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Prognostic value of soluble urokinase plasminogen activator receptor (suPAR) in patients with sepsis attended at an emergency department

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Información de artículo

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Abstract

Objective: validation of Soluble urokinase plasminogen activator receptor (suPAR) as a prognosis biomarker in patients attended for sepsis in an Emergency Department.

Methods: patients diagnosed of severe inflamatory response syndrome (SIRS), sepsis and septic shock at the La Paz University Hospital (HULP) emergency department (ED) were eligible for the study. The study was approved by the hospital etical committee [CEIC] and all patients signed a written consent. Clinical, analitical, and microbiological data, as well as a serum sample to measure the suPAR level, were collected in the first 6 hours since diagnosis. Windows 15 SPSS program was used for statistical analysis. Chi-square test (or Fisher exact test) and Student-T or ANOVA (or Mann-Whitney U-test, or Kruskal-Wallis test) were applied to evaluate the prognosis usefulness of suPAR, C-reactive protein (CRP), procalcitonine (PCT) and lactate. A Receiver Operating Characteristic (ROC) Curve of Sensibility against [1-Specificity] was created in order to decide whether suPAR plasmatic level could determine the global survival rate in these patients.

Results: 36 patients were enrollled (6,1% with SIRS, 69,7% with sepsis, and 24,2% with septic shock) with a median age of 69,1+15,0 years old. 12 patients (33,3%) were admitted at the Intensive Care Unit (ICU). 10 patients (27,8%) died during the first 30 days. Plasma suPAR levels (ng/mL) in the group of patients who died were 8,6 + 3,8 versus 6,1 + 2,5 in the surviving group. CRP levels (mg/L) were 185,5 + 109,1 versus 121,22 + 137,7. PCT levels (ng/mL) were 16,7 + 7,2 versus 12,8 + 4,1. Lactate levels (mmol/L) were 4,6 + 3,9 versus 2,5 + 1,3. Only plasmatic suPAR levels showed statistical relationship with mortality during the first 30 days. The ROC curve for suPAR plasmatic values showed an Area Under the Curve (AUC) of 0,717 (95% CI 0,517-0,917, p=0.046). The best sensibility-specificity balanced cut-off point for predicting mortality was 6,9 ng/mL (70% sensibility and 65,4% specificity).

Conclusions: a single suPAR plasmatic level measure is an independent biomarker with an acceptable predictive value in septic patients with different stages of disease severity. Its routinary use in the daily clinical practice could improve sepsis management and avoid progression to more severe stages of the disease.

Resumen

Objetivo: validación de suPAR como biomarcador pronostico en pacientes sépticos en un Servicio de Urgencias Hospitalario.

Materiales y métodos: pacientes: se incluyeron pacientes con SIRS, sepsis y shock séptico diagnosticados en el SU del Hospital Universitario La Paz (HULP). Se recogieron variables clínicas, analíticas y microbiológicas, así como una muestra para la determinación de suPAR en las 6 primeras horas desde el diagnostico. Este estudio ha sido aprobado por el CEIC del HULP y todos los pacientes firmaron su consentimiento informado. Análisis estadístico: Se empleó el programa SPSS versión 15 para Windows. Se utilizó el test Chi-cuadrado (o el test exacto de Fisher) y la T de Student o el ANOVA (o la U de Mann-Whitney o el test de Kruskal-Wallis) para evaluar la utilidad pronóstica del suPAR, PCR, PCT y lactato. Se generó una curva ROC (Receiver Operating Characteristic) de sensibilidad versus 1-especificidad para determinar si el nivel plasmático de suPAR podía discriminar supervivencia global en pacientes sépticos en el SUH.

Resultados: se incluyeron un total de 36 pacientes (6,1% con SRIS, 69,7% con sepsis y 24,2% en shock séptico) con una media de edad de 69.1 ± 15.0 años. Diez pacientes (27,8%) murieron en los primeros 30 días, y 12 (33,3%) ingresaron en la Unidad de Cuidados Intensivos. Los niveles de suPAR para los pacientes exitus son de 8.6 ± 3.8 (ng/ml)y en los no exitus 6,1 ± 2.5(ng/ml), los niveles de PCR para los éxitus fueron de 185.5 ± 109.1 (mg/l) y para los no éxitus 121.22 ± 137.7(mg/l), los valores de PCT para los éxitus fueron 16.7 ± 7.2 (ng/ml)y para los no éxitus 12.8 ± 4.1 (ng/ml), los niveles de lactato para los éxitus fueron de 4,6 ± 3.9 (mmol/l) y para los no exitus de 2,5 ± 1,3 (mmol/l). Únicamente los niveles de suPAR se asociaron a mortalidad en los primeros 30 días. La curva ROC de valores de suPAR presentó un AUC de 0.717 (95% CI: 0.517-0.917, p = 0.046). El punto de corte con mejor balance de sensibilidad-especificidad para discriminar mortalidad en pacientes sépticos en el SUH fue de 6,9 ng/mL (sensibilidad de 70% y especificidad de 65,4%).

Conclusión: una única determinación de suPAR en un SUH es un biomarcador independiente con un buen valor predictivo en pacientes sépticos en diversos estadios de gravedad. La implementación rutinaria de esta determinación en la práctica clínica habitual podría mejorar el manejo de la sepsis en los SUH y reducir la progresión de SRIS a sepsis o shock séptico.

Introduction

Sepsis is an inflammatory response of a host to infection (suspected or documented), and when uncontrolled may result in severe sepsis (acute organ dysfunction) or Septic shock (sepsis with fluids infussion refractory hipotensión)[1].

The documented incidence of sepsis worldwide is 1.8 million each year, but this number is confounded by a low diagnostic rate and difficulties in tracking sepsis in many countries. Surviving Sepsis estimate that with an incidence of 3 in 1000 the true number of cases each year reaches 18 million, and with a mortality rate of almost 30% it becomes a leading cause of death worldwide[3,4]. The incidence is set to rise as the population ages, the elderly being worse affected[3]. Sepsis costs on average US$22 000 per patient, and its treatment therefore has a great impact on hospitals' financial resources, with US$16.7 billion each year being spent in the USA alone[3]. The cost of treating an ICU patient with sepsis is six times greater than that of treating a patient without sepsis[3]. In Spain, an anual incidence of 14,1/10.000 inhabitants has been reported, being máximum in patients older than 84 years old (230,8/10.000). Microorganisms more often involved in our media were Streptococcus sp., Staphylococcus sp., Escherichia coli y Candida sp. Overall mortality was 33%, but it was even greater in patients with more than one organ dysfunction, or with liver dysfunction, or in patients with cancer. The annual spent on treating severe sepsis was estimated in 70 millions euros in the Madrid Community[2].

More than 170 molecules has been investigated as likely diagnostic or prognostic biomarkers for sepsis. Some of them has been already validated and its use has become routinary, for instance C-reactive protein (CRP), procalcitonine (PCT) or lactate. Early recognition of evolution prognostic markers (biological or whatever they are) could be really useful in the emergency department (ED) to decide earlier interventions and final admission destination for patients with sepsis, which may help on decreasing the associated morbi-mortality of this disease.

Recently a new molecule has been suggested as one of these biomarkers. The soluble urokinase-type plasminogen activator receptor (suPAR) is a cell membrane protein formed by 3 different dominiums which can be found on several immunologically active cells as monocytes and activated T lymphocytes, and also on endothelial cells, keratinocytes, fibroblasts, plain muscle-cells, megakaryocytes, and some tumoral cells. The soluble form can be found on plasma, urine, blood, serum or cerebrospinal fluid in different concentrations pending on the immune system activation level. That is why suPAR levels has been linked to severity in various infective diseases[13-18].

However its value as an early prognostic marker for sepsis in the ED has not been well defined yet. Some studies have compared suPAR levels with other blood biomarkers levels[5-10] or with severity indexes as APACHE II[5,12] or SOFA. However, in the ED media, these indexes are not commonly used, and the implementation of a biomarker with prognostic value should be extremely useful in this media, even more if it is a simple, fast, single and reproductible measure.

Objectives

The ultimate aim of this study is to check suPAR level as an early prognostic factor (when it is measured within the first 6 hours) for patients with sepsis, severe sepsis, or septic shock in the ED, and determine the best mortality discriminating level for these patients.

Methods

This is an observational study with prospective follow up of adults patients (aged 18 years or older) attended at the La Paz Universitary Hospital ED during the year 2013, and diagnosed of sepsis, severe sepsis, or septic shock (as per the ACCP/SCCM criteria [Crit. Care Med. 1992][20]) during the first 6 hours after arrival. Patients aged less than 18 year-old, who did not sign informed consent, or with previously known Human Immunodeficiency Virus (HIV) infection were excluded.

Demographic data, past medical history, previous medications (specially antibiotics), clinical findings, blood, radiological and microbiological tests (requested under criteria of the attending doctor), and patient's final destination (Medical Ward, Intensive Care Unit, discharge, or death). Main investigation variable was mortality rate in the 30 days period after diagnosis.

All patients enrolled had their blood tested (Haematology, Biochemistry and coagulation tests as decided by the treating doctor) and measurement of CRP, PCT and lactate was done in all cases. Two plasma aliquots were collected and stored in a freezer at -20º Celsius for further testing for suPAR levels. All blood samples were collected during the first 6 hours since arrival, and once diagnosis of sepsis, severe sepsis or septic shock was achieved. In all patients, suPAR levels were measured with the suPARnostic ® Standard ELISA Assay (Viro Gates (r)) technique.

The study was approved by the Hospital Ethical Committee (CEIC) and all patients signed the written informed consent prior to their enrollment.

Statistical analysis: a descriptive analysis of data was performed, showing categoric variable as absolute value and percentage. Cuantitative variable were shown as mean + standart desviation (SD), or median (range). For cuantitative variable, univariate analysis was made using T-student, and for categoric (or its non parametric equivalent) was made using Chi-square. A Receiver Operating Characteristic (ROC) Curve was created to calculate the death predicitive value of suPAR (largest specificity point with a mínimum sensibility of 70%). Positive (PPV) and negative (NPV) predicitive value, and positive and negative likelyhood ratio were estimated for this suPAR value.

Table 1.
CLINICAL PROFILE OF PATIENTS ATTENDING ER WITH SEPSIS

	Media	SD
Age (years)	69,1	15,0
Sex (womans %)	58,3	
Temperature (ºC)	36,8	1,6
Cardiac frecuency (lpm)	101,8	19,5
RF (rpm)	19,6	5,1
SAT (mmHg)	94,7	20,9
DAT (mmHg)	56,9	10,8
Hb (gr/dL)	13,0	2,5
White cells (célls/mL)	13150,0	6,4
Plateles (célls/mL)	262414,0	114,3
Glucose (g/dL)	121,1	41,1
Urea (mg/dL)	86,2	58,1
Albúmin (g/dL)	3,0	0,4
Na (mEq/L)	137,7	8,7
pH	7,3	0,2
$SatO^2$ (%)	68,3	24,0
pO^2 (mmHg)	42,3	18,0
pCO^2 (mmHg)	38,4	9,1
PCR (mg/L)	139,6	131,9
Lactate (mmol/L)	3,3	2,7
PCT (ng/mL)	13,8	5,2
PA (%)	76,1	27,5
suPAR(ng/mL)	6,8	3,1

A multivariate logistic regresion model was made including all the variable which have shown to be predictive for mortality in septic patients (even if no statistical significance was noted on univariate analysis) as well as the suPAR values. Using binary logistic regresión, suPAR levels were used to calculate death probability. Statistical software SPSS 15 for Windows (spanish version) was employed for these purposes, and a $p < 0,05$ was found to be statistically significative.

Results

36 patients were enrolled in the study, with a mean age of 69 + 15,0 years old. Clinical data are shown on table 1. Cases were classified as sepsis, severe sepsis, or septic shock following ACCP/SCCM[18] criteria, as previously reported.

6,1% of patients had the diagnosis of sepsis, 69,7% had severe sepsis, and 24,2% had septic shock. 10 out of 36 patients (28%) died in the first 30 days after diagnosis (whichever the reason was), and 33,3% were admitted at the Intensive Care Unit. Clinical data and blood tests results in both the survival and the non-survival groups are shown in table 2. Statistically significative diferences were found on the suPAR levels between both groups, being higher on the non-survival

Table 2.
CLINICAL, ANALITICAL AND BIOMARKERS RESULTS IN PATIENTS WITH SEPSIS ATTENDING TO MORTALITY. COMPARACIÓN DE VARIABLES CLÍNICAS, ANALÍTICAS Y BIOMARCADORES EN PACIENTES SÉPTICOS SEGÚN MORTALIDAD

Media (DS)	Éxitus (N=10)	No éxitus (N=26)	Significancia (p)
White cells (célls/mL)	11820 (4839)	13660 (2058)	0,447
SAT (mmHg)	95,3 (18,4)	94,5 (22,2)	0,922
DAT (mmHg)	55,2 (8,2)	57,7 (11,7)	0,553
RP (rpm)	22,1 (4,5)	18,6 (4,9)	0,069
CF (lpm)	107,4 (14,7)	99,5 (21,0)	0,287
suPAR (ng/mL)	8,7 (3,8)	6,1 (2,5)	0,018
PA (%)	59 (28,3)	82 (25)	0,050
PCT (ng/mL)	16,7 (7,2)	12,8 (4,1)	0,055
CRP(mg/L)	185,5 (109,1)	121,2 (137,7)	0,197
Lactate (mmol/L)	4,6 (3,9)	2,5 (1,3)	0,209

The values are expressed as mean(SD).

one (8,7ng/ml ± 3,8ng/ml vs 6,1ng/ml ± 2,5ng/ml, $p = 0,018$). Neither any other sepsis related biomarkers, nor demographic, nor clinical findings, reached statistical significance in the univariate analysis.

The ROC curve built to determine the best balanced cut-off point of suPAR levels in order to predict mortality is shown in figure 1. It has an area under the curve (AUC) of 0.717 (95% CI: 0.517-0.917, $p = 0.046$). Best balanced cut-off point of suPAR levels was 6,9 ng/mL (Sensibility 70%, Specificity 65%). SuPAR levels death prediction profit is shown in table 3.

Known sepsis prognostic factors and any other which reached a $p < 0,1$ in univariate analysis were included in a multivariate logistic regresión model. As it is shown in table 4, prothrombine activity, respiratory rate and suPAR levels are maintained in the model ($p = 0.013$). The mortality forecast likelyhood curve according to suPAR levels is shown in figure 2.

Table 3.
MORTALITY FORECAST RENTABILITY OF SUPAR EQUAL OR LARGER THAN 6.9 NG/ML

	suPAR > = 6,9 ng/mL
Sensibility	70%
Specifity	65%
PPV	44%
NPV	85%
LRP	2,02
LRN	0,46

Table 4.
STEPWISE LOGISTIC REGRESSION

Variable	OR	95% CI	Significance
SuPAR	1.408	0.956-2.076	0.084
Respiratory rate	0.967	0.934-1.001	0.055
Prothrombine activity	1.247	0.971-1.602	0.084

Discussion

Sepsis is an increasingly common entity in our environment and is an important cause of morbidity and mortality, especially in patients who go to an ED, and in which is often difficult to determine the prognosis in the short-medium term[19]. Determining this prognosis early could prevent the development of serious complications and premature deaths.

In recent years numerous working groups have tried to answer questions about markers that allow to discriminate the septic patients at high risk of death, developing multiple scales of severity and studies of biomarkers (f.i., CRP, lactate, or PCT among others). Recently the suPAR has been proposed as biomarker able to discriminate septic patients at high risk of death.

The data available in the literature are disparate, since the published series involve a limited number of patients. Serum levels of suPAR significantly higher in those patients who died were apparent in a study of 151 patients with criteria of SIRS (systemic inflammatory response syndrome)[20]. Another study which recruited 141 patients with pneumococcal pneumonia showed that suPAR serum levels were higher in comparison with 31 healthy volunteers. In addition, serum levels of the deceased were greater than the survivors[21].

There are multiple studies that attempt to test its usefulness as a predictive marker in cases of sepsis, most of them in ICU[20-22], with the peculiarities of patients admitted to this type of units[5, 21]. However, limited outcomes exist in hospital ED, where it is justified to study the role that this new molecule (suPAR) may play in early stages of sepsis, well on an individual basis, as in combination with other biomarkers, clinical parameters and severity scales. A heterogeneous population of patients[10], which limit its results to medical patients with a suspected infection, was investigated in a study conducted in an ED. However, their data show clearly that suPAR levels are not related to the presence and severity of (bacterial) infection, in line with previous reports[8, 13, 16, 24]. In fact, the results of other studies[5,20,21,22] have suggested that suPAR serum concentrations are directly related to the presence and severity of organ dysfunction. Our study demonstrates that suPAR values

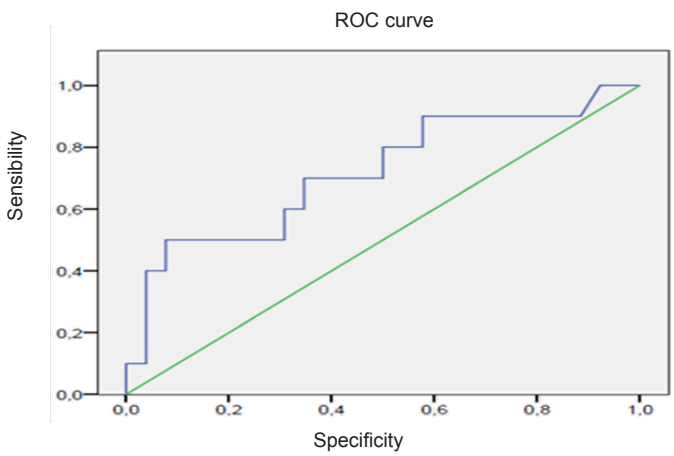

Figure 1.

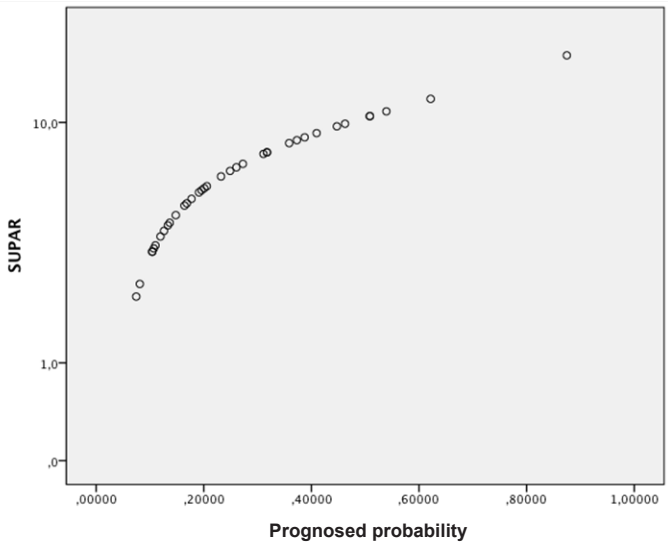

Figure 2. Death probability attending to suPAR results.

are higher in patients with severe sepsis and septic shock that in patients with sepsis (SIRS) (table 2).

Bearing in mind that the first hours are crucial and that they define the morbidity and mortality of septic patients, being these "Golden hours" the target of the greater part of international consensus and action guides, and that, on the other hand, is the ED specialist who can act earlier in the septic patient, there are not many studies focussed in the ED of early biomarkers of sepsis.

Hence the importance of our study aimed at the early identification of a biomarker that helps the ED doctor to identify patients at greater risk of evolving from a septic picture to severe sepsis and septic shock, with a morbidity and mortality progressively higher. This is also a common problem. In ED sepsis, severe sepsis and septic shock represent 15% of treated patients, so it is necessary to ascertain the severity as soon as possible for a quick performance, establishing early treatment and further location of these patients.

Classically PCT and CRP have been used for several years in hospitals for the diagnosis and follow-up of sepsis in critical patients. Some studies compared the levels of PCT with CRP levels in septic patients, suggesting that the former can be a more reliable marker than the latter[25, 26]. A study determined that PCT had 97% of sensitivity and 78% specificity in the diagnosis of sepsis, while another study reported that PCT levels could be low or undetermined in the early stage of the disease[27, 28]. On the other hand, it has been noted that the PCT levels can be high in conditions not related to infection[29]. In addition, studies on CRP have demonstrated that it has no differential power with respect to sepsis, severe sepsis and septic shock[30].

In our study, CRP and PCT levels do not reach statistically significant difference between deceased and survived groups. The analysis revealed that none of the 2 parameters could be used as a prognostic marker. This implies an increase in the importance of the diagnosis using other biomarkers as the suPAR.

We have observed a statistically significant difference in levels of suPAR in relation to mortality of septic patients, with a NPV of 85% and a PPV of 44%, meaning that 85% of patients with a serum concentration of less than 6.9 ng/mL will not die because of the the infectious process. For this reason has been chosen the cut-off point where there is more specificity and sensitivity, not only the greater specificity one as other authors[4-7], due to the more useful application in ED of the biomarker with a proper NPV, identifying low-risk patients.

With our study we can conclude that a single determination of suPAR, within six hours of evolution of the infection at the ED, is an independent marker with a good negative predictive value in septic patients in various stages of severity. The routine use of this determination in daily clinical practice could improve the management of sepsis in the ED by reducing progression to severe sepsis or septic shock.

More studies with larger sample size, in order to prospectively validate a semiqualitative tests measuring suPAR as prognostic tool in the septic patient in the ED, should be developed.

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