Hansen TW, Eugen-Olsen J, Linneberg A, Madsbad S, et al. The immune marker soluble urokinase plasminogen activator receptor is associated with new-onset diabetes in non-smoking women and men. Diabet Med. 2012 Apr;29(4):479-87. DOI: 10.1111/j.1464-5491.2011.03513.x

38. http://suparnostic.com/Result-Interpretation. [Accessed on Sep 20th, 2012].

39. Lodes U, Bohmeier B, Lippert H, Konig B, Meyer F. PCR-based rapid sepsis di-agnosis effectively guides clinical treatment in patients with new onset of SIRS. Langenbecks Arch Surg. 2012 (Mar);397(3):447–55. DOI: 10.1007/s00423-011-0870-z

40. Hoenigl M, Raggam RB, Wagner J, Valentin T, Leitner E, Seeber K, et al. Diag-nostic accuracy of soluble urokinase activator receptor (suPAR) for prediction of bacteremia in patients with systemic inflammatory response syndrome. Clin Bio-chem. 2013 Feb;46(3):225-9. DOI: 10.1016/j.clinbiochem.2012.11.004

41. Yilmaz G, Koksal I, Karahan SC, Mentese A. The diagnostic and prognostic significance of soluble urokinase plasminogen activator receptor in systemic in-flammatory response syndrome. Clin Biochem. 2011 Oct;44(14-15):1227-30. DOI: 10.1016/j.clinbiochem.2011.07.006

42. Wittenhagen P, Kronborg G, Weis N, Nielsen H, Obel N, Pedersen SS, et al. The plasma level of soluble urokinase receptor is elevated in patients with Strep-tococ-cus pneumoniae bacteraemia and predicts mortality. Clin Microbiol Infect 2004 May; 10(5):409–15. DOI: 10.1111/j.1469-0691.2004.00850.x

43. Meijers B, Poesen R, Claes K, Dietrich R, Bammens B, Sprangers B, et al. Soluble urokinase receptor is a biomarker of cardiovascular disease in chronic kidney disease. Kidney Int. 2015 Jan;87(1):210-6. DOI: 10.1038/ki.2014.197

44. Kofoed K, Eugen-Olsen J, Petersen J, Larsen K, Andersen O. 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 May;27(5):375-83. DOI: 10.1007/s10096-007-0447-5

45. Kofoed K, Andersen O, Kronborg G, Tvede M, Petersen J, Eugen-Olsen J, et al. Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migra-tion inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diag-nose infections: a prospective study. Crit Care. 2007;11(2):R38. DOI: 10.1186/cc5723

46. Raggam RB, Wagner J, Pruller F, Grisold A, Leitner E, Zollner-Schwetz I, et al. Soluble urokinase plasminogen activator receptor predicts mortality in patients with systemic inflammatory response syndrome. J Inter Med. 2014 Mar;19. DOI: 10.1111/joim.12238

47. Molkanen T, Ruotsalainen E, Thorball CW, Jarvinen A. Elevated soluble urokinase plasminogen activator receptor (suPAR) predicts mortality in Staphylococus aure-us bacteremia. Eur J Clin Microbiol Infect Dis. 2011 Nov;30(11):1417-24. DOI: 10.1007/s10096-011-1236-8

48. Moller HJ, Moestrup SK, Weis N, Wejse C, Nielsen H, Pedersen SS, et al. Macro-phage serum markers in pneumococcal bacteremia: prediction of survival by solu-ble CD163. Crit Care Med. 2006 Oct;34(10):2561–6. DOI: 10.1097/01.CCM.0000239120.32490.AB

49. Kaya S, Köksal I, Menteşe A, Sönmez M, Sümer A, Yıldırım SS, et al. The signi-ficance of serum urokinase plasminogen activation receptor (suPAR) in the di-agnosis and follow-up of febrile neutropenic patients with hematologic malignan-cies. Int J Infect Dis. 2013 Nov;17(11):e1056-9. DOI: 10.1016/j.ijid.2013.04.004